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ReActiv8®
Implantable Electrical Stimulation System

Clinical Summary

Mainstay Medical

ReActiv8® Clinical Summary

The clinical use of the Mainstay Medical ReActiv8 Implantable Neurostimulation System (ReActiv8 System) is supported by the clinical studies summarized in this manual. All patients were implanted to aid in the management of intractable chronic low back pain (CLBP) associated with multifidus muscle dysfunction, also referred to throughout this document as mechanical CLBP. The studies described in this summary were submitted in regulatory applications to the U.S. Food and Drug Administration in support of Mainstay Medical ReActiv8 System approval.

Multifidus dysfunction can result from a loss of neuromuscular control. This can cause a lack of spinal support, leading to uncontrolled loading of spinal joints and discs, resulting in mechanical CLBP.[1,2] ReActiv8 aids in the management of CLBP by improving long-term functionality for patients by aiming to address the underlying cause. ReActiv8 is a restorative therapy designed to address multifidus muscle dysfunction linked to mechanical CLBP.

A. <u>Executive Summary</u>

The ReActiv8-B trial, conducted under an investigational device exemption (IDE), provided evidence of safety and effectiveness of the ReActiv8 therapy in the management of intractable chronic low back pain associated with multifidus muscle dysfunction. The study was an international, multi-center, prospective, randomized, double-blind, active-sham controlled blinded trial comparing the ReActiv8 System (patient appropriate stimulation level – Treatment group) to an active sham (ReActiv8 programmed to deliver sub-therapeutic stimulation – Control group). Although the primary efficacy endpoint was inconclusive at the 120-day visit, the totality of evidence, including other outcome data at the 120-day visit and long-term data at annual visits through five years,[3–6] provides compelling support in favor of the treatment. The prespecified cumulative proportion of responder analysis of the primary endpoint data (ITT) showed that the difference between the Treatment and Control groups was statistically significant (p=0.0499).

Patients in the trial had an average CLBP duration of 14 years and suffered pain on 97% of the days in the year prior to enrollment. The overall results demonstrated that patients moved from severe pain and borderline severe disability to mild pain and disability. Benefits that emerged in the Treatment group within the blinded phase continued to increase through the 5-year visit, demonstrating durability of the gained improvements. The reversal of trajectory and subsequent substantial and significant improvements documented in the Control group post crossover at 120 days provides further support in favor of ReActiv8 therapy effectiveness.

Clinically meaningful and durable improvements were consistently demonstrated across all outcome measures. In addition, 69% of patients who were on opioids at baseline had discontinued or reduced their use as of the 5-year visit.

Given the public health concern over the chronic use of opioids, physicians and patients are now looking for non-opioid options for treating pain. This data supports that ReActiv8 is a safe, effective, and durable nondrug treatment option for mechanical CLBP associated with multifidus dysfunction.

The clinically meaningful benefits across all outcome measures, the favorable safety profile, and positive impact on opioid reduction creates a favorable benefit/risk ratio for the use of this therapy in patients severely impacted with refractory mechanical CLBP.

B. Background

The ReActiv8-B trial, conducted under an investigational device exemption (IDE), provided evidence of safety and effectiveness of ReActiv8 therapy in the management of intractable chronic low back pain associated with multifidus muscle dysfunction. Data from this trial was the basis for FDA approval.

C. Study Design

The study was an international, multi-center, prospective, randomized, double-blind, active-sham controlled blinded trial comparing the ReActiv8 System (patient appropriate stimulation level – Treatment group) to an active sham (ReActiv8 programmed to deliver low level stimulation – Control group).

Between September 13, 2016, and June 14, 2018, 561 patients were enrolled at 26 investigational sites. A total of 204 patients met all enrollment criteria and were randomized in a 1:1 ratio to the Treatment and Control groups. After the primary endpoint at 120 days, patients randomized to the Control group were allowed to cross over to receive stimulation at a therapeutic level. Patients continued to be followed annually for five years.

Considering emerging improved quality standards, such as those discussed at the November 2018 Initiative on Methods, Measurement, and Pain Assessments in Clinical Trials (IMMPACT) XXII meeting, the ReActiv8-B trial incorporated many rigorous design and implementation methods. As such, the quality of the methods used in this trial are higher than that seen in many trials of implantable neurostimulation devices for chronic pain, including various types of CLBP. Prospectively defined actions demonstrating the sponsor's commitment to conducting a high-quality trial include the following:

- Minimization of bias
    - Randomized, controlled trial
        - Randomization post implant
        - Active sham control
    - Blinded
        - Patients
        - Investigator and site personnel
        - Sponsor
        - Oversight committees
        - Monitors
    - Maintained equipoise
        - Balanced interactions with both treatment groups
        - Setting of neutral expectations
    - Outcome data collected prior to interaction with the patient and prior to programming
    - Rigorous screening process, including review by independent physician experts
- Independent trial oversight
    - Independent, blinded physician experts on several committees
        - Data Monitoring Committee (DMC)
        - Clinical Events Committee (CEC)
        - Baseline MRI Review by independent orthopedic spine surgeons
        - Overview of inclusion/exclusion criteria by Study Chair Principal Investigator
    - Independent statisticians
- Early and frequent monitoring
- Comprehensive training, including a requirement for up-to-date Good Clinical Practice (GCP) training for all site personnel involved in the trial
- Minimization of financial conflict of interest

1. <u>Key Enrollment Criteria</u>

Enrollment in the ReActiv8-B trial was limited to patients who met the following key *inclusion* criteria:

- Age ≥22 years, ≤75 years
- 7-day recall of average Low Back Pain Visual Analogue Scale (VAS) of ≥6.0 cm and ≤9.0 cm at baseline.
- Oswestry Disability Index (ODI) score ≥21% and ≤60% at the baseline visit.
- Chronic Low Back Pain that has persisted >90 days prior to the baseline visit, and that has resulted in pain in at least half of the days in the 12 months prior to the baseline visit.
- Evidence of lumbar multifidus muscle dysfunction by the Prone Instability Test (PIT).
- Continuing low back pain despite >90 days of medical management including at least one attempt of physical therapy treatment and attempted medications for low back pain.

Patients were not permitted to enroll in the ReActiv8-B trial if they met any of the following key *exclusion* criteria:

- Body mass index (BMI) >35
- Back pain characteristics, such as: any surgical correction procedure for scoliosis at any time or a current clinical diagnosis of moderate to severe scoliosis (>25 degree cobb angle), severe lumbar spine stenosis in patients with lower extremity pain, and pathology seen on MRI that is clearly identified and is likely the cause of the CLBP that is amenable to surgery.
- Leg pain described as being worse than back pain, or radiculopathy below the knee.
- Surgical or other procedures exclusions, such as: any previous rhizotomy (or radiofrequency ablations RFA) within 1 year prior to the baseline visit, anesthetic block or injections at or below the T8 vertebra in the 30 days prior to the baseline visit, any previous instrumented back surgery at or below segmental level T8, or spinal fusion at any level.
- Any comorbid chronic pain conditions.
- Have an assessment of current active depression significant enough to impact perception of pain, compliance with intervention, and/or ability to evaluate treatment outcome.
- Have evidence of an active disruptive psychological or psychiatric disorder or other known condition significant enough to impact perception of pain, compliance with intervention, and/or ability to evaluate treatment outcome.
- Any other active implantable device.
- A condition currently requiring or likely to require use of MRI or diathermy while implanted with the ReActiv8.

2. Follow-up Schedule

Patients who met the enrollment criteria proceeded to the ReActiv8 System implant. Once implanted, the patients were randomized to one of the two study groups at 14 days post-implant where stimulation was programmed accordingly based on the randomization. Patients returned for visits at 14 days, 45 days, 75 days, 120 days, 180 days, 240 days, and 1 year post randomization/activation of the ReActiv8 System and annually thereafter for a minimum of 5 years.

The assessments required at each visit are shown in Table 1 below. Adverse events were collected at every visit beginning at enrollment.

Table 1: Study Assessment Timepoints

Study Requirement	**Enrollment & Baseline**	**ReActiv8 Implant**	**Randomization & Activation**	**14 Day Visit**	**45 Day Visit**	**75 Day Visit**	**Primary Endpoint: 120 Day Visit**	**180 Day Visit**	**240 Day Visit**	**Annual Follow-up**
Screening	✓									
ODI	✓					✓	✓	✓	✓	✓
Back pain VAS (Journal)	✓				✓	✓	✓			
Back pain VAS (Single Point)	✓			✓	✓	✓	✓	✓	✓	✓
Medications questionnaire	✓	✓			✓	✓	✓	✓	✓	✓
EQ-5D	✓					✓	✓	✓	✓	✓
$DASS_{21}$	✓									
Low back pain descriptive characteristics	✓				✓	✓	✓	✓	✓	✓
Work status evaluation	✓				✓	✓	✓	✓	✓	✓
Percent Pain Relief (PPR)						✓	✓	✓	✓	✓
Subject Global Impression of Change (SGIC)						✓	✓	✓	✓	✓
Treatment Satisfaction Questionnaire (TSQ)						✓	✓	✓	✓	✓
Clinical Global Impression (CGI)						✓	✓	✓	✓	✓
Health care utilization	✓							✓	✓	✓
Blinding assessment questionnaire							✓			
X-Ray (AP and lateral)		✓		✓						
Device measurements & stimulation thresholds		✓	T	T	T	T	T	✓	✓	✓
Interrogate IPG for lead impedance & compliance				✓	✓	✓	✓	✓	✓	✓
Physical exam & surgical site exam	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events		✓	✓	✓	✓	✓	✓	✓	✓	✓
Pregnancy test	✓									

✓= Required for all patients; T=Required for Treatment group Only (Control group – programming performed but no stimulation thresholds checked)

3. Clinical Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint was a comparison of responder rates between the Treatment group and the Control group at the 120-day visit. A "responder" was defined as a patient with ≥30% reduction from baseline in a 7-day recall of average low back pain Visual Analogue Scale (VAS) without any increase from baseline in pain medication and/or muscle relaxants prescribed and taken in the two weeks prior to the visit. Per the IMMPACT guidelines, a reduction of 30% is considered a clinically meaningful reduction.

Patients were also asked at each follow-up visit if they had taken any new prescribed pain medications or had a dose change for any prescribed medications in the two weeks prior to the visit. Any increase in pain medications in the two weeks prior to the 120-day visit was considered a significant change in medications for the purposes of the primary endpoint. Rescue medications taken on an exceptional basis for acute pain conditions other than back pain were also documented and their impact on the estimated treatment effect examined.

Components of the Primary Efficacy Endpoint

The individual components of the primary efficacy endpoint (VAS and medications) were also analyzed and presented separately.

