SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Stimulator, neuromuscular, lower back muscles, totally implanted for pain relief

Device Trade Name: ReActiv8 Implantable Neurostimulation System

Device Procode: QLK

Applicant's Name and Address: Mainstay Medical Limited
6601 Shingle Creek Parkway, Suite 200
Brooklyn Center, MN, 55430, USA

Premarket Approval Application (PMA) Number: P190021

Date of FDA Notice of Approval: June 16, 2020

II. INDICATIONS FOR USE

The ReActiv8 System is indicated for bilateral stimulation of the L2 medial branch of the dorsal ramus as it crosses the transverse process at L3 as an aid in the management of intractable chronic low back pain associated with multifidus muscle dysfunction, as evidenced by imaging or physiological testing in adults who have failed therapy including pain medications and physical therapy and are not candidates for spine surgery.

III. CONTRAINDICATIONS

The ReActiv8 System should not be used for those patients who are:

- Unable to operate the system
- Unsuitable for ReActiv8 implant surgery

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the ReActiv8 System labeling.

V. DEVICE DESCRIPTION

The ReActiv8 System is an implantable electrical neurostimulation system that stimulates the nerves that innervate the lumbar multifidus muscles for the treatment of mechanical chronic low back pain. The ReActiv8 System is shown in Figure 1:

Figure 1: *ReActiv8 Neurostimulation System Implantable Pulse Generator (IPG) and Percutaneous Leads*

A. Implanted Components

The implanted components of the ReActiv8 Neurostimulation System include the following:

- Implanted Pulse Generator (IPG) (Model 5100): The IPG is a two-channel, programmable device that accepts two Leads (each lead with four electrodes). The IPG is powered by a 2.9V nominal Lithium Carbon Monofluoride primary cell battery. The two separate output channels facilitate bilateral stimulation of motor nerves that supply the lumbar multifidus muscles, and the electrode configuration (combination of + and – electrodes) can be programmed independently for each channel. Approximate dimensions of the IPGs are 65mm, 48mm (width) and 12mm (thickness). The stimulation output parameters are listed in Table 1 below:

Table 1: Stimulation Output Parameters

Parameter	Programmable range			Nominal value	Typical Programmed Setting
	Minimum value	Maximum value	Step		
Channel for Terminals 1 - 8	Left, Right			Left: T1 - T4 Right: T5 - T8	
Polarity for Terminals 1 - 8	Positive, Negative, Disconnected			Disconnected	
Channel for IPG Can (+ polarity)	Left, Right, Left and Right, Disconnected			Disconnected	
Amplitude	0.0 mA	7.0 mA	0.1 mA	0.0 mA	2.5 mA
Pulse Width	31 µs	336 µs	31 µs	214 µs	214 µs
Rate	1 Hz	26 Hz	1 Hz	20 Hz	20 Hz
On-Ramp	0 s	5 s	1 s	2 s	
Off-Ramp	0 s	5 s	1 s	2 s	
Cycle-On	2 s	20 s	2 s	10 s	

Cycle-Off	20 s	120 s	2 s	20 s	
Session	1 m, 2 m, 5 m, 10 m, 15 m, 20 m, 25 m, 30 m			30 m	
IPG Mode	On, Off			Off	

- Percutaneous Leads (Models 8145 and 8165): The lead specifications are depicted in Table 2. Lead materials are summarized in Table 3.

Table 2: Percutaneous Lead Specifications

Parameter	Specification
Lead lengths available	45 cm and 65 cm
Lead body diameter	1.2 mm
Lead lumen	Min 0.4 mm inner diameter
Terminal configuration	1.3 mm diameter – 2.8 mm pitch
Electrode dimensions	1.3mm diameter – 3mm length – 12 mm^2 surface area
Electrode spacing	4 mm
Tines	3-point tines
Tine spacing	6 mm
End cap	Closed / Full Radius

Table 3: Percutaneous Lead Materials

Component	Material
Terminal contacts and set-screw retainer	MP35N
Terminal spacer	Pellethane 2363-75D
Lead body tubing	Pellethane 2363-90A
Conductor coil	Polyimide coated DFT/MP35N 25% Ag
Electrode	90/10 Platinum/Iridium
Tine component	Pellethane 2363 90A
End cap	316L Stainless Steel

- Lead suture sleeve (Optional): The optional suture sleeve may be used to attach the Lead body to the superficial fascia and features a 1.3 mm inner-diameter. The suture sleeve is molded out of NuSil MED-4870 silicone rubber.

B. External Components

- Clinician Programmer (Model 7500): Used by the clinician to program output stimulation parameters. It is an off-the-shelf laptop installed with proprietary Mainstay software to allow the programming of the IPG via the Programmer Wand.

- Patient Activator (Model 7000): A handheld battery-operated unit able to communicate via short range inductive telemetry with the IPG
- Programmer Wand (Model 6000): The Programmer Wand allows the Clinician Programmer to communicate with the IPG. The Programmer Wand connects to the Programmer laptop through a USB port and communicates via short range inductive telemetry with the IPG.
- Magnet (Model 4000): The IPG can be programmed by a clinician using the ReActiv8 Programmer System so that therapy sessions can be controlled with the Magnet. There are three possible responses for the IPG when the Magnet is placed over it.
    1. Stop Session (Default setting) – Placing the Magnet over the IPG only stops a Session. The Magnet cannot be used to start a Session.
    2. Start/Stop Sessions – Placing the Magnet over the IPG starts or stops a Session.
    3. None – Placing the Magnet over the IPG has no effect.
- Surgical Accessories:
    - Torque Wrench: Used to tighten the set screws that lock the Lead into the IPG.
    - Stylets: Used to maneuver the Lead through back tissue to the desired implant location.
    - Mainstay Tunneler: Used to tunnel subcutaneous pathways for Lead routing from the Lead insertion location to the IPG pocket location or vice versa.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are alternatives for the treatment of mechanical chronic low back pain (CLBP), although none are curative. Patients are typically treated on a continuum with less invasive therapies prescribed first. Established non-surgical treatment options include, but are not limited to oral medications; massage therapy; physical/occupational/exercise therapy; psychological therapies (e.g., behavior modification, hypnosis); lumbar extensor strengthening exercises; watchful waiting (i.e., no therapy); traction therapy; ultrasound therapy; transcutaneous electrical nerve stimulation (TENS); acupuncture; sympathetic nerve blocks, epidural blocks, intrathecal blocks, and facet joint blocks; osteopathic therapy; thermotherapy; nerve ablation and rhizotomy; and lumbar stabilization exercises. Surgical treatment options include sympathectomy, implantable intrathecal drug delivery systems, partially implanted spinal cord stimulator (SCS) systems (power source is external) and commercially available fully implantable SCS systems.

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The ReActiv8 System has been in commercial distribution in the European Union (EU) (approval in May 2016). The device has not been withdrawn from marketing for any reason.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of potential adverse effects (e.g., complications) associated with the use of the ReActiv8 System. The adverse effects include: (1) those associated with any surgical procedure and (2) those specifically associated with having an implanted ReActiv8 System. In addition to the risks listed below, there is the risk that the ReActiv8 therapy may not be effective in relieving symptoms or may cause worsening of symptoms. Additional intervention may be required to correct some of the adverse effects.

- Risks associated with any surgical procedure: abscess; cellulitis; excessive fibrotic tissue; wound dehiscence; wound, local or systemic infection; wound necrosis; edema; inflammation; foreign body reaction; hematoma; seroma; thrombosis; ischemia; embolism; thromboembolism; hemorrhage; thrombophlebitis; adverse reactions to anesthesia; hypertension; pulmonary complications; organ, nerve or muscular damage; gastrointestinal or genitourinary compromise; seizure, convulsion, or changes to mental status; complications of pregnancy including miscarriage and fetal birth defects; inability to resume activities of daily living; and death.
- Risks associated with the use of the ReActiv8 System: lead migration; IPG migration; allergic response or tissue reaction to the implanted system material; hematoma or seroma at the implant site; skin erosion at the implant site; persistent pain at the IPG or lead sites; nerve or muscular damage; premature battery depletion leading to loss of therapy; loss of pain relief over time; and uncomfortable stimulation or ineffective pain control caused by failure of the system components or battery, changes in electrode position, loose electrical connections, lead insulation breaches or fractures.

For the specific adverse events that occurred in the clinical study, see Section X.3.D below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

1. Implanted Pulse Generator (IPG)

   Testing was conducted on the Model 5100 IPG, including: mechanical design verification, electrical and firmware design verification testing, electromagnetic compatibility testing, and medical procedure compatibility testing. Key testing on the IPG is summarized in Table 4. Testing demonstrated the IPG operated according to specifications after exposure to the tested conditions (i.e., passed testing).

Table 4: Summary of Key Testing Performed and Passed on the ReActiv8 System IPG

Test	Test Purpose	Acceptance Criteria
Measurement of Output Pulses	The characteristics of the output pulses shall be measured as described in ISO 14708-3 clause 6.101. Verify proper output (amplitude, pulse width, frequency, etc.) of the IPG function are within specified tolerances.	Amplitude, Pulse width, Frequency, and Inter pulse delay are within output specifications.
Dimensional Requirements	To demonstrate IPGs meet shape and profile requirements.	IPG samples must meet size specifications for IPG width, height, thickness, volume, mass, and radius.
DC Leakage Current	Verify the leakage current is in an acceptable range. Leakage current was measured with a 500 Ω load per the instructions in ISO 14708-3, clause 16.2.	The maximum leakage current < 1 µA
Environmental Conditions	Atmospheric Pressure Exposure: To expose each IPG to pressure extremes the device may encounter during storage and distribution.	Testing per ISO 14708-3, 25
	Operating Temperature: To demonstrate the IPG remains mechanically intact and capable of normal operation during exposure to low and high temperatures.	Testing per ISO 14708-1, 26.2. The IPG shall remain mechanically intact and capable of normal operation during exposure to low (0°C) and high temperatures (45°C)
	Mechanical Forces: Verify device conforms to functional requirements and is not damaged by mechanical forces that may occur during conditions of use	Testing per ISO 14708-1, 23
Hermetic Leak Test	To demonstrate that the IPG (including feedthroughs) maintains hermeticity after exposure to environmental testing.	Must be hermetically- sealed titanium can, helium leak shall be < 1x10-8 std/cc/s.
Lead Retention Force	To demonstrate that the IPG and Lead meet specified interface requirements for retention force (with setscrew engaged)	Lead retention force shall be more than 15N.
Lead Insertion and withdrawal Forces	To demonstrate that the IPG and lead meet specified interface requirements for insertion force and withdrawal force (without setscrew engaged).	Lead insertion force shall be < 8.9N (2.0 Lbf).

