SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Stimulator, Spinal-Cord, Totally Implanted for Pain Relief

Device Trade Name: Saluda Medical Evoke® SCS System
Device Product Code: LGW

Applicant's Name and Address: Saluda Medical Pty Ltd.
407 Pacific Highway Level 1
Artarmon, New South Wales 2064
Australia

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P190002

Date of FDA Notice of Approval: February 28, 2022

II. INDICATIONS FOR USE

The Saluda Medical Evoke SCS System is indicated as an aid in the management of chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with the following: failed back surgery syndrome, intractable low back pain and leg pain.

III. CONTRAINDICATIONS

The Evoke SCS System should not be used in patients who:

- Do not receive effective pain relief during trial stimulation
- Are unable to operate the Evoke SCS System
- Are unsuitable surgical candidates

IV. WARNINGS AND PRECAUTIONS

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

V. DEVICE DESCRIPTION

The Saluda Medical Evoke Spinal Cord Stimulation (SCS) System (Evoke System) is a rechargeable, upgradeable, totally implantable spinal cord stimulation system that delivers electrical stimulation to the spinal cord for the treatment of chronic intractable pain of the trunk and/or limbs.

SCS consists of applying an electrical stimulus to the spinal cord which causes the activated fibers (e.g., Aβ-fibers) to generate action potentials. Aβ-fibers are the low-threshold sensory fibers in the dorsal column that contribute to inhibition of pain signals in the dorsal horn (1). The action potentials summed together form the electrically evoked compound action potential (ECAP). Therefore, ECAPs are a direct measure of spinal cord fiber activation that generates pain inhibition for an individual.

The Evoke System is designed to operate in either of two modes: ECAP-controlled closed-loop stimulation mode, or open-loop (fixed-output) stimulation mode. The open-loop stimulation mode is equivalent to other commercially available SCS systems but has an additional feature to measure ECAPs. The Evoke System has the ability to measure ECAPs following every stimulation pulse from two electrodes not involved in stimulation. The recorded ECAP signal is sampled by the stimulator and processed to allow measurement of the ECAP amplitude. ECAP measurement may be performed in either stimulation mode. Additionally, the Evoke System can use ECAPs in a feedback mechanism to deliver closed-loop stimulation. The feedback mechanism minimizes the difference between the measured ECAP amplitude and the ECAP amplitude target (set by the clinician and adjusted by the patient using the pocket console) by automatically adjusting the stimulation current for every stimulus. In doing so, it maintains spinal cord activation near the target level (Figure 1).

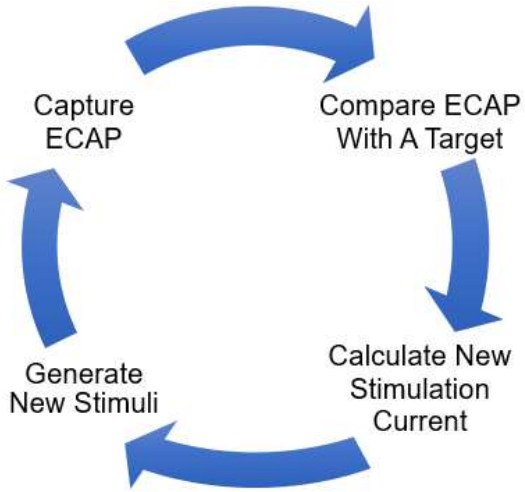

Figure 1. ECAP-controlled, Closed-Loop Stimulation

A. Implanted Components

The implanted components of the Evoke System include the following:

- Closed Loop Stimulator (CLS): A rechargeable, 25-channel implantable pulse generator (IPG or stimulator) which generates an electrical stimulus and measures and records the nerve fibers' response to stimulus (i.e., ECAPs). It has a lithium ion rechargeable battery and connects to two 12-contact leads. Although named "Closed Loop Stimulator", this stimulator delivers both open-loop and closed-

loop stimulation modes. The CLS has a single current source with four scaled outputs that can deliver controlled current to each of the active stimulation electrodes. In addition, the CLS can be programmed with up to four stimulation programs and up to four stimulation sets per program that may be interleaved using up to 25 independently programmable channels (lead(s) plus CLS case for recording ECAPs only). The stimulation output parameters are listed in Table 1.