VAS

VAS was analyzed using the following additional methods:

- The mean change in VAS was calculated and compared between the Treatment group and Control group.
- The cumulative proportion of responder curves (i.e., cumulative distribution functions) were constructed for each treatment group separately, overlaid, and compared. This analysis compares patient responses, measured by change in VAS, across each possible threshold change level rather than dichotomizing the responses at the single cut point of 30% reduction in VAS.

Pain Medications

Records of pain medications were collected along with all other medications used for treatment of low back pain, which were also being collected for analysis of secondary and cost-effectiveness endpoints. At each scheduled follow-up visit, patients reported medications taken. Rescue medications taken on an exceptional basis for acute pain conditions other than back pain were also documented.

In a supplementary analysis, prespecified in the clinical protocol and statistical analysis plan (SAP) prior to the start of the trial, patients found to have taken medications for reasons other than back pain were excluded to evaluate the potential impact on estimates of treatment group differences.

Primary Safety Assessment

The primary safety assessment evaluated serious device- and/or procedure-related adverse events at the 120-day visit. All reported adverse events were documented and reported with summary statistics presented for observed rates.

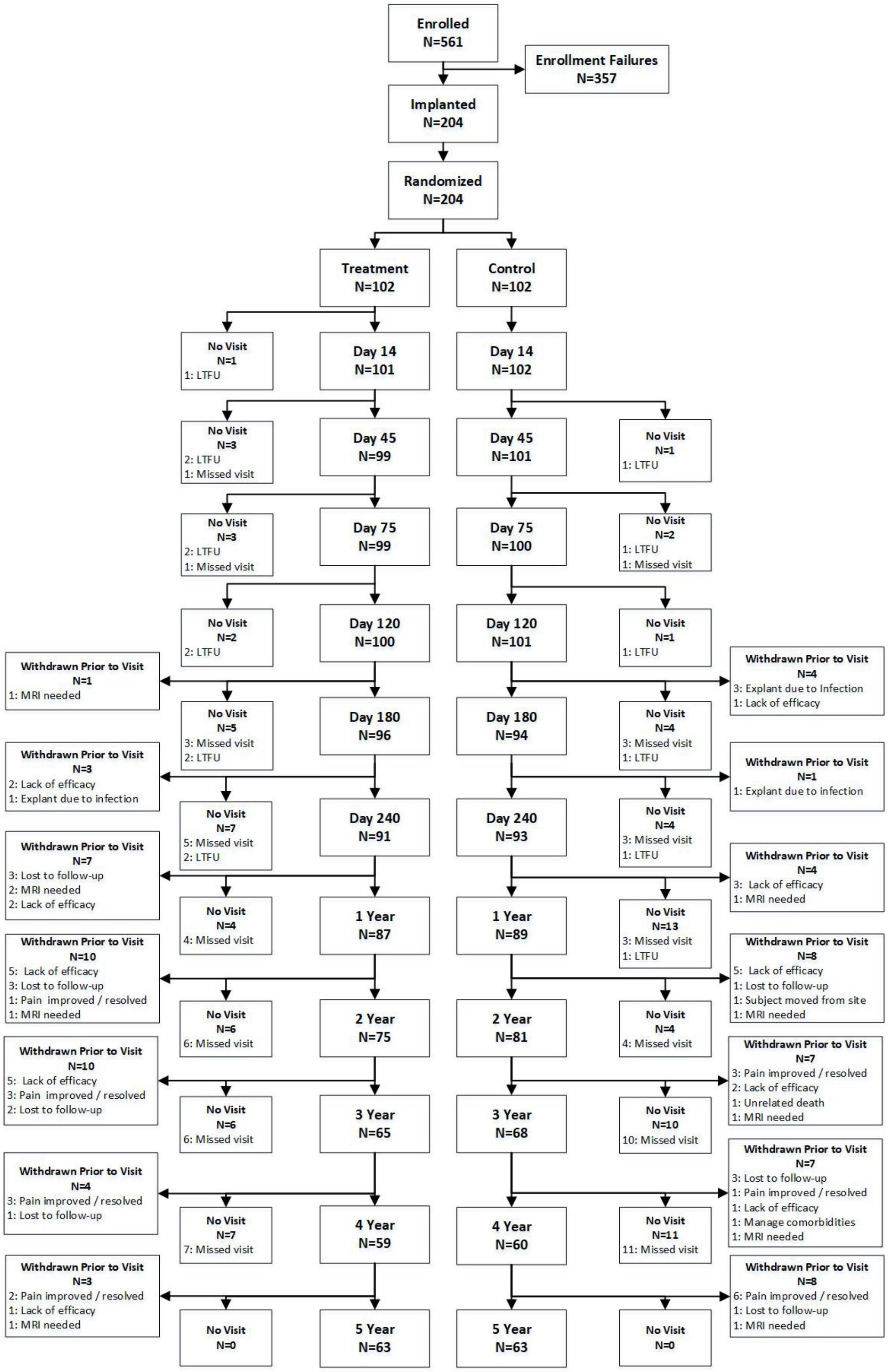
Secondary Endpoints

The following secondary endpoints were evaluated:

a. Comparison of change from baseline in Oswestry Disability Index (ODI) between Treatment and Control groups at the 120-day visit.
b. Comparison of change from baseline in EQ-5D between Treatment and Control groups at the 120-day visit.
c. Comparison of Percent Pain Relief (PPR) between Treatment and Control groups reported by the patient at the 120-day visit.
d. Comparison of Subject Global Impression of Change (SGIC) between Treatment and Control groups at the 120-day visit.
e. Comparison of proportion of patients with Resolution of Low Back Pain (defined as a VAS score ≤2.5 cm) between Treatment and Control groups at the 120-day visit.
f. Evaluation of changes in primary and secondary efficacy metrics in the Crossover group following the 120-day visit.

D. Accountability of PMA Cohort

At the time of the database lock for the PMA report, there were 561 patients enrolled in the study. Of those, 204 patients met the inclusion criteria and had the ReActiv8 System implanted. At the randomization visit 14 days after implant, 102 patients were randomized to the Treatment group and 102 patients were randomized to the Control group. A total of 100 patients in the Treatment group and 101 in the Control group returned for the primary endpoint visit at 120 days. A total of 176 patients completed the 1-year follow-up, and 126 completed the 5-year follow-up. See Figure 1 below.



LTFU: Lost to follow-up
Missed Visit: Includes scheduling difficulties, noncompliance, and safety reasons (e.g., broken ankle)
To account for the timing of withdrawal, patients count only once within the time interval in which they were withdrawn

Figure 1: Patient Disposition by Visit through Five Years

E. Study Population Demographics and Baseline Parameters

The demographics of the study population were typical for a pain study. The study groups were well balanced across all factors with the exception of previous rhizotomy. Of the 12% of patients who had one or more previous rhizotomies, a higher percentage of patients in the Control group had a previous rhizotomy compared to the Treatment group (17% and 8%, respectively). Since the enrollment criteria required that the previous rhizotomy had to have been >12 months prior to enrollment, history of a previous rhizotomy was not expected to impact the study results. See Table2 for summary.

Table 2: Medical History and Baseline Demographics

Characteristic	Treatment N=102 Mean ± SD (Min, Max) or n (%)	Control N=102 Mean ± SD (Min, Max) or n (%)	Total N=204 Mean ± SD (Min, Max) or n (%)	p-value[1]
Age (years)	46 ± 10 (22, 66)	48 ± 9 (26, 71)	47 ± 9 (22, 71)	0.140
Gender				
Female	56 (55%)	54 (53%)	110 (54%)	0.779
Male	46 (45%)	48 (47%)	94 (46%)	
BMI	28 ± 4 (19, 35)	28 ± 4 (17, 40)	28 ± 4 (17, 40)	0.707
Race				
White or Caucasian	96 (94%)	96 (94%)	192 (94%)	1.000
Black or African American	3 (3%)	3 (3%)	6 (3%)	
American Indian or Alaskan Native	1 (1%)	0 (0%)	1 (0%)	
Asian	1 (1%)	1 (1%)	2 (1%)	
Native Hawaiian or other Pacific Islander	0 (0%)	0 (0%)	0 (0%)	
Other	1 (1%)	2 (2%)	3 (1%)	
Ethnicity – Hispanic/Latino	4 (4%)	5 (5%)	9 (4%)	0.748
Pain duration (years from onset of the 1st occurrence)	14.4 ± 10.8 (1.0, 49.7)	13.9 ± 10.4 (0.6, 44.1)	14.2 ± 10.6 (0.6, 49.7)	0.736
Percent of days with LBP	97 ± 8 (60, 100)	97 ± 8 (58, 100)	97 ± 8 (58, 100)	0.703
Leg pain	32 (31%)	30 (29%)	62 (30%)	0.761
Associated with back pain	28 (88%)	25 (83%)	53 (85%)	0.728
Side				
Both	10 (31%)	9 (30%)	19 (31%)	0.744
Left	11 (34%)	9 (30%)	20 (32%)	
Right	11 (34%)	12 (40%)	23 (37%)	
Number of prior PT sessions	30 ± 39 (1, 300)	32 ± 63 (1, 600)	31 ± 52 (1, 600)	0.758

Characteristic	Treatment N=102 Mean ± SD (Min, Max) or n (%)	Control N=102 Mean ± SD (Min, Max) or n (%)	Total N=204 Mean ± SD (Min, Max) or n (%)	p-value[1]
Previous rhizotomy	8 (8%)	17 (17%)	25 (12%)	0.055
Months from most recent rhizotomy	62.7 ± 126.5 (12.0, 375.2)	35.8 ± 33.5 (12.0, 147.7)	44.4 ± 74.7 (12.0, 375.2)	0.414
Previous injection procedure	53 (52%)	46 (45%)	99 (49%)	0.327
Number of prior injections	2.6 ± 1.8 (1.0, 9.0)	2.7 ± 2.6 (1.0, 12.0)	2.6 ± 2.2 (1.0, 12.0)	0.981
History of depression	32 (31%)	38 (37%)	70 (34%)	0.376
Current, active depression	7 (7%)	11 (11%)	18 (9%)	0.323
Use of pain medication at baseline	77 (75%)	85 (83%)	162 (79%)	0.166
Use of opioid-containing medication at baseline	36 (35%)	40 (39%)	76 (37%)	0.562

[1] p-values are Chi-square (or Fisher's Exact as appropriate) for binary parameters, Cochran-Mantel-Haenszel for multi-level parameters and ANOVA for continuous variables.

F. Safety and Effectiveness Results

Safety Results

The analysis of safety was based on the 204 patients implanted (102 in the Treatment group and 102 in the Control group).

The key safety outcome for this study was assessment of any serious device- or procedure-related adverse events reported by the 120-day visit. All adverse events were also documented and reported in the summary statistics including the observed rates through the 5-year visit.