Test	Test Purpose	Acceptance Criteria
Particulate matter	Verify there is no unacceptable release of particulate matter when the device is used as intended.	The excess average count of particles from the test specimen compared to a reference sample shall not exceed 100 counts/ml greater than 5.0 µm and shall not exceed 5 counts/ml greater than 25 µm.
Battery	Electrical, Visual, Dimensional, Hermeticity, Short Circuit Testing, Environmental, and Forced Discharge Tests.	Longevity was demonstrated via bench testing to demonstrate the device would perform under nominal conditions for the required operational life (5 yrs) in active and standby conditions (see table 29) Reliability testing demonstrated safe reliable use of the battery. The device is designed with a failsafe fuse in case of a high current discharge. A soft short did not exceed a maximum temperature rise of the device is 2 ºC. Extensive testing was provided to demonstrate battery safety, short circuit and forced discharge safety.

2. Percutaneous Lead Testing

The percutaneous leads underwent numerous testing for dimensional verification, electrical safety, environmental, and mechanical conditions. Key testing on the leads is summarized in Table 5. Testing demonstrated the percutaneous leads operated according to specifications after exposure to the tested conditions (i.e., passed testing).

Table 5: Summary of Key Testing Performed on the Percutaneous Leads

Test	Purpose	Acceptance Criteria
Dimensional	To ensure the Leads meet dimensional requirements for Overall Lead Length Lead Body Diameter, Distal Electrode Dimensions, Lead Tip Length, Connector Dimensions.	Meets dimensional specifications.
DC Resistance	Demonstrate protection from electricity.	DC resistance between electrodes and contact shall not exceed 100 Ohms.
Stylet Interactions – Insertion/ Removal	To demonstrate the force required to fully insert or remove each stylet into the Lead	Measure peak insertion and withdrawal forces for a 0.4 mm stylet. The Lead shall not exhibit any signs of damage. Maximum stylet insertion and withdrawal force shall not exceed 5 N.
Hipot	Demonstrate the safety of the electrical insulation.	The leakage current shall not exceed 2 mA when 20V is applied between any two conductor pairs or any conductor pair and reference electrode.
Pull Test	Demonstrate the integrity of the Lead body joints after the Lead is stressed by a saline soak and wet pull.	No Lead bond separation, cracks, tears, permanent elongation in excess of 5% lead resistance stay within specification after the tensile force is applied. Lead leakage current ≤ 2 mA when 20V is applied between any two conductor pairs or any conductor pair and reference electrode.
Lead Body Flex Fatigue	Demonstrate that the Lead bodies do not fatigue after flexural stressors.	The Lead body shall withstand a minimum of 47,000 cycles without fracture of any conductor or conductive path.
Connector End Flex Fatigue	Demonstrate that the Lead connector ends do not fatigue after flexural stressors.	The Lead connector end shall withstand a minimum of 82,000 cycles without fracture of any conductor or conductive path.
Electrode Flex Fatigue	Demonstrate that the Lead electrode ends do not fatigue after flexural stressors.	The Lead electrode end shall withstand a minimum of 82,000 cycles without fracture of any conductor or conductive path.

3. Programmers

The software associated with the Clinician Programmer, Patient Activator, and Programmer Wand was tested in accordance with the FDA guidance document entitled, “Guidance for the Content of Pre-market Submission for Software Contained in Medical Devices” (May 11, 2005), and all requirements were met. Electrical and mechanical verification and environmental testing (per ISO 14708-3 and IEC 60601-1, ed. 3.1) were also performed, and all testing met specifications.

4. Electromagnetic Compatibility (EMC) and Wireless Technology

EMC testing was performed using appropriate essential performance criteria in accordance with the relevant clauses of the following standards and met specified acceptance criteria:

- IEC 60601-1-2: 2014, “Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral standard: Electromagnetic compatibility - Requirements and tests”
- ISO 14708-3:2017: Implants for surgery – Active implantable medical devices – Part 3: Implantable neurostimulators”, Part 27
- Wireless radio testing per United States FCC CFR Title 47 Part 15

5. System Testing

Testing to verify that system-level design requirements were met for interactions between ReActiv8 System components was performed. All test articles met defined acceptance criteria for the system integration tests conducted. System validation testing demonstrated that the system operated as expected and has been validated for safe and effective use.

6. IPG Medical Compatibility Testing

The ReActiv8 System was tested for compatibility with external defibrillation, High Power Electric Fields, and diagnostic ultrasound exposure (Table 6). All samples met all functional requirements of the testing after exposure to medical therapy conditions, verifying that the IPG meets requirements for compatibility with these therapies. The ReActiv8 System has not been evaluated for MRI compatibility.

Table 6: IPG Medical Compatibility Testing

Test	Acceptance Criteria
External Defibrillator Test	Verify that the device meets functional electrical test requirements after exposure to external defibrillation per ISO 14708-3, clause 20.2
High Power Electrical Fields Test	Verify protection from high power electrical fields according to standard ISO 14708-3, clause 21
Diagnostic Ultrasound Test	Verify that the IPG withstands exposure to ultrasound specified in EN45502-1:1997 and ISO 14708-3, clause 22

B. Animal Studies

Safety of ReActiv8 System and electrical stimulation was evaluated in goats.

The study was a non-blinded, randomized, prospective, controlled, Intent to Treat study design that enrolled 12 female goats, with 6 at each of two timepoints (5 weeks and 13 weeks).

The study was conducted in accordance with FDA Regulations on Good Laboratory Practices (GLP) for Nonclinical Laboratory Studies 21 CFR Part 58, the Animal Welfare Act 9 CFR Parts 1 and 2.

This study required evaluation in an in vivo model, as the anticipated use was in humans. The goat model was selected for this evaluation because goats were an established animal species for spinal cord stimulation. Additionally, the goat spine is similar to that of humans and was considered to be large enough to appropriately accommodate the devices to be implanted. Finally, the sponsor and test facility had previous experience with this model.

One objective of the study was to describe the safety of the ReActiv8 System and electrical stimulation based upon 5 weeks and 13 weeks of implantation and electrical stimulation through an evaluation of ease of implantation, radiographic imaging, daily observations, veterinarian examination, adverse events, clinical hematology, neurological examinations, gross pathology and histologic evaluation of the medial branch of the dorsal ramus and muscles near the implant site, as assessed by a board-certified veterinary pathologist.

A second objective of the study was to describe the local effects of implantation based upon histology of the capsules surrounding the ReActiv8 System implant in compliance with ISO 10993-part 6, as assessed by a board-certified veterinary pathologist.

A third objective of this study was to describe the tissue healing around the implanted system and electrical performance of the ReActiv8 System based upon periodic

(weekly) impedance checks. Analysis of the study endpoints, as they pertain to the 5 week and 13-week cohorts of this study, indicate that the ReActiv8 System and electrical stimulation are safe, with no significant local effects after implant, in a chronic goat model.

C. Biocompatibility

Biocompatibility testing was performed for all patient-contacting components of the ReActiv8 System in accordance with ISO 10993-1 Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process, on the finished sterilized devices. All biocompatibility studies were conducted in compliance with Good Laboratory Practices (GLP), 21 CFR Part 58. The implanted components of the ReActiv8 System are considered permanent (> 30 days) implants in contact with tissue and bone. The ReActiv8 System also contains external communicating and skin-contacting components with limited (≤ 24 hours) tissue and bone contact. All pre-specified test acceptance criteria were met, and all tests passed.

D. Sterility and Packaging

The ReActiv8 System components that are provided sterile are terminally sterilized using a 100% ethylene oxide (EO) sterilization process to provide a minimum sterility assurance level (SAL) of 10^{-6}. Validation of the sterilization process is in compliance with ANSI/AAMI/ISO 11135-1:2007, Sterilization of health care products – Ethylene oxide – Part 1: Requirements for development, validation, and routine control of a sterilization process for medical devices. Sterilant residuals conform to the maximum allowable limits of EO and ethylene chlorohydrin (ECH) residuals specified in ISO 109937: 2008, Biological Evaluation of Medical Devices – Part 7: Ethylene Oxide Sterilization Residuals. The product bacterial endotoxin limits are based on FDA's Guidance for Industry - Pyrogen and Endotoxins Testing: Questions and Answers (June 2012) and are verified using Limulus Amebocyte Lysate (LAL) testing.

Packaging and shelf- life validation tests were completed in compliance with ISO 11607-1:2009, Packaging for Terminally Sterilized Medical Devices. Part 1: Requirements for materials, sterile barrier systems and packaging systems.

Shelf-life for the ReActiv8 Lead and Mainstay Tunneler have been established as three years from the date of manufacturing.

Shelf-life for the ReActiv8 IPG and Torque Wrench have been established as two years from the date of manufacturing.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the ReActiv8 System for treatment of mechanical, intractable chronic low back pain in the US, Europe and Australia under IDE #G150018.

A summary of the clinical study is presented below.

A. Study Design

Patients were enrolled between September 13, 2016 and June 14, 2018. The database for this PMA reflected data collection through May 31, 2019 and included 561 enrolled patients (signed consent). There were 26 investigational sites.

The study was an international, multi-center, prospective, randomized, 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).

Patients were blinded as to their treatment assignment as were the study personnel performing patient assessments at the 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.

- The study incorporated the following: Minimization of bias
  - Randomized, controlled trial
    - Randomization post implant
    - Active sham control
  - Blinded
    - Patients
    - Investigator and site personnel performing patient assessments
    - 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 changes
  - 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. Clinical Inclusion and Exclusion Criteria

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

- Age ≥22 years, ≤75 years
- 7-day recall of average Low Back Pain (LBP) VAS of ≥6.0 cm and ≤9.0 cm at baseline (on a 10 cm scale)
- Oswestry Disability Index score ≥21% and ≤60% at the baseline visit
- Chronic Low Back Pain defined as pain and discomfort localized below the costal margin and above the inferior gluteal fold (with or without referred leg pain) that has persisted >90 days prior to the baseline visit, which has resulted in pain in at least half of the days in the 12 months prior to the baseline visit, as reported by the patient
- Evidence of lumbar multifidus muscle dysfunction by the Prone Instability Test (PIT)
- Continuing low back pain despite >90 days of medical management including:
    i. At least one attempt of physical therapy treatment for low back pain, which may optionally be accomplished over multiple episodes or flare-ups of low back pain.

        NOTE 1: Patients who start a physical therapy program but are unable to complete it are still eligible with regards to this inclusion criterion.

        NOTE 2: Patients who participated in a physical therapy program in the past since the onset of low back pain but are unwilling or unable to participate in a new physical therapy program are still eligible with regards to this inclusion criterion.

ii. For patients with medications prescribed and used for chronic low back pain, usage shall be at a stable dose in the 30 days prior to the baseline visit as reported by the patient.

NOTE 3: A stable dose means the patient reports no significant change in regular use of medications, which may include *pro re nata* use, in the 30 days prior to the baseline visit.