Table 1. Stimulation Output Parameters

Number of Programs	1 to 4
Number of Channels	25; 24 epidural electrodes and the CLS case (case may be used for recording ECAPs only)
Waveform	Charge Balanced Biphasic or Triphasic
Pulse Shape	Symmetrical, Rectangular Biphasic or Rectangular Triphasic
Current or Voltage Regulated	Current
Maximum Current Amplitude	0-12.5 mA per current source output (maximum 50 mA and a total of 20 mA at 750 Ω)
Maximum Output Voltage	7.5 – 15 V
Pulse Width	20 – 1000 μs
Frequency	10 – 1500 Hz (Open-loop) 10 – 250 Hz (Closed-loop)
Current Path Options	Bipolar or Multipolar

- Percutaneous Leads: Electrical current is delivered to the spinal cord via the electrodes on leads that are introduced into the epidural space through an epidural needle and connected to the stimulator. ECAPs are measured using the non-stimulating contacts of the leads. The lead specifications are listed in Table 2.

Table 2. Percutaneous Lead Specifications

Lead Length (cm)	60, 90 cm
Lead Diameter (mm)	1.32 mm
Number of Electrodes	12
Electrode Material	Platinum/Iridium
Electrode Spacing (edge-to-edge) (mm)	4 mm
Electrode Span (mm)	80 mm
Electrode Surface Area (mm^2)	12.44 mm^2
Impedance (Ω)	<16 Ω

- Lead Extension: Used to provide additional length if needed to connect the implanted lead to the CLS or external closed loop stimulator (eCLS).

- Suture Anchors and Active Anchors: Used to anchor the lead to the supraspinous ligament or deep fascia.

- CLS Port Plug: Used to block unused ports in the CLS header.

B. External Components

- Accessory Belt: Aids the patient in holding the external charging coil and eCLS in place during use.

- Clinical Interface (CI): Used by the clinician to program output stimulation parameters and measure and record ECAP signals. It is an off-the-shelf tablet computer installed with proprietary Saluda Medical software to allow programming of the CLS, eCLS, as well as data collection and analysis.

- Clinical System Transceiver (CST): Connects to the CI via a USB port to provide wireless communication between the CI and the stimulator (CLS and eCLS).

- Pocket Console (EPC): A handheld battery-operated unit that allows patients to adjust stimulation within clinician prescribed program limits stored on the stimulator (CLS or eCLS). Adjustments include starting and stopping stimulation, increasing and decreasing stimulation intensity, and toggling between stimulation programs. The EPC batteries are disposable and non-rechargeable.

- Chargers: A battery-operated unit used to inductively charge the CLS transcutaneously. The Charger battery is non-removable and rechargeable.

- External Closed Loop Stimulator (eCLS): Provides stimulation by emulating the CLS during the intraoperative test and during the stimulation trial. The eCLS stimulation parameters are the same as the CLS.

- Intraoperative Cables: Used during intraoperative testing to connect the eCLS to the implanted lead(s).

- Lead Adapter: Used during the stimulation trial to connect the eCLS to the implanted lead(s).

- Surgical Accessories:

    - Epidural Needle: Consists of a cannula and stylet assembly that is used to introduce the percutaneous lead into the epidural space.

    - Stylets: Used to steer the lead in the epidural space to the desired location. Available in two tip shapes: straight and bent.

    - Tunneling Tool: Consists of the tool and passing straw assembly that is used to create a subcutaneous path from the CLS pocket to the lead incision site. It may also be used to create a path to an intermediate incision point or lead extension point when needed.