Among the 204 randomized patients, 8 serious adverse events (SAEs) related to the device/procedure were reported in 8 patients (3 in the Treatment group and 5 in the Control group) for an overall related serious adverse event rate of 4% at the 120-day primary endpoint visit. See Table3 below. There were no unanticipated SAEs related to the device or procedure.

No further SAEs related to the device/procedure were reported after the 120-day visit.

Table 3: Serious Device or Procedure-Related Event through Day 120

Adverse Event	Treatment N=102		Control N=102		Total N=204	
	AE # Events (Pt, %Pt)	Number Resolved /Total	AE # Events (Pt, %Pt)	Number Resolved /Total	AE # Events (Pt, %Pt)	Number Resolved /Total
Overall	**3 (3, 3%)**	**3/3**	**5 (5, 5%)**	**4/5**	**8 (8, 4%)**	**7/8**
Implant site pocket infection	2 (2, <2%)	2/2	4 (4, 4%)	4/4	6 (6, 3%)	6/6
Intra-procedural upper airway obstruction	1 (1, <1%)	1/1	0	0/0	1 (1, <1%)	1/1

Adverse Event	Treatment N=102		Control N=102		Total N=204	
	AE # Events (Pt, %Pt)	Number Resolved /Total	AE # Events (Pt, %Pt)	Number Resolved /Total	AE # Events (Pt, %Pt)	Number Resolved /Total
Numbness in leg (non-radicular)	0	0/0	1 (1, <1%)	0/1	1 (1, <1%)	0/1

A total of 25 unrelated SAEs occurred during the study as shown in Table 4. All events were reviewed by the CEC and adjudicated as "not related." Nineteen of the adverse events resolved. The patient with a malignant Stage IV melanoma was withdrawn from the study to focus on treatments for the cancer diagnosis. This event remained ongoing at the time of patient withdrawal but was closed for study purposes.

Table 4: Serious Unrelated Events through Five Years

	Treatment N=102		Control N=102		Total N=204	
Adverse Event	**AE # Events (Pt, % Pt)**	**Number Resolved/ Total**	**AE # Events (Pt, % Pt)**	**Number Resolved/ Total**	**AE # Events (Pt, % Pt)**	**Number Resolved/ Total**
Unrelated	**12 (12, 12%)**	**10/12**	**13 (12, 12%)**	**9/13**	**25 (24, 12%)**	**19/25**
Acute appendicitis	2 (2, 2%)	2/2	1 (1, <1%)	1/1	3 (3, 1%)	3/3
Ankle fracture	1 (1, <1%)	1/1	0	0/0	1 (1, <1%)	1/1
Biliary dyskinesia	1 (1, <1%)	1/1	0	0/0	1 (1, <1%)	1/1
Breast cancer	0	0/0	1 (1, <1%)	0/1	1 (1, <1%)	0/1
CVA	0	0/0	1 (1, <1%)	0/1	1 (1, <1%)	0/1
Cellulitis	0	0/0	1 (1, <1%)	1/1	1 (1, <1%)	1/1
Chest pain	0	0/0	1 (1, <1%)	1/1	1 (1, <1%)	1/1
Cholecystitis	0	0/0	1 (1, <1%)	1/1	1 (1, <1%)	1/1
Concussion	0	0/0	1 (1, <1%)	1/1	1 (1, <1%)	1/1
Detached retina	1 (1, <1%)	1/1	0	0/0	1 (1, <1%)	1/1
Elbow fracture	1 (1, <1%)	1/1	0	0/0	1 (1, <1%)	1/1
Gallstones	0	0/0	1 (1, <1%)	1/1	1 (1, <1%)	1/1
Hyperthyroidism	1 (1, <1%)	0/1	0	0/0	1 (1, <1%)	0/1
Malignant melanoma stage IV	1 (1, <1%)	0/1	0	0/0	1 (1, <1%)	0/1
Meningitis	1 (1, <1%)	1/1	0	0/0	1 (1, <1%)	1/1
Migraine headache	1 (1, <1%)	1/1	0	0/0	1 (1, <1%)	1/1
Myocardial infarction	0	0/0	1 (1, <1%)	1/1	1 (1, <1%)	1/1
Non ST segment elevation myocardial infarction	0	0/0	1 (1, <1%)	1/1	1 (1, <1%)	1/1
Pancreatitis due to gallstones	1 (1, <1%)	1/1	0	0/0	1 (1, <1%)	1/1
Seizure	0	0/0	1 (1, <1%)	1/1	1 (1, <1%)	1/1
Stomach cancer	0	0/0	1 (1, <1%)	0/1	1 (1, <1%)	0/1
TIA	1 (1, <1%)	1/1	0	0/0	1 (1, <1%)	1/1
Trauma	0	0/0	1 (1, <1%)	0/1	1 (1, <1%)	0/1

As summarized in Table5, a total of 853 adverse events (192 events [23%] were related and 661 events [77%] were unrelated) were reported within five years. Of these, 8 (1%) were serious and related, and 25 (3%) were serious and unrelated. Of those that were related, 51 occurred in the first 120 days after implant, which includes events that can happen with any surgical procedure. Of the related events, 90% have resolved.

When adjudicating events, if there was any uncertainty regarding relatedness, the CEC adjudicated the event as related.

Table 5: Overall Summary of Adverse Events Through Five Years

AE Category	Treatment # Events (% Events)	Control # Events (% Events)	Total # Events (% Events)
Overall	**438**	**415**	**853**
By Seriousness			
Serious Adverse Events	15 (3%)	18 (4%)	33 (4%)
Related	3 (1%)	5 (1%)	8 (1%)
Unrelated	12 (3%)	13 (3%)	25 (3%)
Non-Serious Adverse Events	423 (97%)	397 (96%)	820 (96%)
Related	86 (20%)	98 (24%)	184 (22%)
Unrelated	337 (77%)	299 (72%)	636 (75%)
By Relatedness[1]			
Related	89 (20%)	103 (25%)	192 (23%)
Device	33 (8%)	39 (9%)	72 (8%)
Procedure	39 (9%)	41 (10%)	80 (9%)
Stimulation	19 (4%)	25 (6%)	44 (5%)
Unrelated	349 (80%)	312 (75%)	661 (77%)
By Outcome			
Resolved	345 (79%)	314 (76%)	659 (77%)
Not Resolved	93 (21%)	101 (24%)	194 (23%)

[1] 4 events were adjudicated by the CEC as possibly related to the device and possibly related to stimulation. Therefore, the sum of the relatedness categories does not add up to the total number of related events.

Deaths

There has been one unrelated death reported in the ReActiv8-B trial, which occurred approximately three years after enrollment.

All Study-Related Adverse Events

Table6 provides a summary of all study-related adverse events (both serious and non-serious) by treatment group through 120 days. After the 120-day visit, the Control patients elected to receive stimulation at a therapeutic level; therefore, both patient groups are summarized together through the 5-year visit. Events that could occur with any surgical procedure and were not specific to receiving an implantable device are also listed in the table below the thick horizontal line.

Table 6: Study-Related Adverse Events through Five Years

Event	0-120 Days			Treatment Groups Combined - Crossover for Control					Total N=204 # Events (Pt, % Pt)	Number Resolved/ Total
				1 Year	2 Years	3 Years	4 Years	5 Years		
	Treatment N=102 # Events (Pt, % Pt)	Control N=102 # Events (Pt, % Pt)	Total N=204 # Events (Pt, % Pt)	Total N=204 # Events (Pt, % Pt)	Total N=171 # Events (Pt, % Pt)	Total N=159 # Events (Pt, % Pt)	Total N=142 # Events (Pt, % Pt)	Total N=132 # Events (Pt, % Pt)		
Related	**51 (37, 36%)**	**50 (35, 34%)**	**101 (72, 35%)**	**48 (37, 18%)**	**19 (18, 11%)**	**11 (11, 7%)**	**5 (5, 4%)**	**8 (7, 5%)**	**192 (114, 56%)**	**172/192**
Implant site pocket pain	12 (11, 11%)	11 (11, 11%)	23 (22, 11%)	14 (13, 6%)	9 (9, 5%)	3 (3, 2%)	1 (1, <1%)	4 (4, 3%)	54 (42, 21%)	48/54
Device overstimulation of tissue	7 (7, 7%)	0	7 (7, 3%)	20 (18, 9%)	3 (3, 2%)	3 (3, 2%)	0	0	33 (31, 15%)	29/33
Lead conductor fracture	2 (2, 2%)	0	2 (2, <1%)	4 (4, 2%)	3 (3, 2%)	1 (1, <1%)	0	1 (1, <1%)	11 (11, 5%)	11/11
Back pain aggravated	1 (1, <1%)	3 (3, 3%)	4 (4, 2%)	0	1 (1, <1%)	0	0	2 (1, <1%)	7 (6, 3%)	5/7
Implant site pocket infection	2 (2, 2%)	4 (4, 4%)	6 (6, 3%)	0	0	0	0	0	6 (6, 3%)	6/6
Medical device site injury	0	1 (1, <1%)	1 (1, <1%)	0	0	1 (1, <1%)	2 (2, 1%)	0	4 (4, 2%)	4/4
Medical device discomfort	1 (1, <1%)	1 (1, <1%)	2 (2, <1%)	1 (1, <1%)	0	0	0	0	3 (3, 1%)	3/3
Coccyx pain	0	1 (1, <1%)	1 (1, <1%)	1 (1, <1%)	0	0	0	0	2 (2, <1%)	2/2
Numbness in leg	1 (1, <1%)	1 (1, <1%)	2 (2, <1%)	0	0	0	0	0	2 (2, <1%)	1/2
Buttock pain	0	0	0	1 (1, <1%)	0	0	0	0	1 (1, <1%)	0/1
Complication of device removal	0	0	0	0	0	1 (1, <1%)	0	0	1 (1, <1%)	1/1
Facial paresthesia	0	1 (1, <1%)	1 (1, <1%)	0	0	0	0	0	1 (1, <1%)	1/1
Groin pain	0	0	0	1 (1, <1%)	0	0	0	0	1 (1, <1%)	0/1
Headache	0	1 (1, <1%)	1 (1, <1%)	0	0	0	0	0	1 (1, <1%)	1/1
Healing abnormal	0	0	0	0	0	1 (1, <1%)	0	0	1 (1, <1%)	1/1
Implant site infection	0	0	0	0	0	1 (1, <1%)	0	0	1 (1, <1%)	1/1
Implant site warmth	0	0	0	0	1 (1, <1%)	0	0	0	1 (1, <1%)	1/1
Medical device site reaction	0	0	0	1 (1, <1%)	0	0	0	0	1 (1, <1%)	1/1
Neuropathic pain	0	1 (1, <1%)	1 (1, <1%)	0	0	0	0	0	1 (1, <1%)	0/1
Paresthesia lower limb	0	1 (1, <1%)	1 (1, <1%)	0	0	0	0	0	1 (1, <1%)	1/1
Post procedural diarrhea	0	0	0	0	0	0	1 (1, <1%)	0	1 (1, <1%)	1/1
Radicular pain	0	1 (1, <1%)	1 (1, <1%)	0	0	0	0	0	1 (1, <1%)	1/1
Sciatica	0	1 (1, <1%)	1 (1, <1%)	0	0	0	0	0	1 (1, <1%)	1/1
Shoulder pain	0	0	0	1 (1, <1%)	0	0	0	0	1 (1, <1%)	1/1
Sore throat	0	0	0	0	0	0	0	1 (1, <1%)	1 (1, <1%)	0/1
Throat sore	0	0	0	1 (1, <1%)	0	0	0	0	1 (1, <1%)	1/1
Wound pain	3 (3, 3%)	3 (3, 3%)	6 (6, 3%)	0	1 (1, <1%)	0	0	0	7 (7, 3%)	6/7
Implant site dermatitis	2 (2, 2%)	2 (2, 2%)	4 (4, 2%)	1 (1, <1%)	0	0	0	0	5 (5, 2%)	5/5