- Be willing and capable of giving Informed Consent
- Ability to comply with the instructions for use and to operate ReActiv8, and to comply with this Clinical Investigation Plan
- Suitable for ReActiv8 surgery as determined by the implanting physician prior to inclusion

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

- Body mass index (BMI) >35
- Back pain characteristics:
  i. Any surgical correction procedure for scoliosis at any time or a current clinical diagnosis of moderate to severe scoliosis (Cobb angle ≥25°).
  ii. Lumbar spine stenosis, as defined by an anterior-posterior diameter of the spinal canal of <10 mm in patients with lower extremity pain.
  iii. Neurological deficit possibly associated with the back pain (e.g., foot drop).
  iv. Back pain due to pelvic or visceral reasons (e.g., endometriosis or fibroids) or infection (e.g.: post herpetic neuralgia).
  v. Back pain due to inflammation or damage to the spinal cord or adjacent structures (e.g., arachnoiditis or syringomyelia).
  vi. Pathology seen on MRI that is clearly identified and is likely the cause of the CLBP that is amenable to surgery.
  vii. Back pain due to vascular causes such as aortic aneurysm and dissection.
- An independent assessment of any current indication for back surgery according to appropriate guidelines or has indications for back surgery but cannot undergo surgery for other reasons.
- Leg pain described as being worse than back pain, or radiculopathy (neuropathic pain) below the knee.
- Source of pain is the sacroiliac joint as determined by the Investigator.
- Drug use per patient report as follows:
  i. Current baseline use of >120 mg oral morphine equivalent per day of opioids.
  ii. Current use of breakthrough dose of >60 mg oral morphine equivalent per

day.

iii. Current requirement of opioids for treatment of a condition other than low back pain.

iv. History of any substance abuse at any time in the five years prior to the baseline visit.

v. Currently taking >15 mg Diazepam per day or equivalent.

- Surgical or other procedures exclusions:
  i. Any previous rhizotomy or rhizolysis procedure, including cryoablation, RF ablation, or pulsed RF on the dorsal root ganglion (DRG) or the medial branch of the dorsal ramus nerve that crosses or lies below the T8 vertebra, within one year prior to the baseline visit.
  ii. Anesthetic block of the DRG or medial branch of the dorsal ramus nerve that crosses or lies below the T8 vertebra or injection of epidural steroids for back pain in the 30 days prior to the baseline visit.
  iii. Any previous back surgery including laminectomy or discectomy at or below segmental level T8, or spinal fusion at any level.
  iv. Any previous thoracic or lumbar sympathectomy.
- Any prior diagnosis of lumbar vertebral compression fracture, lumbar pars fracture, pars defect, or lumbar annular tear with disc protrusion that is amenable to surgery
- Planned surgery:
  i. Any major surgery (including elective surgery) planned in the twelve months following the baseline visit (does not include minor surgeries not expected to impact the lumbar spine (e.g., colonoscopy)).
  ii. Any elective surgery of any kind (including, for example, tooth extraction, gynecological surgery, or cosmetic surgery) in the time between the baseline visit and the primary endpoint assessment visit.
- Any comorbid chronic pain conditions.
- Other clinical conditions:
  i. Pregnant or planning to be pregnant in the next 12 months, at the time of inclusion.
  ii. Pregnancy at any time in the 6 months, or lactating in the 3 months, prior to the baseline visit.
  iii. Any condition unrelated to the CLBP such as muscle wasting, muscle atrophy, other disability (e.g., paraplegic, amputee, cerebral palsy) or muscular or skeletal disease (e.g., arthritis in trunk or limbs, multiple sclerosis, rheumatoid arthritis) which, in the opinion of the Investigator, could limit physical movement or compliance with the protocol, or interfere

with the assessment of effectiveness of the investigational procedure.

iv. Poorly controlled diabetes (Type I or Type II) determined by HbA1c >8.
v. Past or current neurological disorders (e.g., known multiple sclerosis, motor neuron disease, Guillain-Barré syndrome, Parkinson's, Huntington's Disease, Alzheimer's, epilepsy, stroke, brain cancer, traumatic brain injury).
vi. Cancer requiring treatment during the study.
vii. Any drugs (e.g., immunosuppressive drugs) or comorbidity that might inhibit wound healing or electrode scarring, or drugs associated with reduced effectiveness of neuromodulation for other applications.
viii. Any medical condition requiring anticoagulation (other than aspirin) that, in the opinion of the physician prescribing the anticoagulant, cannot be safely suspended for 5 days prior to device implantation surgery and an appropriate period after implantation surgery.
ix. Any active infection in the vicinity of the implant site or any systemic infection.

- Psycho-social exclusions:
  i. Be involved in an injury claim under current litigation.
  ii. Have a pending or approved financial compensation claim (e.g., worker's compensation claim, long-term disability claim) or any financial compensation (including social welfare payments) related to the patient's CLBP.
  iii. Current incarceration (prison or jail).
  iv. Have an assessment of current active depression significant enough (DASS depression score >9) to impact perception of pain, compliance with intervention, and/or ability to evaluate treatment outcome.
  v. 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 (e.g., active depression, bipolar disease, Alzheimer's disease) as determined by a psychologist or psychiatrist.
- Protocol Compliance Exclusions:
  i. Inability or unwillingness to comply with all protocol requirements.
  ii. Inability to maintain the prone or side lying position in a relaxed manner for the duration of each stimulation session.
  iii. Inability to operate the Activator, such as arthritis that limits arm or shoulder movement, or inability to learn how to operate.
  iv. Inability to assess changes in pain intensity or perform wound care.
  v. Inability or unwillingness to complete the Journal.

- General exclusions:
    i. Any other active implantable device, including an implantable device for back pain (such as an implantable drug pump or Spinal Cord Stimulator), pacemaker, implantable defibrillator, cochlear implant, deep brain stimulator, implantable drug pump, or other implanted neurostimulation device.
    ii. Prior exposure to an implantable neurostimulator for treatment of pain, including spinal cord stimulation (including trial implant of SCS leads), occipital nerve stimulation, or peripheral nerve stimulation.
    iii. A condition currently requiring or likely to require use of MRI or diathermy while implanted with the ReActiv8.
    iv. Therapy with any other investigational intervention (drugs, devices, or procedures) for the treatment of back pain at the time of the baseline visit, or at any time in the past if the past investigational intervention did not subsequently gain regulatory approval.
    v. Current or planned participation in any other clinical trial during participation in this trial.
    vi. Life expectancy <1 year.

2. Follow-up Schedule

All patients were consented during the baseline visit. If they met the enrollment criteria, the patient proceeded to the ReActiv8 system implant. Once implanted, the patients were randomized to one of the two study groups at 14 days post-implant and stimulation programmed accordingly based on the randomization. Patients returned for visits at 14 days, 45 days, 75 days, 120 days, 180 days, 240 days and one-year post randomization and activation of the ReActiv8 system. All patients were consented to continue to be followed for a minimum of 5 years.

At baseline, patients had a physical exam, pregnancy test, psychological assessment, medical history collected, pain characteristics collected, patient questionnaires, the prone instability test and MRI imaging. The medical history, baseline pain characteristics, patient questionnaires and MRI were reviewed by one of two independent orthopaedic surgeons. The results of their assessment, along with the medical history, baseline characteristics, and psychological assessment were then provided to the Study Principal Investigator for review to determine if the patient met the enrolment criteria.

At certain timepoints post implant and after randomization and activation, the following parameters were collected: pain assessment (using the visual analog scale (VAS) and collection of the percent pain relief compared to baseline), the

Oswestry Disability Inventory (ODI), European Quality of Life 5 dimension (EQ-5D), patient and clinician satisfaction and impression of change measures; Subject Global Impression of Change (SGIC), Treatment Satisfaction Questionnaire (TSQ), and Clinical Global Improvement (CGI). The key timepoints for each assessment are shown in Table 7 below. Adverse events were collected at every visit beginning at the baseline visit.

Table 7: Study Assessment Timepoints

Visit Number	**1**	**2**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Study Requirement	**Informed Consent, Baseline Data, Inclusion Decision**	**ReActiv8 Implant Procedure (1-45 days post inclusion)**	**Randomization and Activation (14 ± 3 days)**	**14 ± 7 Days Post Randomization**	**45 ± 7 Days Post Randomization**	**75 ± 10 Days Post Randomization**	**Endpoint: 120 -0/+20 Days Post Randomization**	**180 ± 30 Days Post Randomization**	**240 ± 30 Days Post Randomization**	**12 Months -30/+60 Days Post Randomization**	**Annual Follow-Up 360 ± 60 Days Post Randomization**
Screening data (including PIT) and MRI review	✓										
Psychological Assessment	✓										
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 Effectiveness Endpoint

The primary effectiveness endpoint is a comparison of responder rates between the Treatment group and the Control group at the 120-day visit, where a "responder" is defined as a patient with ≥30% reduction from baseline in a 7-day recall of average low back pain VAS without any increase from baseline in pain medication or muscle relaxants prescribed and taken in the two weeks prior to the visit.

Patients were also asked at each follow-up visit if he/she 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 Effectiveness Endpoint

The individual components of the primary effectiveness 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.

Primary Safety Assessment

The primary safety assessment evaluated serious device- and procedure-related adverse events in all patients in the Intent to Treat cohort at the 120-day visit. All reported adverse events were documented and reported with summary statistics

presented for observed rates. No plan for testing statistical hypotheses was part of the safety assessment. Supporting safety analyses were specified in the statistical analysis plan (SAP), including summarizing adverse events collected through the 1-year visit.