    - Torque Wrench: Used to tighten and loosen set screw connector systems that lock the lead into the active anchor, lead extension, and CLS header.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of chronic intractable pain of the trunk and/or limbs. Patients are typically treated on a treatment 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), transcutaneous electrical nerve stimulation (TENS), acupuncture, sympathetic nerve blocks, epidural blocks, intrathecal blocks, and facet joint blocks. The surgical treatment options for these patients include sympathectomy, implantable intrathecal drug delivery (IDD) systems, partially implanted 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 Evoke System has not been marketed in the United States. The Evoke System has been approved for commercial distribution in Europe. The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

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 SCS systems. The adverse effects include: (1) those associated with any surgical procedure, (2) those associated with the SCS system placement procedures, and (3) those associated with having an implanted SCS system to treat pain, including the Evoke System. In addition to the risks listed below, there is the risk that the SCS 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 SCS system placement procedures: temporary pain at the implant site, infection, cerebrospinal fluid (CSF) leakage, CSF fistula, epidural hemorrhage, bacterial meningitis, seroma, hematoma, paralysis, skin irritation, inadequate wound healing or wound dehiscence, spinal cord compression; nerve, nerve root, or spinal cord injury. Patient use of anticoagulation therapies may increase the risk of procedure-related complications such as hematomas, which could produce paralysis.

- Risks associated with the use of a SCS system: lead/IPG migration or suboptimal placement; 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 implant site; dysesthesia; decubitus; premature battery depletion; loss of pain relief over time; uncomfortable stimulation; unwanted stimulation (e.g., radicular chest wall stimulation, gastrointestinal symptoms, bladder symptoms); increased pain; weakness, clumsiness, numbness or pain below the level of lead implantation; and failure or malfunction resulting in ineffective pain control or other undesirable changes in stimulation, and possibly requiring explant and re-implantation.

For specific adverse events that occurred in the clinical study, please see Section X.D.1 below.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

1. Closed Loop Stimulator (CLS)

Testing was conducted on the Evoke CLS, including: mechanical design verification (including testing on devices subjected to accelerated aging), standards compliance testing, electrical basic safety testing, and medical procedure compatibility testing. Key testing on the CLS is summarized in Table 3. Testing demonstrated that the CLS operated according to specifications after exposure to the test conditions and thus passed all testing.

Table 3. Summary of Key Testing Performed and Passed on the Evoke System CLS

Test	Test Purpose	Acceptance Criteria
Dimensional Requirements	Confirms CLS meets volume requirements	Meets specification for total volume ≤ 45cc
Lead Insertion and Withdrawal Forces	Confirms lead can be inserted and withdrawn from the CLS lead port without excessive force.	Insertion and withdrawal force ≤ 14N
DC Leakage Current	Confirms CLS meets requirements of ISO 14708-1:2014 §16.2	DC Leakage currents to patient shall be less than $0.75\mu A/mm^2$
Protection from External Defibrillators	Confirms CLS meets requirements of ISO 14708-1:2014 §20.2	CLS meets functional requirements and maximum current requirements after exposure.
Mechanical Stress	Confirms CLS is able to function within specification after exposure to random vibration, shock, pressure and temperature conditions set out in ISO 14708-1.	Passes final production functional test.
Hermetic Leak Test	Confirms CLS battery area is maintained under a hermetic seal	Helium leak shall not exceed 6.6 x 10^{-8} std/cc/s.
Particulate Matter	Confirms CLS meets requirements for particulate per ISO 14708-1:2014	(Particulate size, acceptable number/volume) ≥ 5µm, ≤100 particles/ ml ≥ 25µm, ≤5 particles/ ml
Battery	Confirms Battery Charge/Discharge Cycle Verification (Longevity)	Acceptable for intended use.
	Electrical, Visual, Dimensional, Hermeticity, Short Circuit Testing, Environmental, and Forced Discharge Tests	Meets acceptance criteria
Header Bond Strength	Confirms the CLS header is able to withstand applied mechanical forces and remain functional	Passes visual inspection with no sign of header delamination and passes final electronic control test