Event	0-120 Days			Treatment Groups Combined - Crossover for Control					Total N=204 # Events (Pt, % Pt)	Number Resolved/ Total
	Treatment N=102 # Events (Pt, % Pt)	Control N=102 # Events (Pt, % Pt)	Total N=204 # Events (Pt, % Pt)	1 Year Total N=204 # Events (Pt, % Pt)	2 Years Total N=171 # Events (Pt, % Pt)	3 Years Total N=159 # Events (Pt, % Pt)	4 Years Total N=142 # Events (Pt, % Pt)	5 Years Total N=132 # Events (Pt, % Pt)		
Implant site hematoma	2 (2, 2%)	2 (2, 2%)	4 (4, 2%)	1 (1, <1%)	0	0	0	0	5 (5, 2%)	5/5
Implant site inflammation	3 (3, 3%)	1 (1, <1%)	4 (4, 2%)	0	0	0	0	0	4 (4, 2%)	4/4
Implant site paresthesia	0	2 (2, 2%)	2 (2, <1%)	1 (1, <1%)	0	0	0	0	3 (3, 1%)	3/3
Pain in hip	2 (2, 2%)	0	2 (2, <1%)	0	1 (1, <1%)	0	0	0	3 (3, 1%)	3/3
Procedural vomiting	2 (2, 2%)	0	2 (2, <1%)	0	0	0	1 (1, <1%)	0	3 (3, 1%)	3/3
Allergic reaction to antibiotics	1 (1, <1%)	1 (1, <1%)	2 (2, <1%)	0	0	0	0	0	2 (2, <1%)	2/2
Implant site hypoesthesia	1 (1, <1%)	1 (1, <1%)	2 (2, <1%)	0	0	0	0	0	2 (2, <1%)	0/2
Postoperative nausea	1 (1, <1%)	1 (1, <1%)	2 (2, <1%)	0	0	0	0	0	2 (2, <1%)	2/2
Postoperative vomiting	2 (2, 2%)	0	2 (2, <1%)	0	0	0	0	0	2 (2, <1%)	2/2
Vaginal yeast infection	1 (1, <1%)	1 (1, <1%)	2 (2, <1%)	0	0	0	0	0	2 (2, <1%)	2/2
Adverse drug reaction	0	1 (1, <1%)	1 (1, <1%)	0	0	0	0	0	1 (1, <1%)	1/1
Anesthetic complication cardiac	0	1 (1, <1%)	1 (1, <1%)	0	0	0	0	0	1 (1, <1%)	1/1
Bradycardia	1 (1, <1%)	0	1 (1, <1%)	0	0	0	0	0	1 (1, <1%)	1/1
Calf pain	1 (1, <1%)	0	1 (1, <1%)	0	0	0	0	0	1 (1, <1%)	1/1
Hypertrophic scar	1 (1, <1%)	0	1 (1, <1%)	0	0	0	0	0	1 (1, <1%)	1/1
Implant site discharge	0	1 (1, <1%)	1 (1, <1%)	0	0	0	0	0	1 (1, <1%)	1/1
Implant site erythema	0	1 (1, <1%)	1 (1, <1%)	0	0	0	0	0	1 (1, <1%)	1/1
Implant site seroma	0	1 (1, <1%)	1 (1, <1%)	0	0	0	0	0	1 (1, <1%)	1/1
Open wound	0	1 (1, <1%)	1 (1, <1%)	0	0	0	0	0	1 (1, <1%)	1/1
Pharyngeal injury	1 (1, <1%)	0	1 (1, <1%)	0	0	0	0	0	1 (1, <1%)	1/1
Post concussion syndrome	0	1 (1, <1%)	1 (1, <1%)	0	0	0	0	0	1 (1, <1%)	1/1
Syncope vasovagal	0	1 (1, <1%)	1 (1, <1%)	0	0	0	0	0	1 (1, <1%)	1/1
Upper airway obstruction	1 (1, <1%)	0	1 (1, <1%)	0	0	0	0	0	1 (1, <1%)	1/1
Unrelated	80 (48, 47%)	68 (47, 46%)	148 (95, 47%)	194 (109, 53%)	110 (65, 38%)	92 (58, 36%)	64 (43, 30%)	53 (32, 24%)	661 (172, 84%)	487/661

Over the five-year period, 42% of the patients underwent an additional surgical intervention. In most cases, the need for an intervention was independent of the randomization assignment. A summary of the additional procedures is presented in Table7 below.

In this study, 13% of the patients underwent permanent system explant due to lack of effectiveness, 9% due to pain improving or resolving, 5% due to the need for MRI, 3% due to pocket infection, and 2% due to other comorbidities and patient relocation. One additional patient that had a pocket infection was explanted and re-implanted after the infection resolved.

Notably, in this study, 19 patients had their device removed and withdrew from the study for resolution of back pain. Each year, the number of patients choosing this option has increased (Figure 2). This trend further supports the restorative nature of this therapy for this subset of patients. 27 patients chose to explant the implanted system due to lack of effectiveness.

Table 7: Additional Surgical Procedures through Five Years

ReActiv8 Surgical Intervention	Treatment (N=102) Pt (% Pt)	Control (N=102) Pt (% Pt)	Total (N=204) Pt (% Pt)
Any ReActiv8 Surgical Intervention[1]	**41 (40%)**	**45 (44%)**	**86 (42%)**
System explants	30 (30%)	33 (33%)	63 (31%)
Lack of effectiveness	*15 (15%)*	*12 (12%)*	*27 (13%)*
Pain improved / resolved	*9 (9%)*	*10 (10%)*	*19 (9%)*
MRI needed	*5 (5%)*	*5 (5%)*	*10 (5%)*
Infection	*1 (1%)*	*4 (4%)*	*5 (3%)*
Manage comorbidities	*0 (0%)*	*1 (<1%)*	*1 (<1%)*
Patient relocation	*0 (0%)*	*1 (<1%)*	*1 (<1%)*
Lead revisions	8 (8%)	10 (10%)	18 (9%)
IPG repositioning	2 (2%)	8 (8%)	10 (5%)
Re-implant post-infection[2]	1 (1%)	0 (0%)	1 (<1%)

[1] Patients may have had more than one procedure; therefore, the total does not equal the sum of the categories.
[2] One patient was re-implanted after the infection cleared.

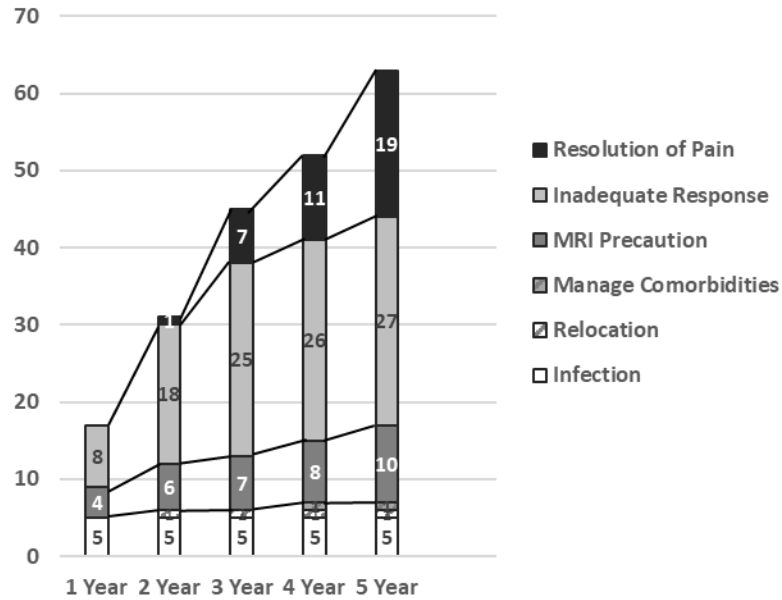


Figure 2: Reasons for Device Removal

Because the Control group was an active sham control (ReActiv8), an assessment of the safety benefits would be better contextualized by comparing the safety profile of ReActiv8 while delivering treatment to similar active implantable systems such as spinal cord stimulation (SCS), even though the indication is different.

When evaluating some of the more common risks with this type of procedure, the ReActiv8 safety profile compares favorably to that of SCS devices. One typical risk in SCS systems that notably did not occur in the ReActiv8-B trial is lead migration (Table8).

Table 8: Safety Comparison of ReActiv8 to SCS Devices

Device/Procedural Events	**SCS Articles Reporting, N**	**SCS Articles Range (%)**	**ReActiv8-B 204 Patients**
Infection	12	1.6 - 58.3%	2.9%
Implant related pain	12	0 - 24.6%	21%
Lead fracture / malfunction	5	0.4 - 10.2%	5%
Lead migration	10	1.7 - 27%	0%
Surgical Interventions			
System explants	12	2.0 - 58.3%	15.7%[2]
Explant for therapy failure	7	0 - 9.8%	13.2%
Explant for pain resolution	5	0 - 1.8%	9.3%
System revisions	7	2.6 - 34%	10.8%

[1] SCS literature review comprises more than 23,000 patients across 22 articles (2 systematic reviews with meta-analysis[7,8], 1 literature review[9], 8 RCTs[10–17], 2 prospective studies[18,19], 1 prospective surveillance registry[20], and 8 retrospective studies[21–28]).

[2] Excludes subjects explanted due to improvement or resolution of back pain, patient relocation, and to manage other comorbidities, as these are not safety issues related to the ReActiv8 device or procedure.

The overall rate of safety events associated with ReActiv8 is summarized below.

- The occurrence of adverse events was similar between the Treatment and Control groups.
- No lead migrations were reported.
- 90% of related adverse events resolved.
- 28% of the events can occur with any surgical procedure and are not specific to receiving an implantable device.