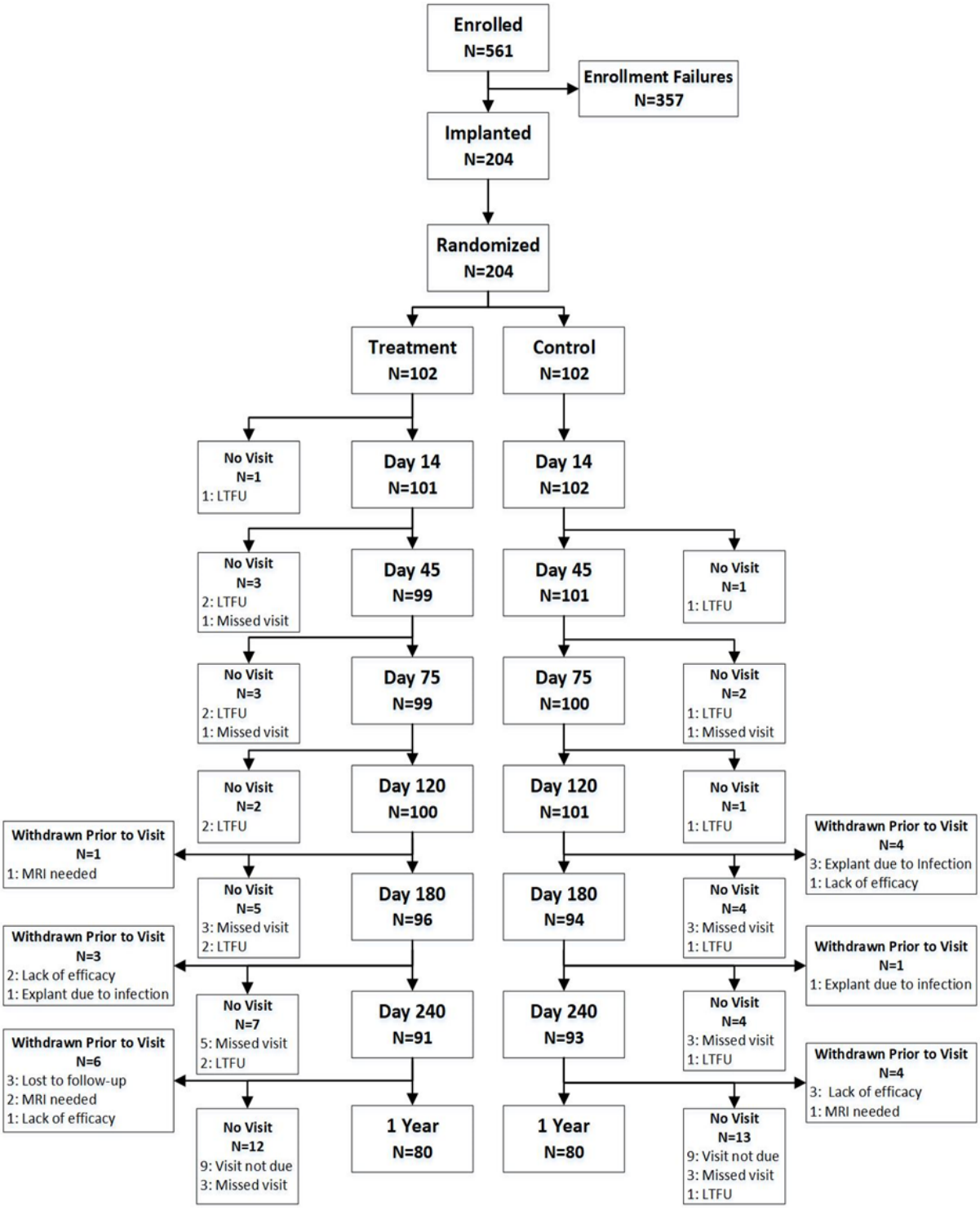
Secondary Endpoints

The following secondary endpoints were evaluated:

a. Comparison of change from baseline in the 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 effectiveness metrics in the Crossover group following the 120-day visit.

B. Accountability of PMA Cohort

At the time of the database lock for this PMA report, there were 561 patients enrolled in the IDE 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 200 patients in the Treatment group and 201 in the Control group returned for the primary endpoint visit at 120 days. Not all patients have reached the 1-year visit yet; however, a total of 160 patients have completed the 1-year follow-up visit with 80 patients in each of the study groups. See FIGURE 2 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 2: Patient Disposition by Visit through 1 Year Check LTFU

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are 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 rhizotomy, a higher percentage of patients in the Control Group had a previous rhizotomy compared to the Treatment group (17% and 8%, respectively). Since the enrolment criteria required that the previous rhizotomy had to have been >12 months prior to enrolment, history of a previous rhizotomy was not expected to impact the study results. See Table 8.

- The average age of the population was 47 ± 9 years with a fairly even split between male (46%) and female (54%).
- On average, patients had back pain for 14.2 ± 10.6 years, with 97 ± 8 percent of days in the past year with LBP.
- Average pain intensity was “Severe” (on average 7.3 ± 0.7 on VAS 7-day recall), and the average disability was borderline “Severe” (on average 39 ± 10% on ODI).
- This pain and disability profile persisted despite all having attempted physical therapy with an average of 31 ± 52 prior physical therapy sessions, and nearly half (49%) of the patients had at least one injection.
- All patients had attempted pain medications prior to baseline. A total of 162 (79%) of patients were prescribed and taking at least one low back pain medication at baseline, including 76 (37%) on an opioid-containing medication.
- About a third of the patients had leg pain, and for 85% of those, the leg pain was associated with their back pain.
- On average patients had missed 20.2 ± 66.9 days of work due to back pain in the previous year.

Table 8: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
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. P-Values for descriptive purposes only.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the ITT population which included 102 in the Treatment group and 102 in the Control group (4 Roll-in patients are included in this analysis since they were randomized and handled like all of the ITT patients) for a total of 204 patients implanted. Of the 204 patients, 201 patients returned for the primary endpoint visit at 120 days with 160 of those patients (80 patients in each group) out to one-year post activation of the ReActiv8 System as of 31 May 2019.

On average, Treatment patients had an implant for 78 weeks, while Control patients had an implant for 75 weeks, resulting in a total of 152 implant-years for Treatment patients and 147 implant-years for Control patients (combined 299 implant-years).

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 one-year visit. There were no formal, statistical hypotheses tested in the safety assessment.

Among the 204 randomized patients, 8 serious adverse events (SAEs) that were 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 Table 9 below. There were no unanticipated SAEs related to the device or procedure.

No further serious adverse events that are related to the device/procedure have been reported post the 120-day visit throughout the study.

Table 9: Serious Device or Procedure-Related Event through Day 120

	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**
Related Total SAEs	**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
Numbness in leg (non-radicular)	0	0/0	1 (1, <1%)	0/1	1 (1, <1%)	0/1

Serious unrelated adverse events are listed in Table 10. All events were reviewed by the CEC and adjudicated as not related. A total of seven serious unrelated adverse events occurred during the study. Six 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 10: Serious Unrelated Events through 1 Year

	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 Total SAEs	**4 (4, 4%)**	**3/4**	**3 (3, 3%)**	**3/3**	**7 (7, 3%)**	**6/7**
Acute appendicitis	1 (1, <1%)	1/1	0	0/0	1 (1, <1%)	1/1
Ankle fracture	1 (1, <1%)	1/1	0	0/0	1 (1, <1%)	1/1
Appendicitis	1 (1, <1%)	1/1	0	0/0	1 (1, <1%)	1/1
Chest pain	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
Gallstones	0	0/0	1 (1, <1%)	1/1	1 (1, <1%)	1/1
Malignant melanoma stage IV	1 (1, <1%)	0/1	0	0/0	1 (1, <1%)	0/1

As summarized in Table 11, a total of 476 adverse events (146 events [31%] were related and 330 events (69%) were unrelated) were reported within one year and prior to the report cutoff date. Of these, 8 were serious and related and 7 were serious and unrelated. Of those that were related, 53% occurred in the first 30 days after implant, which includes events that can happen with any surgical procedure. Of the related events, 83% have resolved.

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

Table 11: Overall Summary of Adverse Events Through One Year

AE Category	Treatment # Events (% Events)	Control # Events (% Events)	Total # Events (% Events)
Overall	**239**	**237**	**476**
By Seriousness			
Serious Adverse Events	7 (3%)	8 (3%)	15 (3%)
Related	3 (1%)	5 (2%)	8 (2%)
Unrelated	4 (2%)	3 (1%)	7 (1%)
Non-Serious Adverse Events	232 (97%)	229 (97%)	461 (97%)
Related	60 (25%)	78 (33%)	138 (29%)
Unrelated	172 (72%)	151 (64%)	323 (68%)
By Relatedness			
Related	63 (26%)	83 (35%)	146 (31%)[1]
Device	13 (5%)	28 (12%)	41 (8%)
Procedure	35 (15%)	38 (16%)	73 (15%)
Stimulation	16 (7%)	19 (8%)	35 (7%)
Unrelated	176 (74%)	154 (65%)	330 (69%)
By Outcome			
Resolved	186 (78%)	186 (78%)	372 (78%)
Not Resolved	53 (22%)	51 (22%)	104 (22%)

[1] 3 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 were no deaths reported in the ReActiv8-B trial.

All Study Related Adverse Events

Table 12 provides a summary of all study-related adverse events (both serious and non-serious) by treatment group through one year. 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 12: Study Related Adverse Events through 1 Year

Event	Total Related Adverse Events through 1 Year		
	Treatment N=102 # Events (Pt, %Pt)	Control N=102 # Events (Pt, %Pt)	# Resolved/ # Events
Related	**63 (42, 41%)**	**83 (50, 49%)**	**121/146**
Implant site pocket pain/discomfort	14 (12, 12%)	22 (18, 18%)	27/36
Device overstimulation of tissue	13 (12, 12%)	12 (12, 12%)	20/25
Implant site pocket infection	2 (2, 2%)	4 (4, 4%)	6/6
Lead conductor fracture	4 (4, 4%)	2 (2, 2%)	6/6
Back pain aggravated	1 (1, <1%)	3 (3, 3%)	3/4
Medical device discomfort	2 (2, 2%)	1 (1, <1%)	2/3
Coccyx pain	0	2 (2, 2%)	2/2
Numbness in leg	1 (1, <1%)	1 (1, <1%)	1/2
Buttock pain	0	1 (1, <1%)	0/1
Facial paresthesia	0	1 (1, <1%)	1/1
Groin pain	0	1 (1, <1%)	0/1
Headache	0	1 (1, <1%)	1/1
Medical device site injury	0	1 (1, <1%)	1/1
Medical device site reaction	0	1 (1, <1%)	1/1
Neuropathic pain	0	1 (1, <1%)	0/1
Paresthesia lower limb	0	1 (1, <1%)	1/1
Radicular pain	0	1 (1, <1%)	0/1
Sciatica	0	1 (1, <1%)	1/1
Shoulder pain	0	1 (1, <1%)	1/1
Throat sore	0	1 (1, <1%)	1/1
Wound pain	3 (3, 3%)	3 (3, 3%)	5/6
Implant site dermatitis	2 (2, 2%)	3 (3, 3%)	4/5
Implant site hematoma	2 (2, 2%)	3 (3, 3%)	5/5
Implant site inflammation	3 (3, 3%)	1 (1, <1%)	4/4
Implant site paresthesia	1 (1, <1%)	2 (2, 2%)	3/3
Allergic reaction to antibiotics	1 (1, <1%)	1 (1, <1%)	2/2
Implant site hypoesthesia	1 (1, <1%)	1 (1, <1%)	0/2
Pain in hip	2 (2, 2%)	0	2/2
Postoperative nausea	1 (1, <1%)	1 (1, <1%)	2/2
Postoperative vomiting	2 (2, 2%)	0	2/2
Procedural vomiting	2 (2, 2%)	0	2/2
Vaginal yeast infection	1 (1, <1%)	1 (1, <1%)	2/2
Adverse drug reaction	0	1 (1, <1%)	1/1
Anesthetic complication cardiac	0	1 (1, <1%)	1/1
Bradycardia	1 (1, <1%)	0	1/1
Calf pain	1 (1, <1%)	0	1/1
Hypertrophic scar	1 (1, <1%)	0	1/1
Implant site discharge	0	1 (1, <1%)	1/1
Implant site erythema	0	1 (1, <1%)	1/1
Implant site seroma	0	1 (1, <1%)	1/1
Open wound	0	1 (1, <1%)	1/1
Pharyngeal injury	1 (1, <1%)	0	1/1
Post concussion syndrome	0	1 (1, <1%)	1/1
Syncope vasovagal	0	1 (1, <1%)	1/1
Upper airway obstruction	1 (1, <1%)	0	1/1

There were 13% of the patients that underwent an additional surgical intervention for a system explant, lead replacement, or IPG repositioning through the 1-year visit. The need for an intervention (e.g., infection, lead replacement, IPG repositioning) was independent of the randomization assignment. A summary of these additional procedures is presented in Table 13 below.