Test	Test Purpose	Acceptance Criteria
Temperature	Confirms ability of CLS charging system to disable charging if CLS temperature reaches a maximum temperature limit.	Verified to disable charging at 41°C.
Stimulation Verification	Confirms that stimulation parameters programmed produce appropriate stimulation	Meets acceptance criteria
Feedback Mechanism	Confirms ECAP measurement, stimulation adjustment and stimulation monitoring function per requirements.	Meets acceptance criteria

2. Percutaneous Lead Testing

The percutaneous leads underwent testing for dimensional verification, electrical safety, environmental, and mechanical conditions. Key testing on the leads is summarized in Table 4. Testing was performed on pre-conditioned leads and demonstrated that they operated according to specifications after exposure to the test conditions and thus passed all testing.

Table 4. Summary of Key Testing Performed on the Percutaneous Leads

Test	Test Purpose	Acceptance Criteria
Dimensional	Confirm lead overall and electrode dimensions	As per specifications
Stylet Insertion/ Removal	Confirm ability to fully insert / remove straight and bent stylets from lead lumen without penetrating lead lumen or distal end of lead	Full insertion / removal without damage or change to electrical property with insertion force of 15N. Distal end of lumen not penetrated after applying 5N of force with stylet.
Lead/ Needle Interaction – Insertion/Removal	Confirm lead remains electrically and mechanically undamaged after 5 insertions/ removals from needle	Lead meets DC resistance criteria and lead body is free of damage to insulation or conductors
Lead Retention in CLS	Confirm ability of lead to be retained in the CLS lead port	Lead shall not be removed with a force less than 14N.
DC Resistance	Confirm electrical continuity after mechanical bending along body, at header, at anchor and with acute bends and torque	Lead meets DC resistance criteria and lead is free of damage to insulation or conductors

Test	Test Purpose	Acceptance Criteria
Dielectric Strength	Confirms Lead meets requirements of ISO 14708-1:2014 §16.3	Leakage current between any two Lead conductors, as well as between any Lead conductor and a reference electrode, shall not exceed 480uA in RMS magnitude
Lead Body Flex Fatigue	Confirm ability of lead body to withstand mechanical bending simulating actual use	Lead meets DC resistance criteria and lead body is free of damage to insulation or conductors after 47,000 cycles of flexural fatigue
Connector End Flex Fatigue	Confirm ability of lead connectors to withstand mechanical bending simulating actual use	Lead meets DC resistance criteria and lead body is free of damage to insulation or conductors after 82,000 cycles of flexural fatigue

3. External Closed Loop Stimulator, Clinical Interface, and Evoke Pocket Console

The software associated with the External Closed Loop Stimulator, Clinical Interface and Patient Console was developed and tested in accordance with IEC 62304:2015, Edition 1.1 - Medical device software – Software life cycle processes, and all requirements were met. Software information provided is based on guidance from the FDA document "Guidance for the Content of Pre-market Submission for Software Contained in Medical Devices" (May 11, 2005). Electrical, mechanical and environmental testing for the devices was also performed and all testing met specifications.

- External Closed Loop Stimulator (eCLS, Trial Stimulator)

  The External Closed Loop Stimulator was subjected to the following types of testing: electrical/firmware design verification, mechanical, shipping, environmental (storage and operational), product safety testing (per IEC 60601-1, Type BF safety classification, and IEC 60601-1-11), drop testing (per IEC 60601-1, 3rd edition), EMC testing (per IEC 60601-1-2). All test articles met defined acceptance criteria for the defined verification tests.