It is important to note that the need for removal of the system for MRI imaging is expected to be substantially reduced due to newly approved full-body MR conditional labeling (the MRI labelling was not available during the clinical study). Additionally, resolution of back pain does not require the system to be removed. Many patients prefer to keep the device implanted and use ReActiv8 when they deem appropriate.

Effectiveness Results

Described below are the analyses that were performed per the protocol.

ITT: The intent to treat (ITT) analysis of effectiveness was based on 204 patients at the 120-day timepoint for the primary endpoint. Three patients did not return for the primary endpoint visit (2 in the Treatment group and 1 in the Control group), so their primary endpoint data was imputed.

Completers Cohort: All secondary and supporting analyses used the completers cohort analyses, which are those patients who have a value for a given measurement at baseline and at the follow-up visits.

Crossover Cohort: After the primary endpoint visit at 120 days, the Control group patients were given the choice to receive patient-appropriate treatment. The Crossover cohort is comprised of those patients who elected to cross over to receive stimulation at a therapeutic level at the 120-day visit. Four patients in the Control group had the device explanted prior to the 120-day visit (3 infections and 1 patient request due to lack of efficacy). All patients in the Control group with a device implanted at 120 days chose to cross over.

A total of 102 patients were randomized in each study group in the ITT population (total 204 patients).

While the difference in responder rates grew over time between the Treatment group (57.1%) and the Control group (46.6%), it did not reach statistical significance (p=0.1377) (Table9) at the 120-day primary endpoint visit.

Table 9: Responder Rate Low Back Pain VAS with No Increase in Pain Medications

Primary Efficacy Endpoint[1]	Treatment N=102 %	Control N=102 %	Difference p-value[2]
Responder (≥30% reduction in low back pain VAS and no increase in pain medications)	57.1%	46.6%	10.4% p=0.1377

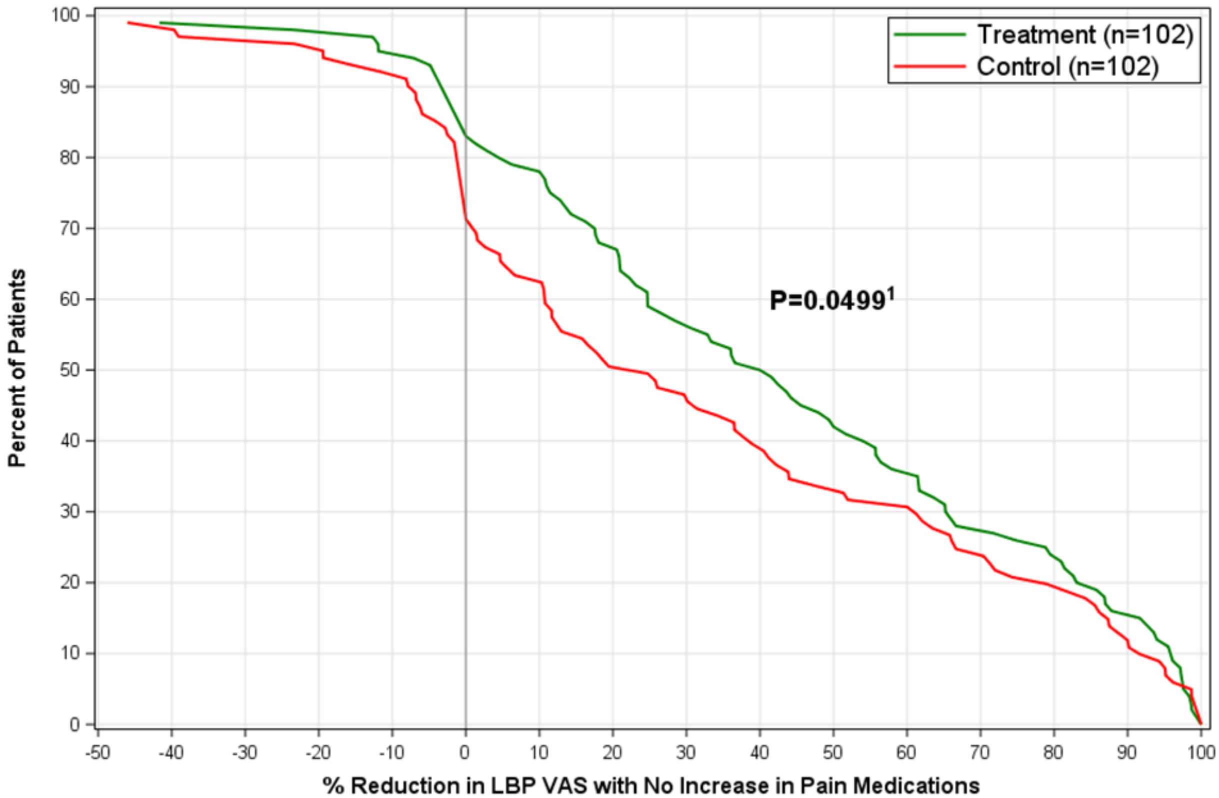
[1] Results for 3 patients (2 Treatment, 1 Control) LTFU were included using multiple imputation.
[2] p-value is based on a Wald asymptotic test of proportions, with multiple imputation to handle missing values, and a Cui et al p-value adjustment.

Cumulative Proportion of Responders Analysis

The Cumulative Proportion of Responders Analysis (CPRA) is a method of evaluating patient responses over a full range of response levels, utilizing the same data as the primary endpoint. Rather than relying on one cut-point for evaluation, the CPRA provides a more accurate reflection of the full nature of the data.[29] This method utilizes the Friedman's regression analysis, which is a comparison of ranks. This test preserves information compared to dichotomizing an endpoint, thereby improving statistical power.[30–32]

The CPRA, which was prespecified in the clinical protocol and SAP prior to the start of the trial, was performed using the same data as used for the primary endpoint analysis. The results of the CPRA (Figure 3) demonstrated a statistically significant difference between the Treatment group and the Control group (p=0.0499).

Notably, the Treatment group showed a higher percentage of responders across all threshold levels.



[1]MI (Rubin) for LTFU, Friedman's regression analysis & p-value for difference between groups. Since multiple imputation provides an overall group estimate, but not a specific estimate for each patient with missing data, these 3 patients that are LTF cannot be plotted in the figure; however, given the small amount of missing data, this is a very close approximation, and the 3 patients are accounted for in the p-value.

Figure 3: Cumulative Proportion of Responders in LBP VAS

Change in Mean VAS Analysis

In addition, the analysis of difference in mean LBP VAS reduction between the Treatment group and the Control group was statistically significant at the 120-day visit (p=0.032) (Table 10).

Table 10: VAS Results at Day 120

VAS Measure	Treatment N=100 Mean ± SD (min, max)	Control N=101 Mean ± SD (min, max)	Difference p-value[1]
Mean change in low back pain VAS	-3.3 ± 2.7 (-8.5, 3.0)	-2.4 ± 2.9 (-8.8, 3.5)	0.9 p=0.032

[1]Three patients were lost to follow-up (2 Treatment, 1 Control). Per the statistical analysis plan, secondary and supporting endpoints do not impute data for missing values. p-value is from a two-sample, two-sided t-test.

Components of the Primary Endpoint

VAS Component of the Primary Endpoint

When evaluating the VAS component of the primary endpoint (without considering pain medication changes), between-groups difference in proportion of patients with ≥30% reduction in LBP VAS grew over time but did not achieve statistical significance (Treatment: 58.8%, Control: 48.6%; p=0.1438). As with the primary endpoint, multiple imputations are utilized to account for missing data; therefore, this analysis is based on N=102 in both study groups.

Medication Component of the Primary Efficacy Endpoint

Data pertaining to all prescribed medications were collected at each scheduled follow-up visit. Patients were instructed to keep medications stable through the 120-day visit. If a medication was prescribed and taken for pain and was increased or added within the two-week interval prior to the 120-day visit, the patient was counted as a treatment failure for the primary efficacy endpoint.

Nine patients in the Treatment group and 9 patients in the Control group had increases in pain medications for any reason within the two-week window prior to the 120-day visit (Table 11), all of which were counted as treatment failures for the primary efficacy endpoint.

Table 11: Increases in Pain Medications at the 120-Day Visit

Reason for Increase	Treatment N=100 n	Control N=101 n
Low back pain	3	9
Reason unrelated to low back pain	6	0
Total	**9**	**9**

Of these 18 patients, 6 patients had increases in pain medications for the following reasons that were unrelated to LBP:

1. Broken ankle
2. Tooth extraction
3. Upper respiratory tract infection (URTI)
4. Anal abscess
5. Knee injury
6. Renal stone

Notably, all 6 of these patients were in the Treatment group.

In the Control group, all 9 patients increased pain medications for LBP, as did the remaining 3 patients in the Treatment group. Three patients (1 in the Treatment group and 2 in the Control group) were on post-operative pain medications, and because the surgery was related to their LBP, they have been counted as medication increases related to LBP.

The adverse events were adjudicated by the Clinical Events Committee, and an independent organization reviewed the medication changes and the adverse events to confirm the accuracy of the categorizations. Change within the two-week window indicates that the patient had taken the medication within the two-week window prior to the visit, but the patient was not taking the medication on the day of the visit.

Secondary Endpoints and Supporting Analyses

Data on all prespecified secondary endpoints were collected at the 120-day visit to compare changes from baseline in physical and social function (ODI), overall quality of life (EQ-5D), percent pain relief (PPR), resolution of low back pain, and subject global impression of change (SGIC) between the Treatment and Control groups. All patient questionnaires were administered prior to any interaction with the patient and prior to unblinding.

Since the primary endpoint did not meet statistical significance, hypotheses for the secondary endpoints were not to be formally tested. P-values are provided in this report for descriptive purposes only.