A total of 9% of the patients underwent permanent system explant due to lack of effectiveness, 4% due to pocket infection, 3% due to infection, 2% due to MRI required and <1% due to unrelated hip pain. One additional patient that had a pocket infection was explanted and re-implanted once the infection resolved.

Table 13: Additional Surgical Procedures through 1 Year

ReActiv8 Surgical Intervention	Treatment N=102 Pt (% Pt)	Control N=102 Pt (% Pt)	Total N=204 Pt (% Pt)
Any ReActiv8 Surgical Intervention[1]	**14 (14%)**	**13 (13%)**	**27 (13%)**
System Explants	9 (9%)	10 (10%)	19 (9%)
Patient Request (Lack of Effectiveness)	*4 (4%)*	*4 (4%)*	*8 (4%)*
Infection[2]	*2 (2%)*	*4 (4%)*	*6 (3%)*
MRI Needed	*2 (2%)*	*2 (2%)*	*4 (2%)*
Unrelated Hip Pain	1 (1%)	0 (0%)	1 (<1%)
Lead Replacement	4 (4%)	2 (2%)	6 (3%)
IPG Repositioning	1 (1%)	3 (3%)	4 (2%)
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.

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 (SCS), even though the population 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 risk that notably did not occur in the ReActiv8-B trial is lead migration (Table 14).

Table 14: Safety Comparison of ReActiv8 to SCS Devices

Device/Procedural Events	SCS (Hayek[1]) Single Center Review 234 Patients	SCS (Eldabe[2]) Literature Review >4000 Patients	ReActiv8-B Prospective 204 Patients
Adverse Events			
Infection	4.3%	2.5-10%	3%
Implant Related Pain	11.1%	9-12%	13.7%‡
Lead Fracture/Malfunction	4.3%	0-10.2%	2.9%
Lead Migration	8.5%	2-27%	0%
Surgical Interventions	48%	0-47%	12.7%
System Explants	23.9%	NA*	9%
Lead Replacement	23.9%	NA*	3%

* Detail not provided in the literature

‡ 17/28 (61%) resolved prior to the data cutoff: 13 resolved without surgical intervention;4 resolved with surgical intervention to reposition the IPG.

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

- The occurrence of adverse events was similar between the Treatment and Control groups.
- No lead migrations were reported.
- 53% of the events occurred within the first 30 days.
- 83% of related adverse events resolved.

2. 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 effectiveness). All patients in the Control Group with a device implanted at 120 days chose to cross over.

One hundred and two patients were randomized in each study group in the ITT population (total 204 patients). This included 4 patients (2 in each group) that were in the roll-in group but were treated (and randomized) just like the ITT population and are included in the ITT population throughout the analyses after the 120-day primary endpoint.

Primary Effectiveness Endpoint

The study failed the prespecified primary effectiveness endpoint analysis. The responder rate in the Treatment and Control groups were 57.1% and 46.6% respectively (p=0.1377) (Table 15) at the 120-day primary endpoint visit.

Table 15: Responder Rate Low Back Pain VAS with No Increase in Pain Medications

Primary Effectiveness 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

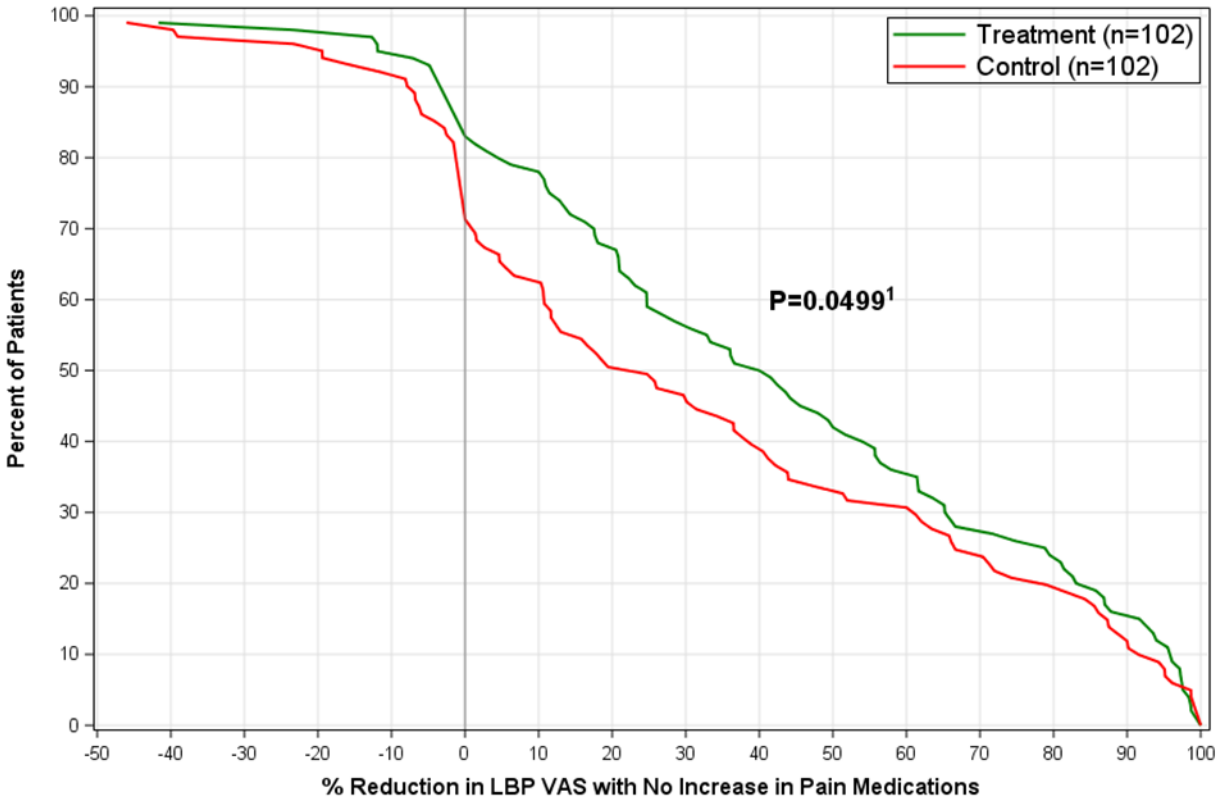
[1] Results for 3 patients (2 Treatment, 1 Control) LTFU were included using multiple imputation.
[2] p-value is based on a Wald asymptotic test of proportions, with multiple imputation to handle missing values, and a Cui et al p-value adjustment. P-Values for descriptive purposes only.

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.[3] This method utilizes the Friedman's regression analysis, which is a comparison of ranks. This test preserves information over dichotomizing an endpoint, thereby improving statistical power.[4,5,6]

The CPRA, which was prespecified in the clinical protocol and statistical analysis plan 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 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. P-Values for descriptive purposes only.

Figure 3: Cumulative Proportion of Responders in LBP VAS

Change in Mean VAS Analysis

In addition, the analysis of the mean LBP VAS reduction between the Treatment group and the Control group demonstrated a meaningful difference at the 120-day visit (p=0.032) (Table 16).

Table 16: 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. P-Values for descriptive purposes only.

Components of the Primary Endpoint

VAS Component of the Primary Endpoint

When evaluating the VAS component of the primary endpoint (without taking into account 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 imputation is utilized to account for missing data; therefore, this analysis is based on N=102 in both study groups.

Medication Component of the Primary Effectiveness 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 2-week interval prior to the 120-day visit, the patient was counted as a treatment failure for the primary effectiveness endpoint.

Nine patients in the Treatment group and nine 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 17), all of which were counted as treatment failures for the primary effectiveness endpoint.

Table 17: 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 2-week window, indicate that the patient had taken the medication within the 2-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 disability (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.

The results for the comparison between the Treatment and Control groups on multiple secondary endpoints and supporting analyses at the 120-day visit (Table 19), demonstrate:

- Greater reduction in pain as measured by mean LBP VAS and PPR
- Greater improvement in disability as measured by ODI,
- 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 18: Secondary Effectiveness 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.

Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

Long Term Results

All effectiveness outcome measures for the Treatment group, and for the Control group post crossover (Crossover group), progressively improved through the 1-year visit (Table 21).

Table 19: Summary of Endpoints at the 1-Year Visit

	Treatment		Crossover		Total	
Endpoint	**N[1]**	**Mean ± SD (Min, Max) or n (%)**	**N[1]**	**Mean ± SD (Min, Max) or n (%)**	**N[1]**	**Mean ± SD (Min, Max) or n (%)**
LBP VAS Responder Rate (≥30% reduction in VAS and no increase in medications)	80	55 (69%)	80	50 (63%)	160	105 (66%)
Change in LBP VAS	80	-4.4 ± 2.6 (-8.2, 1.9)	80	-4.4 ± 2.6 (-8.8, 1.4)	160	-4.4 ± 2.6 (-8.8, 1.9)
Resolution of Back Pain (VAS ≤ 2.5)	80	41 (51%)	80	44 (55%)	160	85 (53%)
Change in ODI	80	-20.9 ± 16.0 (-58.0, 12.0)	80	-20.3 ± 14.5 (-58.0, 25.0)	160	-20.6 ± 15.2 (-58.0, 25.0)
Change in EQ-5D	80	0.218 ± 0.218 (-0.385, 0.782)	80	0.183 ± 0.183 (-0.286, 0.665)	160	0.200 ± 0.201 (-0.385, 0.782)
Percent Pain Relief	80	67 ± 32 (0, 100)	80	66 ± 33 (0, 100)	160	67 ± 32 (0, 100)
SGIC (Much Better or Better)	80	60 (75%)	80	57 (71%)	160	117 (73%)
TSQ (Definitely Satisfied)[2]	79	65 (82%)	79	60 (76%)	158	125 (79%)

[1] Matched data including patients with data at the 1-year visit.