- Clinical Interface (CI)

  The Clinical Interface is an off-the-shelf Microsoft Surface Pro and has been subjected to testing applicable for its general use. The CI has been validated for use with Saluda Medical programming and data viewer

software through System Validation testing.

- Evoke Pocket Console (EPC)

  The Evoke Pocket Console was subjected to the following types of testing: functional verification, mechanical, environmental (storage and operational), product safety testing (per IEC 60601-1, 3rd edition, Type BF, and IEC 60601-1-11), including ingress, protection against electric shock (internally powered equipment), and drop testing. All test articles met defined acceptance criteria for the defined verification tests.

4. Electromagnetic Compatibility Testing and Wireless Technology

EMC and wireless technology (including quality of service (QOS), coexistence, and security of wireless transmissions testing) was performed using appropriate essential performance criteria in accordance with relevant clauses of the following standards. All components met specified acceptance criteria:

- IEC 60601-1-2: 2007, 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(E): Implants for surgery – Active implantable medical devices – Part 3: Implantable neurostimulators, Part 27

5. System Testing

Testing to verify that system-level design requirements were met for interactions between Evoke System components was performed. All test articles met defined acceptance criteria for the system integration tests conducted. System validation testing consisting of the following was conducted on the Evoke system components: evaluating the compatibility, interaction and functional operation of the system components when used together as a system. All validation steps passed. System validation testing demonstrated that the system operated as expected and has been validated for safe and effective use.

6. CLS Medical Compatibility Testing

The Evoke CLS was tested for compatibility with external defibrillation, high power electric fields and diagnostic ultrasound (see Table 5). The implanted SCS system (CLS and leads) was evaluated for effects on its function and programming by exposure to the medical therapies that may occur on a patient during or after implantation of an Evoke System. Functional testing was

performed on each CLS before exposure to confirm that it meets all of its performance requirements, and where appropriate, each was monitored during exposure. Functional testing was then performed post exposure to confirm that the CLS still met all functional requirements, and that the exposure to medical therapy had no effect on device performance, program, or stored calibrations. All samples met all functional requirements of the testing after exposure to medical therapy conditions, verifying that the CLS meets requirements for compatibility with these therapies.

Table 5. Summary of Key CLS Medical Compatibility Testing

Test	Acceptance Criteria
External Defibrillator Test	System meets functional electrical test requirements after exposure to external defibrillation per ISO 14708-1, clause 20.2
High Power Electrical Fields Test	System meets requirements of ISO 14708-1, clause 21
Diagnostic Ultrasound Test	System meets requirements of ISO 14708-1, clause 22.1

B. Animal Studies

1. Recording and Measurement of Evoked Spinal Cord Potentials in Ovine: An Acute Study – First Sheep Study

This study was approved by the animal ethics committee at the University of Melbourne (Melbourne, Victoria, Australia). The purpose of this study was to determine if an evoked response can be measured from the spinal cord. A total of 6 sheep were evaluated in this study. Electrodes were connected to a TDT (Tucker-Davis Technologies, Fl. USA) RZ5 amplifier and bio-processor system and a WPI (World Precision Instruments, Fl. USA) A385 current source. The evoked response was measured after directly stimulating the electrodes in the spinal canal or after stimulating the periphery either electrically or mechanically. Clear evoked responses were measured after stimulating the spinal cord. This study demonstrated that it was possible to record ECAP signals directly from the lead being used to apply the stimulation and characterized neurophysiological properties of nerve fibres activated during SCS in sheep.

2. Recording and Measurement of Evoked Spinal Cord Potentials in Ovine: An Acute Study – MCS Sheep Study

The study was approved by the ethics committee (ACEC) at the Royal North Shore Hospital (Sydney, New South Wales, Australia). The purpose of this study was to further characterize the neurophysiological properties of dorsal column fibres and to evaluate a custom stimulator and recording system (NICTA Multi-

channel stimulation and recording system (MCS); NICTA Implant Systems/Saluda Medical, Sydney Australia). Experiments aimed at understanding properties of the dorsal columns included measuring conduction velocities, rheobase, chronaxie, and refractory periods. Preliminary testing of feedback control was also performed. Twenty-seven sheep were evaluated acutely under this protocol. This study demonstrated the ability to measure ECAPs with the NICTA system in sheep and characterized the neurophysiological properties of nerve fibres activated during SCS in sheep. The results of this study are published in Parker et al. (2013) (2).