Statistical significance was reached for the comparison between the Treatment and Control groups on multiple secondary endpoints and supporting analyses at the 120-day visit (Table 12), demonstrating:

- Greater reduction in pain as measured by mean LBP VAS and PPR
- Greater improvement in physical and social function, including sleep, as measured by ODI, Cumulative Proportion of ODI Responders, and Ability to Work
- Greater improvement in overall quality of life as measured by EQ-5D
- Higher treatment satisfaction as measured by TSQ
- More favorable impression of change as measured by SGIC and CGI

Table 12: Secondary Efficacy Endpoints and Supporting Analyses

	Treatment		Control		
Endpoint	**N[1]**	**Mean ± SD (Min, Max) or n (%)**	**N[1]**	**Mean ± SD (Min, Max) or n (%)**	**Difference p-value[2]**
Change in low back pain VAS	100	-3.3 ± 2.7 (-8.5, 3.0)	101	-2.4 ± 2.9 (-8.8, 3.5)	0.9 p = 0.032
Change in ODI	100	-17.5 ± 15.1 (-58.0, 20.0)	101	-12.2 ± 14.6 (-48.0, 32.0)	-5.4 p = 0.011
Change in EQ-5D	100	0.186 ± 0.199 (-0.365, 0.782)	100	0.115 ± 0.178 (-0.640, 0.665)	0.071 p = 0.009
Percent Pain Relief	100	52 ± 32 (0, 100)	101	35 ± 36 (0, 100)	17 p < 0.001
Subject Global Impression of Change					
Much better	100	32 (32%)	101	18 (18%)	NA p = 0.003
Better	100	22 (22%)	101	16 (16%)	
A little better	100	25 (25%)	101	29 (29%)	
No change	100	10 (10%)	101	24 (24%)	
A little worse	100	6 (6%)	101	5 (5%)	
Worse	100	4 (4%)	101	6 (6%)	
Much worse	100	1 (1%)	101	3 (3%)	
Resolution of back pain (VAS ≤ 2.5)	100	34 (34%)	101	28 (28%)	6.3% p = 0.335
Satisfied with treatment					
Definitely yes	100	61 (61%)	101	40 (40%)	p < 0.001
Maybe	100	29 (29%)	101	37 (37%)	
Definitely not	100	10 (10%)	101	24 (24%)	
Clinician Global Impression					
Much better	100	57 (57%)	100	22 (22%)	p < 0.001
Slightly better	100	26 (26%)	100	29 (29%)	
About the same	100	16 (16%)	100	42 (42%)	
Slightly worse	100	1 (1%)	100	5 (5%)	
Much worse	100	0 (0%)	100	2 (2%)	

[1] 3 patients were lost to follow-up (2 Treatment, 1 Control). 1 patient in the Control group did not complete all sections of the EQ-5D questionnaire; therefore, no score could be completed. Per the SAP, secondary endpoints do not impute data for missing values.

[2] For continuous variables the p-value is from a two-sample, two-sided t-test; for SGIC p-value is from Mann-Whitney; for TSQ and CGI p-value is from Cochran-Mantel-Haenszel; and for Resolution of Back Pain p-value is from Chi-square test. P-values are provided for descriptive purposes only.

Long-Term Results

Studies with long follow-up durations, and particularly those for chronic pain conditions, will inherently have to account for missing data because the final outcome may depend on the method chosen.[33]

To account for missing data, analyses were performed utilizing multiple imputations. This method was used rather than last-observation-carried-forward, as last-observation-carried-forward has been criticized as a source of systematic bias in chronic pain trials.[34] Of the more appropriate, principled methods, the mixed-effects model for repeated measures[35] is the most frequently used imputation approach in chronic pain clinical trials. This method relies on the missing-at-random assumption that future unknown data after subject withdrawal would have likely remained similar if the dropout had not occurred.[33]

The supporting analysis, which follows the intent-to-treat principle (N=204), stratified imputation based on the reason for missingness. For patients who underwent device explant and withdrawal for infection or inadequate response, baseline-observation-carried-forward was used. For missed visits, device explant and withdrawal for resolution of pain, loss to follow-up, and precautionary explant before magnetic resonance imaging (the missing-at-random cohort), the mixed-effects model for repeated measures was used.

All effectiveness outcome measures progressively improved through the 5-year visit. One-year data was collected for 176/204 patients, and at five years data was collected for 126/204 patients (Table 13). The same endpoints are summarized in Table 14 using imputation to account for missing data. The relatively small attenuation between the completed-case and the mixed-effects model for repeated measures instills confidence in the robustness of the data and validity of the conclusions drawn.

Table 13: Summary of Endpoints Through Five Years – Treatment Groups Combined

Visit	Baseline		Year 1		Year 2		Year 3		Year 4		Year 5	
	N	Mean ± SD (Min, Max) or n (%)	N	Mean ± SD (Min, Max) or n (%)	N	Mean ± SD (Min, Max) or n (%)	N	Mean ± SD (Min, Max) or n (%)	N	Mean ± SD (Min, Max) or n (%)	N	Mean ± SD (Min, Max) or n (%)
LBP VAS	204	7.3 ± 0.7 (6.0, 8.9)	176	3.0 ± 2.6 (0.0, 9.8)	155	2.4 ± 2.3 (0.0, 9.3)	131	2.3 ± 2.4 (0.0, 8.6)	116	2.2 ± 2.3 (0.0, 7.7)	124	2.4 ± 2.5 (0.0, 9.5)
Change from BL			176	-4.3 ± 2.6 (-8.8, 2.5)	155	-4.8 ± 2.3 (-8.6, 2.6)	131	-4.9 ± 2.4 (-8.9, 1.5)	116	-5.0 ± 2.4 (-8.8, 0.7)	124	-4.9 ± 2.5 (-8.8, 1.4)
Resolution of LBP			176	91 (52%)	155	103 (66%)	131	88 (67%)	116	75 (65%)	124	83 (67%)
ODI	204	39.1 ± 10.3 (22.0, 64.0)	176	19.0 ± 15.0 (0.0, 86.0)	155	17.5 ± 15.5 (0.0, 66.0)	132	16.6 ± 14.9 (0.0, 70.0)	117	15.2 ± 13.7 (0.0, 68.0)	126	16.5 ± 14.8 (0.0, 66.0)
Change from BL			176	-19.9 ± 15.8 (-58.0, 44.0)	155	-21.4 ± 16.7 (-58.0, 30.0)	132	-22.5 ± 15.0 (-58.0, 18.0)	117	-23.6 ± 15.2 (-64.0, 28.0)	126	-22.7 ± 15.4 (-64.0, 22.0)
EQ-5D	204	0.585 ± 0.174 (-0.077, 0.874)	176	0.780 ± 0.156 (-0.160, 1.000)	154	0.797 ± 0.168 (0.221, 1.000)	132	0.804 ± 0.156 (0.155, 1.000)	118	0.822 ± 0.158 (0.263, 1.000)	125	0.807 ± 0.164 (0.238, 1.000)
Change from BL			176	0.198 ± 0.207 (-0.688, 0.782)	154	0.217 ± 0.219 (-0.373, 0.945)	132	0.218 ± 0.192 (-0.483, 0.588)	118	0.241 ± 0.215 (-0.483, 0.945)	125	0.231 ± 0.203 (-0.194, 0.945)
PPR			176	66 ± 32 (0, 100)	156	72 ± 31 (0, 100)	133	75 ± 28 (0, 100)	118	79 ± 25 (0, 100)	123	78 ± 27 (0, 100)
SGIC (Better or Much Better)			176	126 (72%)	154	121 (79%)	132	106 (80%)	116	94 (81%)	125	104 (83%)
TSQ (Definitely Satisfied)			174	136 (78%)	155	124 (80%)	132	114 (86%)	113	103 (91%)	125	110 (88%)
CGI (Much Better)			176	129 (73%)	153	120 (78%)	129	113 (86%)	117	97 (83%)	118	98 (83%)

Table 14: Summary of Endpoints Through Five Years, Imputed Data – Treatment Groups Combined

Visit	Year 1	Year 2	Year 3	Year 4	Year 5
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)
LBP VAS	3.3 (0.2)	3.1 (0.2)	3.2 (0.2)	3.2 (0.2)	3.3 (0.2)
Change in LBP VAS	-3.9 (0.2)	-4.2 (0.2)	-4.1 (0.2)	-4.0 (0.2)	-3.9 (0.2)
Resolution of LBP	48.0% (3.6)	57.3% (3.6)	55.6% (3.8)	50.8% (3.9)	52.9% (3.8)
ODI	20.6 (1.1)	20.1 (1.1)	20.1 (1.1)	20.1 (1.1)	20.3 (1.1)
Change in ODI	-18.4 (1.1)	-18.8 (1.1)	-18.9 (1.1)	-18.9 (1.1)	-18.6 (1.1)
EQ-5D	0.763 (0.012)	0.769 (0.012)	0.765 (0.012)	0.771 (0.013)	0.768 (0.013)
Change in EQ-5D	0.177 (0.011)	0.183 (0.012)	0.179 (0.012)	0.184 (0.012)	0.183 (0.012)
PPR	60.7 (2.6)	62.3 (2.6)	62.2 (2.7)	62.9 (2.7)	63.2 (2.7)
SGIC **(Better or Much Better)**	66.4% (3.4)	68.8% (3.4)	66.2% (3.6)	64.6% (3.7)	67.5% (3.6)
TSQ **(Definitely Satisfied)**	73.8% (3.2)	71.3% (3.4)	72.2% (3.4)	73.9% (3.5)	72.4% (3.5)
CGI **(Much Better)**	68.7% (3.4)	69.6% (3.4)	68.3% (3.6)	67.3% (3.7)	67.1% (3.7)

Baseline-observation-carried-forward was used for subjects who underwent device explant and withdrawal for infection or inadequate response. All other missing data were assumed missing at random.

<u>Pain and Function</u>

The protocol specified a threshold of ≥30% improvement on LBP VAS for the primary endpoint (per IMMPACT and FDA recommendations). Other commonly reported thresholds for "success" are ≥50% improvement on LBP VAS and absolute LBP VAS scores of ≤2.5 cm (commonly referred to as "Remitter" or "Resolution").

Similarly, the protocol specified a threshold of ≥10 points improvement on ODI as a clinically meaningful change. Other commonly reported thresholds for "success" are ≥15 points and ≥20 points improvements on the ODI scale.

The longitudinal "success rates" using these commonly reported thresholds are summarized in Figure 4 below. For these graphical representations, changes in pain medications were not considered.

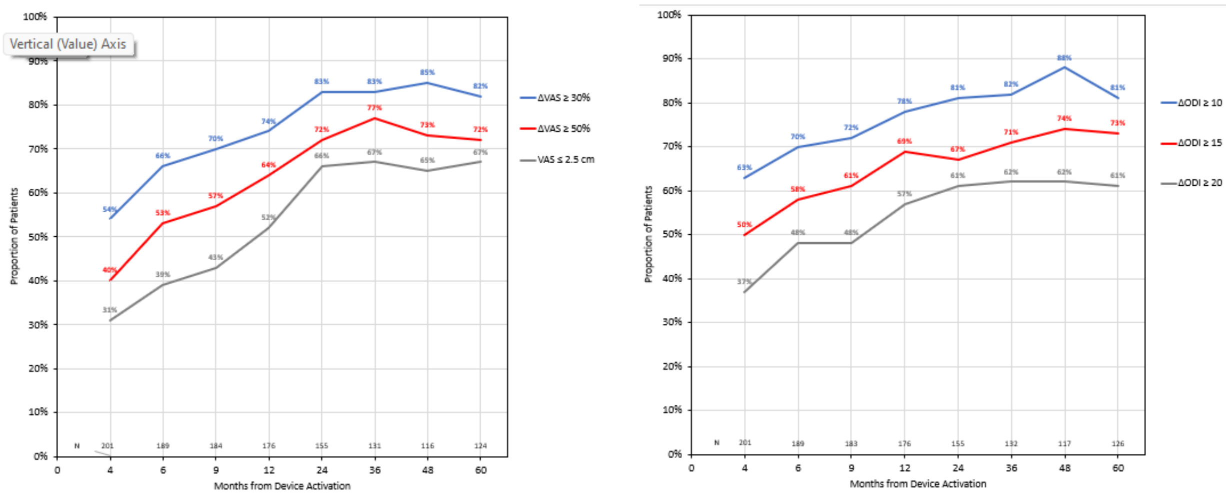


Figure 4: Longitudinal "Success Rates" in Treatment Groups Combined (a) VAS and (b) ODI

Patients suffering from CLBP are continuously balancing their activity level with their level of pain. As their condition improves, patients make personal choices on whether to increase their level of activity while tolerating a certain level of pain, or to continue with the same level of activity as earlier but with less pain, or somewhere in between. These choices are based on the patients' individual circumstances and preferences. Therefore, when evaluating a therapy for CLBP, improvements in pain should be interpreted in conjunction with functional improvements to obtain a complete picture of the benefit provided by the therapy.