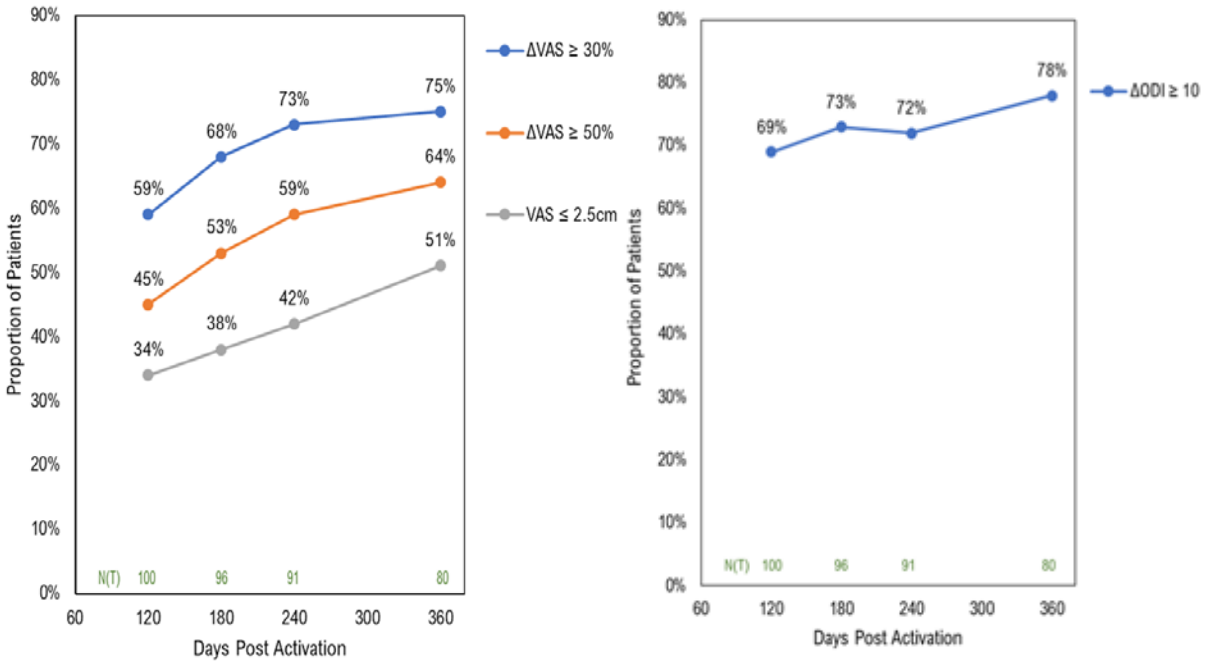
[2] One patient did not complete TSQ at 1 year.

Pain and Function

The protocol specified a threshold of ≥30% improvement on LBP VAS for the primary endpoint. Another commonly reported threshold for "success" is ≥50% improvement on LBP VAS, i.e. responder.

Similarly, the protocol specified a threshold of ≥10 points improvement on ODI as a clinically meaningful change.

The longitudinal “success rates” using these commonly reported thresholds are summarized in Figure 5a and Figure 5b. For these graphical representations, changes in pain medications were not considered.



a) VAS “Success Rates” b) ODI “Success Rates”

Figure 5: “Success Rates” in the Treatment Group (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 rehabilitative 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 1-year data for the magnitude and durability of effect.

Figure 6 below shows the effect of ReActiv8 therapy as a combination of pain and disability on individual patients. Each yellow circle represents one patient unless the number of patients with identical measurements are listed in the larger circles.

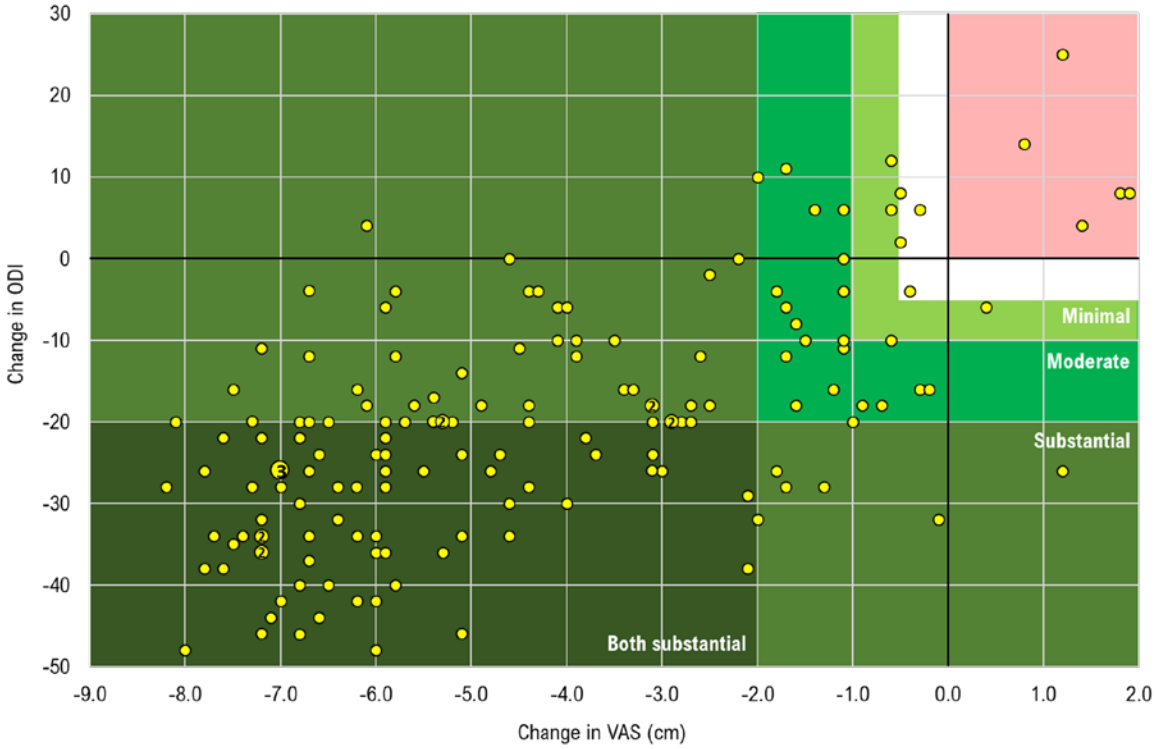


Figure 6: Absolute Change from Baseline in LBP VAS and ODI at 1 Year (n=160)

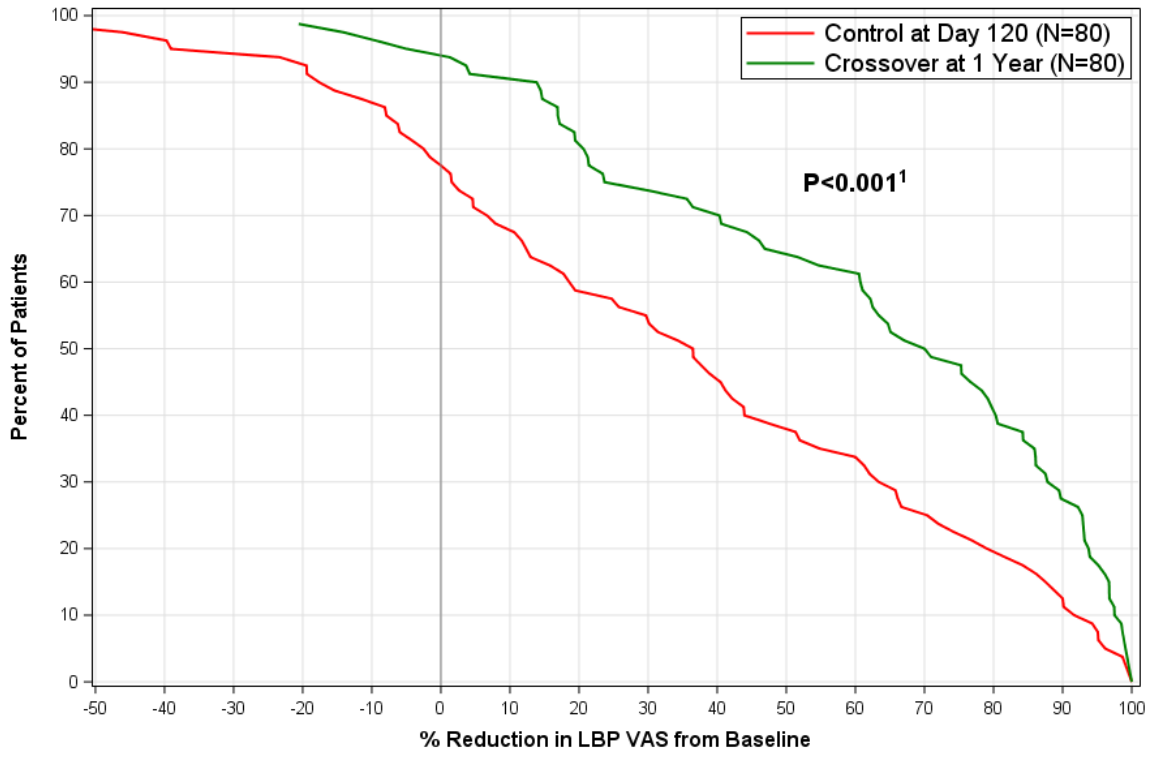
At the 1-year visit, 78% of patients reported a substantial[7] improvement in pain, as measured by LBP VAS, and improvement in physical and social function, as measured by ODI over baseline, or both of these measures (Figure 6). These data suggest that the vast majority of patients have gained increased ability to manage their daily activities.

Crossover Results

An additional prespecified secondary analysis involved a clinical performance assessment of the Crossover group at the 1-year visit (8 months of active therapy) compared to matched 120-day visit data of that same group (patient as their own control).

Following crossover to therapeutic levels of stimulation (at the 120-day visit), the Crossover group showed a significant, additional improvement on all effectiveness measures compared to the 120-day visit.

The Cumulative Proportion of Responders (LBP VAS) in the Control group at the 120-day visit and the Crossover group at the 1-year visit (Figure 7), demonstrated that after switching to therapeutic levels of stimulation, significantly higher responder rates ($p<0.001$) at 1 year across the entire LBP VAS threshold range were achieved.



[1]Friedman's regression analysis & p-value from Multiple Imputation analysis. P-Values for descriptive purposes only.

Figure 7: Difference in Cumulative Proportion of Responders in the Control/Crossover Group between 120 Days and 1 Year

All of the secondary endpoints and supporting analyses showed substantial improvements between the 120 day and the 1 year visits (Figure 8), demonstrating that after the patients crossed over to receive stimulation at a therapeutic level, they experienced significant and clinically relevant additional improvements in LBP, physical and social function, quality of life, treatment satisfaction, and impression of change.