ReActiv8 is a restorative therapy, and progressive improvement can be expected over time, both in magnitude of effect and the proportion of patients who benefit from the treatment. It is hence informative to review the long-term data out to five years for the magnitude and durability of effect.

Figure 5 below shows the effect of ReActiv8 therapy as a combination of pain and disability on individual patients.

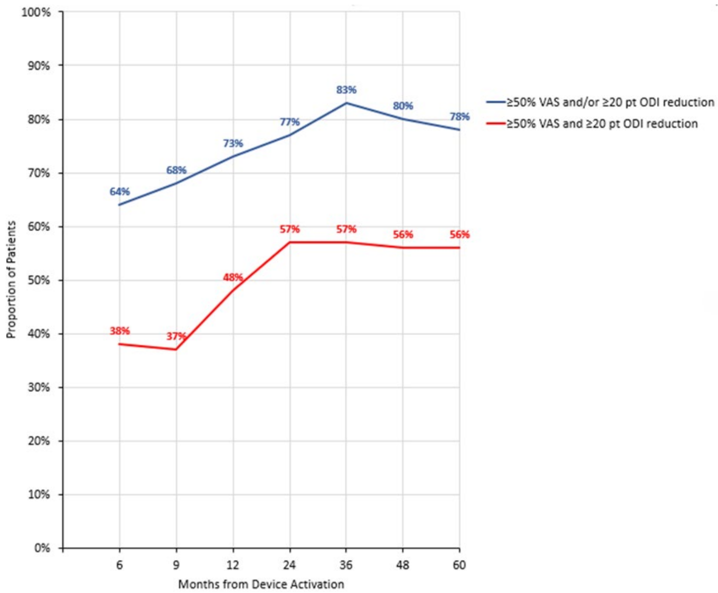


Figure 5: Longitudinal "Success Rates" in Treatment Groups Combined in LBP VAS and/or ODI

At the 5-year visit, 78% of patients reported a substantial[36] improvement in pain, as measured by LBP VAS, and improvement in physical and social function, as measured by ODI over baseline, or both of these measures (Figure 5). These data suggest that the vast majority of patients have gained increased ability to manage their daily activities.

<u>*Changes in Opioid Use*</u>

Of the 65 patients (Treatment and Crossover groups combined) who were on at least one opioid-containing medication at baseline and had a 1-year visit, 48% had discontinued or decreased opioid use (Table 15). These trends continued through the 5-year visit. The patients who decreased or discontinued opioids had been taking opioids for an average of 4 ± 5 years. In addition, 97% of those who were not on an opioid at baseline remained off opioids at the 1-year visit, and 93% remained off opioids at the 5-year visit.

Table 15: Changes in Opioids Through Five Years for Treatment Groups Combined

Opioid Change Status	**1 Year**		**2 Years**		**3 Years**		**4 Years**		**5 Years**	
	N	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**
On opioids at baseline										
Discontinued or decreased	65	31 (48%)	59	35 (59%)	51	36 (71%)	47	33 (70%)	52	36 (69%)
No change	65	29 (45%)	59	21 (36%)	51	15 (29%)	47	12 (26%)	52	13 (25%)
Increased	65	5 (8%)	59	3 (5%)	51	0 (0%)	47	2 (4%)	52	3 (6%)

Opioid Change Status	1 Year		2 Years		3 Years		4 Years		5 Years	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Not on opioids at baseline										
Remained off at annual follow-up	111	108 (97%)	99	96 (97%)	82	79 (96%)	72	69 (96%)	76	71 (93%)
Added	111	3 (3%)	99	3 (3%)	82	3 (4%)	72	3 (4%)	76	5 (7%)

Similarly, when looking at pain medications of any class, discontinued or decreased use is seen over time, and 92% of patients who were not on pain medications at baseline remain off pain medications at the 5-year visit.

Table 16: Changes in Pain Medications Through Five Years for Treatment Groups Combined

Pain Medication Change Status	1 Year		2 Years		3 Years		4 Years		5 Years	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
On pain medications at baseline										
Discontinued or decreased	138	76 (55%)	123	80 (66%)	104	66 (63%)	96	59 (61%)	102	60 (59%)
No change	138	53 (38%)	123	36 (30%)	104	36 (35%)	96	33 (43%)	102	36 (35%)
Increased	138	10 (7%)	123	6 (5%)	104	2 (2%)	96	4 (4%)	102	5 (5%)
Not on pain medications at baseline										
Remained off at annual follow-up	38	37 (97%)	35	34 (97%)	29	28 (97%)	23	22 (96%)	26	24 (92%)
Added	38	1 (3%)	35	1 (3%)	29	1 (3%)	23	1 (4%)	26	2 (8%)

<u>Summary</u>

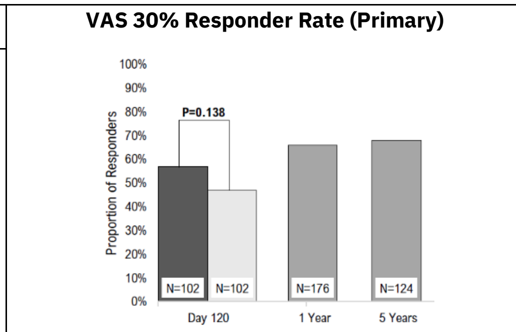
Patients have shown substantial benefits from ReActiv8 therapy, and those benefits have maintained over time: In the analysis of completers at 5-years, the mean improvement in VAS pain from baseline is 4.9 cm, the mean ODI improvement is 23 points, 83% of patients report feeling “much better” or “better,” and 88% of patients report being “definitely satisfied” with the treatment (Figure 6). Therapies of this kind take time for functional and neuromuscular control improvement to take effect. The availability of 5-year follow-up and outcomes data, which based on the literature is unique for prospective studies with implantable neurostimulators, provides clinically relevant insights into this novel treatment for disabling mechanical chronic low back pain.

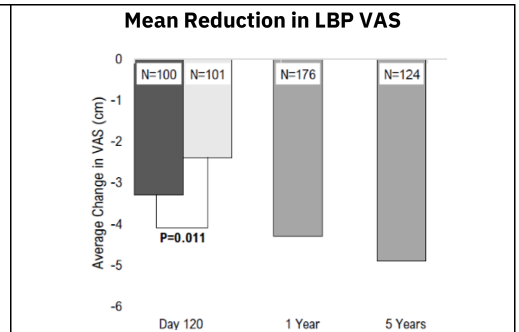
Mainstay Medical

Treatment Control Combined

<u>30% Responder Rate (Primary)</u>
- Day 120: **p=0.138**
- 1 Year: 66%
- 5 Years: 68%

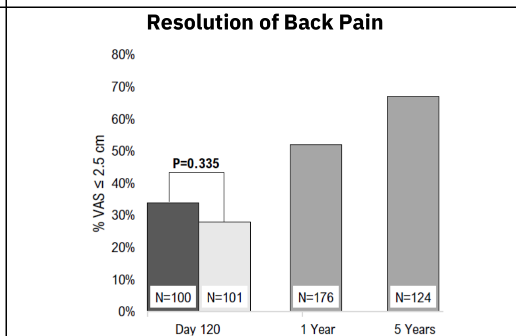
<u>Mean Reduction in LBP VAS</u>
- Day 120: **p=0.032**
- 1 Year: 4.3cm
- 5 Years: 4.9cm

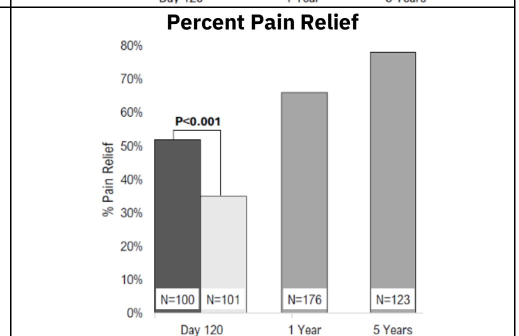




<u>Resolution of Back Pain</u>
- Day 120: **p=0.335**
- 1 Year: 52%
- 5 Years: 67%

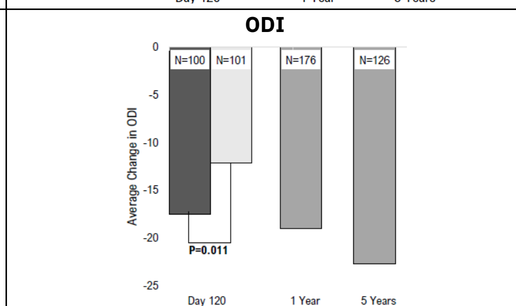
<u>Percent Pain Relief</u>
- Day 120: **p<0.001**
- 1 Year: 66%
- 5 Years: 78%

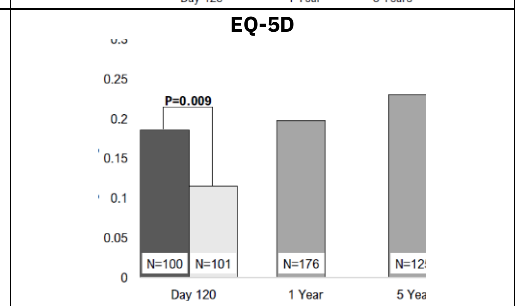




<u>ODI</u>
- Day 120: **p=0.011**
- 1 Year: 20-pt
- 5 Years: 23-pt

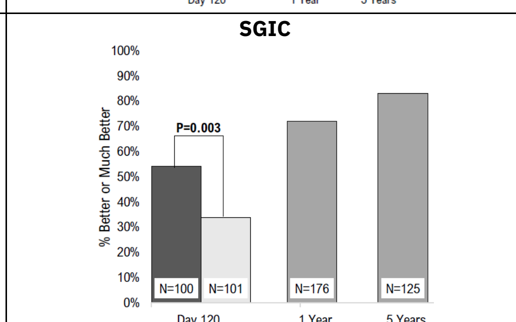
<u>EQ-5D</u>
- Day 120: **p=0.009**
- 1 Year: 0.198
- 5 Years: 0.231