Reduction in Pain:

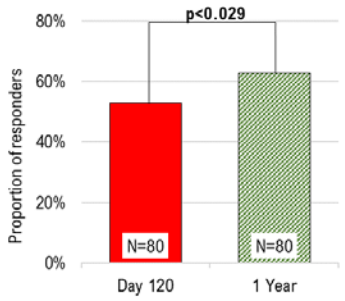
VAS resp: **p=0.029**

Mean VAS: **p<0.001**

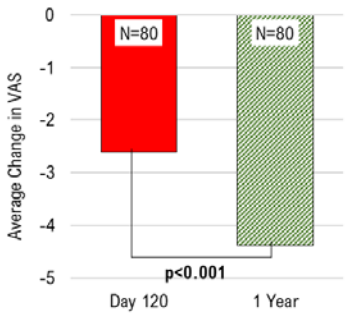
LBP ≤2.5: **p<0.001**

PPR: **p<0.001**

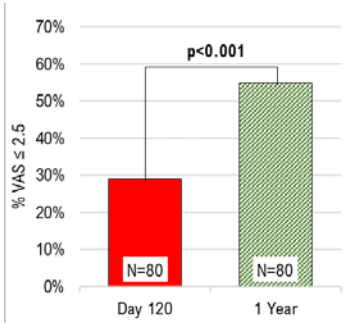
VAS ≥30% Responder Rate (per primary endpoint definition)



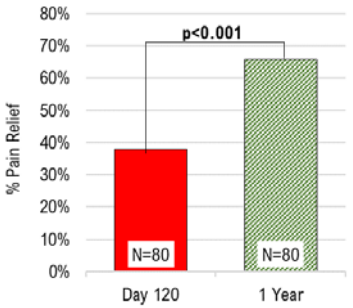
Change in LBP VAS



Resolution of LBP (≤2.5)



Percent Pain Relief

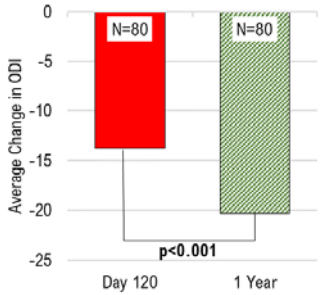


Improvement in Physical and Social Function and Quality of Life:

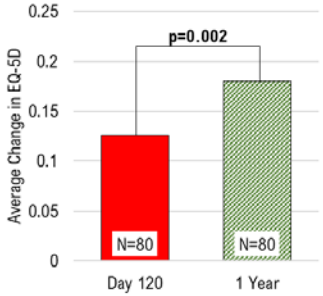
ODI: **p<0.001**

EQ-5D: **p=0.002**

Change in ODI



Change in EQ-5D



Control Crossover

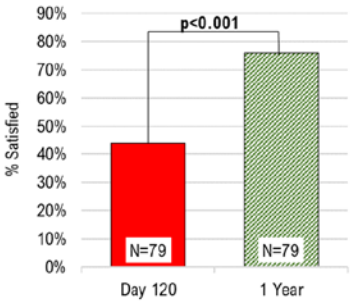
Positive Impact on Satisfaction and Impression of Change:

TSQ: **p<0.001**

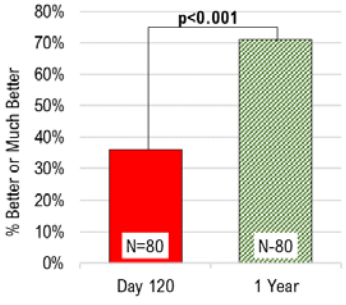
SGIC: **p<0.001**

CGI: **p<0.001**

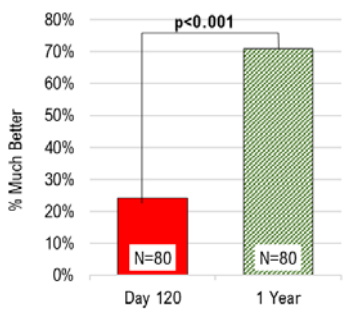
TSQ



SGIC



CGI



For continuous outcomes the difference in means is given with the p-value from a two-sided paired t-test, p-value for binary outcomes is from McNemar's test of agreement.

Figure 8: Differences in Secondary Endpoints and Supporting Analyses in Control/Crossover Group between 120 Days and 1 Year P-values for descriptive purpose only

Changes in Opioid Use

Of the 61 patients (Treatment and Crossover groups combined) who were on at least one opioid-containing medication at baseline and had a 1-year visit, 28% had discontinued use of opioids, and an additional 21% had decreased opioid use, for an overall rate of 49% of patients who decreased or discontinued opioids by the 1-year visit. (Table 22) 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 and had a 1-year visit remained off opioids.

Table 20: Changes in Opioids at 1 Year for Treatment and Crossover Groups Combined

Opioid Change Status	N	Change in Opioid Use n (%)
On Opioids at Baseline		
Discontinued or Decreased	61	30 (49%)
No Change	61	27 (44%)
Increased or Added	61	4 (7%)
Not on Opioids at Baseline		
No Change	99	96 (97%)
Added	99	3 (3%)

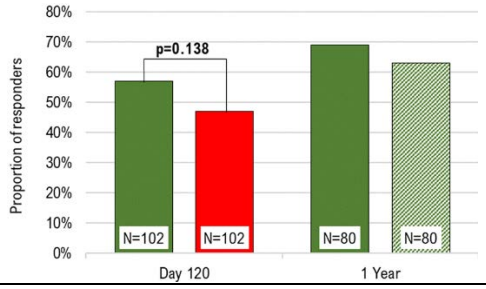
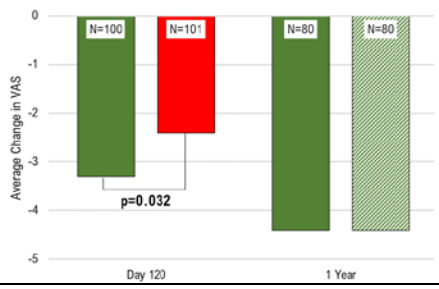
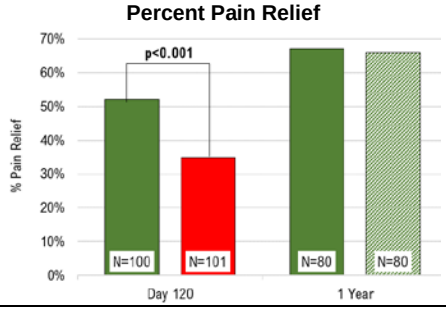
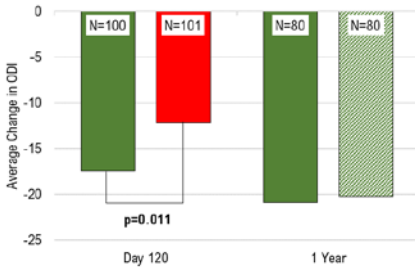
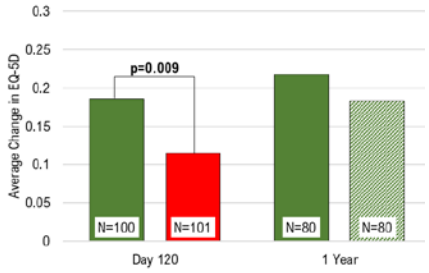
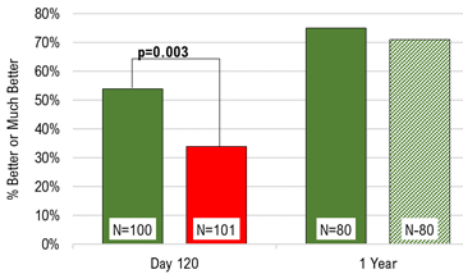
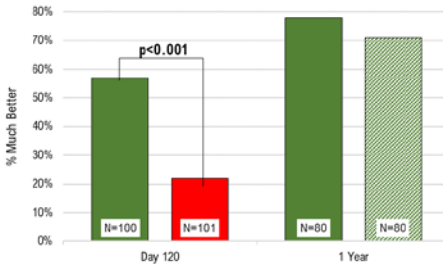
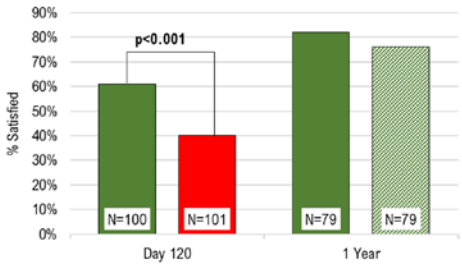
Notably, patients who decreased or discontinued opioids had similar effectiveness results as the overall population (Table 23). Hence, these severe CLBP patients with over a decade of pain on average, and after taking opioids for 4 years on average, had their condition improve substantially with ReActiv8 therapy even as they lowered or stopped opioids.

Table 21: Summary of Endpoints at 1 Year for Patients Who Have Decreased or Discontinued Opioids

	Decreased Opioids		Discontinued Opioids		Total	
Endpoint	**N**	**Mean ± SD (Min, Max) or n (%)**	**N**	**Mean ± SD (Min, Max) or n (%)**	**N**	**Mean ± SD (Min, Max) or n (%)**
LBP VAS (≥30% reduction in VAS and no increase in medications)	13	8 (62%)	17	15 (88%)	30	23 (77%)
Change in ODI	13	-21.7 ± 16.7 (-46.0, 8.0)	17	-20.6 ± 12.8 (-42.0, 6.0)	30	-21.1 ± 14.4 (-46.0, 8.0)
Change in EQ-5D	13	0.196 ± 0.157 (-0.171, 0.432)	17	0.150 ± 0.138 (-0.160, 0.362)	30	0.170 ± 0.146 (-0.171, 0.432)
Percent Pain Relief	13	57 ± 30 (0, 95)	17	72 ± 29 (0, 100)	30	66 ± 30 (0, 100)
Subject Global Impression of Change						
Much better	13	4 (31%)	17	8 (47%)	30	12 (40%)
Better	13	6 (46%)	17	4 (24%)	30	10 (33%)
A little better	13	2 (15%)	17	3 (18%)	30	5 (17%)
No change	13	1 (8%)	17	1 (6%)	30	2 (7%)
A little worse	13	0 (0%)	17	1 (6%)	30	1 (3%)
Worse	13	0 (0%)	17	0 (0%)	30	0 (0%)
Much worse	13	0 (0%)	17	0 (0%)	30	0 (0%)
Remitters (VAS ≤ 2.5)	13	3 (23%)	17	10 (59%)	30	13 (43%)
Treatment Satisfaction						
Definitely yes	11	10 (91%)	19	15 (79%)	30	25 (83%)
Maybe	11	1 (9%)	19	3 (16%)	30	4 (13%)
Definitely not	11	0 (0%)	19	1 (5%)	30	1 (3%)
Clinician Global Impression of Change						
Much better	11	9 (82%)	19	13 (68%)	30	22 (73%)
Slightly better	11	1 (9%)	19	4 (21%)	30	5 (17%)
About the same	11	1 (9%)	19	2 (11%)	30	3 (10%)
Slightly worse	11	0 (0%)	19	0 (0%)	30	0 (0%)
Much worse	11	0 (0%)	19	0 (0%)	30	0 (0%)

Summary

These results are achieved with a therapy that, by its design, is restorative in nature and takes time for its restorative effect to be achieved. Patients have shown substantial benefits from ReActiv8 therapy, and those benefits have expanded over time: by the 1 year follow-up visit, the mean improvement in VAS pain from baseline is 4.4 cm, the mean ODI improvement is 20.6 points, 73% of patients report feeling “much better” or “better”, and 79% of patients report being “definitely satisfied” with the treatment (Figure 9).

■ Treatment ■ Control ■ Crossover	VAS 30% Responder Rate (Primary)	Mean Reduction in LBP VAS
30% Responder Rate (Primary) • At Day 120: **p=0.138** • At 1 Year: •Treatment: 69% •Crossover: 63% Mean Reduction in LBP VAS • At Day 120: **p=0.032** • At 1 Year: •Treatment: 4.4mm reduction •Crossover: 4.4mm reduction		
Percent Pain Relief • At Day 120: **p<0.001** • At 1 Year: •Treatment: 67% •Crossover: 66% ODI • At Day 120: **p=0.011** • At 1 Year: •Treatment: 21-pt reduction •Crossover: 20-pt reduction		
EQ-5D • At Day 120: **p=0.009** • At 1 Year: •Treatment: 0.218 increase •Crossover: 0.183 increase SGIC • At Day 120: **p=0.003** • At 1 Year: •Treatment: 76% Better or Much Better •Crossover: 72% Better or Much Better		
CGI • At Day 120: **p<0.001** • At 1 Year: •Treatment: 78% Much Better •Crossover: 71% Much Better TSQ • At Day 120: **p<0.001** • At 1 Year: •Treatment: 82% Satisfied •Crossover: 76% Satisfied		

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. or continuous the p-value from a two-sample, two-sided t-test; for SGIC p-value is from Mann-Whitney; and for TSQ and CGI p-value is from Cochran-Mantel-Haenszel. P-Values for descriptive purposes only.

Figure 9: Summary of Effectiveness Data at Day 120 and 1 Year

Limitations

There are additional factors that have been considered in determining the probable risks and benefits for the ReActiv8system. These include potential confounding effects such as lack of a true placebo group, the use of adjunctive medications and the use of the recall VAS score. All of these factors could have played a role in impacting the final study results as discussed below.

Because treatment using the ReActiv8 requires stimulation of the multifidus muscle, a "true" placebo would have been likely to unblind patients and investigators. Therefore, an active control that caused a minor twitch was used to maintain the blind. Use of the active control, however, did not allow an assessment of the placebo response. Placebo response is well known in pain studies due to the subjective nature of the pain assessment, and the duration of this response may be long lasting. Given the use of the active control, the extent of the placebo response and the impact on the results is unknown. It is likely that use of the active control provided some benefit to patients in the Control group.

The primary endpoint was a comparison of patients in the active and control groups who achieved a 30% reduction in pain from baseline with no increase in pain medications or muscle relaxants. A 30% reduction in pain was selected to ensure that a successful active treatment would be clinically relevant to the patient. However, using this dichotomous endpoint, the result was not statistically significant as compared to the control. This may have been due to a number of factors including the use of an active control which would be likely to provide some benefit to the subjects in the Control group as well as increase the potential effect of placebo. Importantly, however, the cumulative response analysis did achieve a p-value <0.05. In addition, the patients' percent pain relief and disability as measured by the ODI supported the clinical benefit of the active treatment over the control.

Pain was assessed using recall VAS scores. However, the sponsor also collected diary data for pain assessment. An analysis of the diary data supported the recall VAS assessment.

Medication management throughout the course of a study is important to minimize the influence of medication changes on the study results. During the blinded phase of the study, patients were required to maintain stable doses of their adjunctive pain medications. However, changes to adjunctive pain medications were allowed in the open label phase, which may have affected the 1-year results.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 24 investigators of which none were full-time or part-time employees of the sponsor and two investigators had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none
- Significant payment of other sorts: none
- Proprietary interest in the product tested held by the investigator: none
- Significant equity interest held by investigator in sponsor of covered study: two investigators

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The study was an international, multi-center, prospective, randomized, blinded trial comparing the ReActiv8 System (Treatment group) to an active Sham Control (Control group) using the ReActiv8 System. Although the primary efficacy endpoint was not met at the 120-day visit, the totality of evidence provides support for clinical benefit of the treatment. The cumulative proportion of responder analysis on the same (ITT) population demonstrated a significant difference (p=0.0499) between the Treatment and Control group. Additional potential secondary benefits were observed, with improvement in patient pain symptoms, as seen in the percent pain relief, and improvement in functionality measured by the Oswestry Disability Index.

During treatment patients had improved pain and disability. Benefits which started to emerge in favor of the treatment within the blinded phase continued to improve through the 1-year visit, demonstrating durability of the gained improvements and corroborating the rehabilitative nature of the treatment. The improvements documented in the Control group post crossover at 120 days, provides further support in favor of ReActiv8 treatment effectiveness.

These results were corroborated by all other outcome measures, and the totality of data demonstrated clinical relevance and durability of the improvements.

The results at the 1-year visit were in a population with an average LBP duration of over a decade. In addition, 49% of patients on opioids at baseline, discontinued or reduced their use by the 1-year visit.

Given the public health concern over the chronic use of opioids, physicians and patients are looking for non-opioid options for treating pain. Alternative methods to treat refractory mechanical CLBP that do not create drug dependency issues provide added public health benefits. The totality of the evidence supports that ReActiv8 is an effective nondrug option to treat mechanical CLBP where there is no surgical option.

The totality of evidence is in favor of the ReActiv8 therapy. This, in combination with a favorable safety profile of the therapy leads to a favorable benefit/risk ratio for these severely impacted patients with refractory mechanical CLBP.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Neurological Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Effectiveness for the ReActiv8 System was based on Level 1 evidence from the ReActiv8-B pivotal trial. Two-hundred and four (204) patients were implanted with the ReActiv8 System and randomized to the Treatment group (102) or the Control group (102). Although the primary efficacy endpoint was not met at the 120-day visit, the totality of evidence provides support for the clinical benefit of the treatment. The cumulative proportion of responder analysis on the same (ITT) population demonstrated a difference (p=0.0499) between the Treatment and Control group. Additional potential secondary benefits were observed, with improvement in patient pain symptoms, as seen in the percent pain relief, and improvement in functionality measured by the Oswestry Disability Index.

Comparison between the Treatment and Control groups on multiple secondary effectiveness endpoints and supporting analyses at the 120-day visit (Table 19), demonstrated the following clinical benefit:

- Greater reduction in pain as measured by mean LBP VAS and PPR
- Greater improvement in disability as measured by ODI,
- 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 through 1 year. Across all pre-specified endpoints, the 1-year data demonstrated that patients have reduced pain, decreased disability, improved quality of life, positive subject and clinician impression of change, and high overall treatment satisfaction.

The pre-specified secondary analyses included evaluation of changes in primary and secondary efficacy outcomes in the Crossover Group following the 120-day visit when they were crossed over to receive therapeutic levels of stimulation. Improvements were observed between 120 days and 1 year on all primary and secondary efficacy outcomes in the Control group following crossover to therapeutic treatment levels.

All of these factors are crucial in evaluating the effectiveness of the ReActiv8 therapy.

B. Safety Conclusions

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

Because the control group was an active sham control (ReActiv8), an assessment of the safety benefits was compared to the safety profile of ReActiv8 while delivering treatment, to similar active implantable systems such as Spinal Cord Stimulation (SCS) devices.

When evaluating some of the more common risks with this type of procedure, the ReActiv8 safety profile compares favorably to that of SCS devices.

Regarding total adverse events, the rates were similar in both study groups (40% of the Treatment patients versus 49% of Control patients) and 46% combined. The most common events are summarized. Implant site pain/discomfort occurred in 15% of the patients many of the events began within days of the implant procedure and resolved within days or weeks with no intervention. Device overstimulation was experienced in 12% of the patients and was typically resolved with reprogramming of the device. Implant site pocket infection occurred in 3% of the patients, all resolved with explant of the system and antibiotics. Lead conductor fractures occurred in 2% of the patients requiring lead replacements that was performed without difficulty.

Benefit-Risk Conclusions

The probable benefits of the device are based on the clinical study described above. Effectiveness was demonstrated by improvement in pain, physical function, quality of life, treatment satisfaction, subject and clinician impression of change, despite lack of statistical significance for dichotomous primary outcome at 120 days. The totality of efficacy outcome data demonstrated the effectiveness of the ReActiv8 system. Specifically, considering the cumulative proportion of responders at all levels of response the treatment group outperforms the control group at all levels of response. The benefits observed during the blinded study phase, continued to increase through 1 year. Across all pre-specified endpoints, the 1-year data demonstrated that patients have reduced pain, decreased disability improved quality of life, positive subject and clinician impression of change, and high overall treatment satisfaction. In addition, the total adverse event rate was 46% for both Treatment and Control groups combined

and the risks of the device are similar to those of other active implantable systems such as Spinal Cord Stimulation (SCS) devices. In assessing the clinical benefit demonstrated by the device and the risks associated with the device, the probable benefit outweighs the probable risks.

Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

C. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The results from the clinical study and published literature support a reasonable assurance of the safety and effectiveness of the ReActiv8 System, as well as its performance through one year, when used in a manner consistent with its labeling and intended use. The evidence supporting the safety and effectiveness of the ReActiv8 System is based on a sham-controlled, double-blinded pivotal study and over 10 years of clinical research and experience as documented in the literature. The results from comprehensive pre-clinical testing show that the ReActiv8 System performs as intended. The analyses also support a clinical benefit to risk determination that is favorable.

Although the primary effectiveness endpoint was not met, the cumulative proportion of responders demonstrated a significant difference between treatment and control. This difference demonstrated a reasonable expectation of effectiveness for the intended population. In addition to the cumulative proportion of responder, subjects in the treatment group of the study experienced a greater reduction in LBP, improvement in disability, improvement in overall quality of life, higher treatment satisfaction, and more favorable impression of change when compared to the control group. The study additionally demonstrated the durability of the treatment as the benefits observed during the blinded study phase, continued to increase through 1 year.

Improvements were observed between 120 days and 1 year on all primary and secondary efficacy outcomes in the Control group following crossover to therapeutic treatment levels with 8 months of active therapy. This was in addition to the improvements recorded under the active control conditions, providing further support in favor of the treatment.

As described above, ReActiv8 was determined to be safe. The system, the IPG and the leads, has demonstrated safe electrical and mechanical characteristics, via

extensive bench testing and demonstrated adherence to FDA recognized consensus standards. The ReActiv8 system demonstrated adherence to IEC 60601-1-2:2014 and ISO 14708-3:2017. In addition to the device has demonstrated a reasonable expectation of biocompatibility via GLP animal studies and demonstrated adherence to the FDA recognized ISO 10993-1. The adverse events that were reported were consistent with those reported with the marketed SCS systems as described in the literature. The totality of evidence generated by the ReActiv8-B trial demonstrated a favorable benefit-risk profile which is appropriate in therapies for patients with intractable mechanical CLBP who have no surgical option.

XIV. CDRH DECISION

CDRH issued an approval order on June 16, 2020.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

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