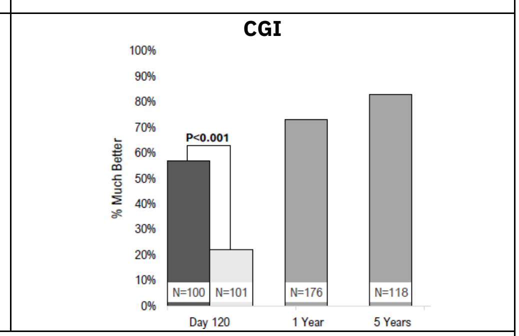




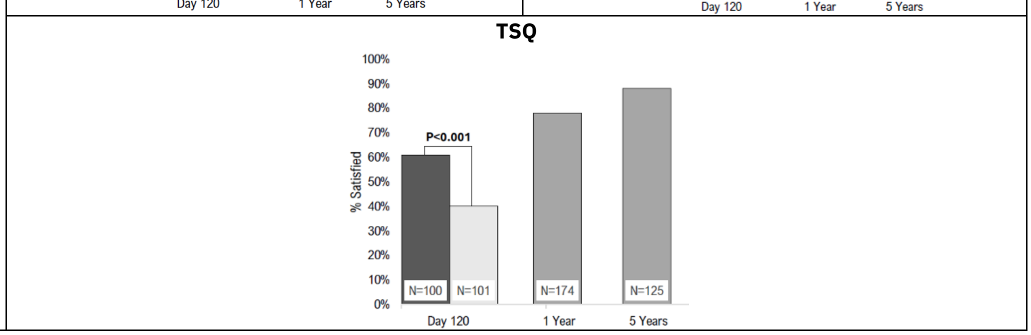
<u>SGIC (Better or Much Better)</u>
- Day 120: **p=0.003**
- 1 Year: 72%
- 5 Years: 83%

<u>CGI (Much Better)</u>
- Day 120: **p<0.001**
- 1 Year: 73%
- 5 Years: 83%





<u>TSQ (Satisfied)</u>
- Day 120: **p<0.001**
- 1 Year: 78%
- 5 Years: 88%



For continuous the p-value from a two-sample, two-sided t-test; for SGIC p-value is from Mann-Whitney; for TSQ and CGI p-value is from Cochran-Mantel-Haenszel; and for Resolution of Back Pain p-value is from Chi-square test. No adjustment for multiplicity was made and the p-values need to be interpreted descriptively.

Figure 6: Summary of Effectiveness Data through Five Years

G. Summary of Clinical Information

The ReActiv8-B trial was an international, multi-center, prospective, randomized, blinded trial comparing the ReActiv8 System programmed to therapeutic stimulation settings (Treatment group) to the ReActiv8 System programmed to minimal stimulation active sham settings (Control group). Although the primary efficacy endpoint was inconclusive at the 120-day visit, the totality of evidence provides compelling support in favor of the treatment. The prespecified cumulative proportion of responder analysis of the primary endpoint data (ITT) showed that the difference between the Treatment and Control groups was statistically significant (p=0.0499).

Patients in the trial had an average CLBP duration of 14 years and suffered pain on 97% of the days in the year prior to enrollment. The overall results demonstrated that patients moved from severe pain and borderline severe disability to mild pain and disability. Benefits that emerged in the Treatment group within the blinded phase continued to increase over time through the 5-year visit, demonstrating durability of the gained improvements. The reversal of trajectory and subsequent substantial and significant improvements documented in the Control group post crossover at 120 days provides further support in favor of ReActiv8 treatment effectiveness.

Clinically meaningful and durable improvements were consistently demonstrated across all outcome measures. In addition, 69% of patients who were on opioids at baseline had discontinued or reduced their use by the 5-year visit.

Given the public health concern over the chronic use of opioids, physicians and patients are now looking for non-opioid options for treating pain. These data support that ReActiv8 is a safe, effective, and durable nondrug treatment option for mechanical CLBP.

The clinically meaningful benefits across all outcome measures, the favorable safety profile, and positive impact on opioid reduction creates a favorable benefit/risk ratio for the use of this therapy in patients severely impacted with refractory mechanical CLBP.

Effectiveness Conclusions

Effectiveness for the ReActiv8 System was based on Level 1 evidence from the ReActiv8-B pivotal trial. Two hundred four (204) patients were implanted with the ReActiv8 System and randomized to the Treatment group (102) and the Control group (102). Although the primary efficacy endpoint was inconclusive at the 120-day visit, the totality of evidence provides compelling support in favor of the treatment. The cumulative proportion of responder analysis on the same (ITT) primary endpoint data demonstrated a significant difference (p=0.0499) between the Treatment and Control groups.

Comparison between the Treatment and Control groups on multiple secondary effectiveness endpoints and supporting analyses at the 120-day visit (Table 12), demonstrated the following clinical benefit:

- Greater reduction in pain as measured by mean LBP VAS and PPR
- Greater improvement in physical and social function, including sleep, as measured by ODI, Cumulative Proportion of ODI Responders, and Ability to Work
- Greater improvement in overall quality of life as measured by EQ-5D
- Higher treatment satisfaction as measured by TSQ
- More favorable impression of change as measured by SGIC and CGI

Benefits that emerged in favor of the treatment within the blinded phase continued to improve over time through the 5-year visit, demonstrating durability of the gained improvements. The five-year data across all prespecified endpoints demonstrated reduced pain, increased physical and social function, improved quality of life, positive subject and clinician impression of change, and high overall treatment satisfaction.

The prespecified secondary analysis of primary and secondary efficacy outcomes in the Control group after crossover to therapeutic stimulation at the 120-day visit, demonstrated clinically relevant improvements over and above the greater than expected sham-response. These improvements continued to grow through five years, providing further support in favor of the treatment.

Safety Conclusions

The risk assessment of the device is based on nonclinical laboratory testing, animal studies, previous ReActiv8 clinical trials, and published literature as well as data collected in the ReActiv8-B clinical trial conducted to support PMA approval as described above. SAEs related to the device or procedure occurred in 4% of the 204 implanted patients and all but one resolved. There were no device-related deaths and no unanticipated adverse device effects (UADE).

Because the Control group also received the implanted ReActiv8 System as an active sham, similar active implantable neurostimulation systems such as spinal cord stimulation (SCS) systems provide a more relevant context for the safety profile, even though the treated population is different.

Across the common risks associated with neurostimulation systems, the ReActiv8 safety profile compares favorably to the published SCS experience. Notably no lead migrations occurred in the ReActiv8-B trial.

Most adverse events occurred within the 120-day period, with similar related adverse event rates in both study groups (36% of the Treatment patients versus 34% of Control patients).

The most commonly reported adverse events were: 1) implant site pain/discomfort (21%), most of which resolved within days or weeks after implant without intervention; 2) device overstimulation (15%) that was typically resolved with reprogramming of the device; 3) lead conductor fractures requiring lead replacements (5%); 4) surgical pocket infection (3%), all of which were resolved with explant of the system and antibiotics. These reported rates are within the range of published rates for SCS therapy.

Benefit-Risk Conclusions

The benefits of the device are based on the clinical study described above. Effectiveness of the ReActiv8 System was demonstrated by the totality of evidence observed. Benefits observed in all prespecified endpoints continued to improve over time through five years. The results through five years consistently show that patients have reduced pain, increased physical and social function, improved quality of life, positive subject and clinician impression of change, and high overall treatment satisfaction.

Overall Conclusions

The data in this report support the reasonable assurance of safety and effectiveness and a favorable clinical benefit to risk determination for this device when used in accordance with the indications for use. The results from comprehensive pre-clinical testing show that the ReActiv8 System performs as intended. Results from the ReActiv8-B sham-controlled, double-blinded pivotal study, prior published studies, and reported clinical experience support the safety and effectiveness of the ReActiv8 System.

Although the primary efficacy endpoint was inconclusive at the 120-day visit, the totality of evidence, including other outcome data at the 120-day visit and long-term data, provides compelling support in favor of the treatment and received PMA approval from the FDA in June 2020. The cumulative proportion of responder analysis at the 120-day visit, on the same (ITT) primary endpoint data, demonstrated a significant difference (p=0.0499) between the Treatment and Control groups.

Comparison between the Treatment and Control groups on multiple secondary effectiveness endpoints and supporting analyses at the 120-day visit (Table 12), demonstrated:

- Greater reduction in pain as measured by mean LBP VAS and PPR
- Greater improvement in physical and social function, including sleep, as measured by ODI, Cumulative Proportion of ODI Responders, and Ability to Work
- Greater improvement in overall quality of life as measured by EQ-5D
- Higher treatment satisfaction as measured by TSQ
- More favorable impression of change as measured by SGIC and CGI

The benefits observed during the blinded study phase continued to increase throughout five years, consistent with the restoration of patient disability and multifidus muscle function. Across all prespecified endpoints, the long-term data demonstrated that patients have reduced pain, increased physical and social function, improved quality of life, positive subject and clinician impression of change, and high overall treatment satisfaction.

The prespecified secondary analysis of primary and secondary efficacy outcomes in the Control group after crossover to therapeutic stimulation at the 120-day visit demonstrated clinically relevant improvements over and above the greater than expected sham-response. These improvements continued to improve over time through five years, providing further support in favor of the treatment.

Clinically relevant and statistically significant improvements were observed between 120 days and 5 years on all primary and secondary effectiveness outcomes in the Control group following crossover to therapeutic treatment levels with 8 months of active therapy. This was in addition to the (greater than expected) improvements recorded under sham conditions, providing further support in favor of the treatment. The study also proved meaningful discontinuation and reduction in opioid use through the 5-year visit.

As described above, ReActiv8 was determined to be safe. The adverse events that were reported were consistent and many favorable to the well-known safety profile of marketed SCS systems as described in the literature.

Post-hoc analysis at the 5-year follow-up, in this patient population, who typically has few effective treatment options, had accrued durable and clinically substantial benefits in all predefined outcome measures including pain, disability, and healthcare-related quality of life ($p<0.0001$ for all), and most participants on opioids eliminated or reduced them. The supporting principled approach for handling missing data instills confidence in the robustness of the data and the validity of the conclusions drawn.

Full transparency was provided about participant disposition, missing data, surgical interventions, and procedure- and therapy-related adverse events. To inform interpretation of the completer data, conservative modeling methods following the intent-to-treat principle have been applied to account for missing data.

The totality of evidence generated by the ReActiv8-B trial demonstrated a favorable benefit-risk profile that is appropriate in therapies for patients with intractable mechanical CLBP.

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