C. Biocompatibility

Biocompatibility was evaluated for all user- and patient-contacting components of the Evoke SCS System in accordance with ISO 10993-1 Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process. FDA's 2016 Biocompatibility Guidance "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process'" was also followed. Testing was conducted in compliance with Good Laboratory Practices (GLP), 21 CFR Part 58, on finished, sterilized devices or representative samples reflecting all materials and manufacturing processes. The implanted components of the Evoke SCS System are considered long-term (> 30 days) implants in contact with tissue/bone. The Evoke SCS System also contains external communicating components with limited (≤ 24 hours) tissue/bone contact and skin-contacting component with limited to long-term (≤ 24 hours to over 30 days) contact. The biocompatibility test data are summarized in Table 6 below.

Table 6. Biocompatibility Test Data on the Implantable, External Communicating, and Skin-Contacting Components of the Evoke SCS System

Biological Effect (Applicable Standard)	Test Method	Results
Implanted (long-term)[a], External Communicating (limited)[b], and Skin-contacting (limited to long-term)[c] Components:		
Cytotoxicity (ISO 10993-5)	MEM Elution Cytotoxicity Assay (implant & external communicating components, and skin-contacting component with long-term contact*)	Non - cytotoxic
	Agar Overlay Cytotoxicity Assay (skin-contacting components)	Non-cytotoxic**
Sensitization (ISO 10993-10)	Guinea Pig Maximization Test (implant & external communicating components, and skin-contacting component with long-term contact*)	Non-sensitizing
	Closed-Patch (Buehler) Test (skin-contacting components)	

Irritation or Intracutaneous Reactivity (ISO 10993-10)	Intracutaneous Reactivity Test (implant & external communicating components, and skin-contacting component with long-term contact*)	Non-irritant
	Skin Irritation Test (skin-contacting components)	
Implanted (Long-term)[a] and External Communicating (limited)[b] Components		
Systemic Toxicity (ISO 10993-11) Material-Mediated Pyrogenicity USP <151>	Material-Mediated Pyrogenicity Test	Non-pyrogenic
Systemic Toxicity (ISO 10993-11) Acute	Acute Systemic Toxicity Test	No acute systemic toxicity
Implanted (long-term)[a] Components		
Systemic Toxicity (ISO 10993-11) Subacute Subchronic, Chronic	13-week Rabbit Subcutaneous Implantation / Systemic Toxicity Study	Acceptable systemic toxicity risks
	Chemical characterization and toxicological Risk Assessment	
Genotoxicity (ISO 10993-3)	Bacterial Reverse Mutation Assay (Ames Test)	Non-genotoxic
	In Vitro Mouse Lymphoma Assay	
	Chemical characterization and toxicological risk assessment	
Local Effects after Implantation (ISO 10993-6)	4-week Rabbit Subcutaneous Implantation Study	Acceptable implantation risks
	13-week Rabbit Subcutaneous Implantation Study	
	90-day Ovine Implantation Study	
Carcinogenicity (ISO 10993-3)	Chemical characterization and toxicological risk assessment	Non-carcinogenetic

[a] Components tested: Evoke Closed Loop Stimulator, Lead, Lead Extension, Port Plug, Lead Anchor
[b] Components tested: Tunneling Tool, Epidural Needle, Torque Wrench
[c] Component tested: Evoke Charger, Pocket Console, Case, Belt Strap, Belt Pouch
* Evoke Pocket Console is an intact skin-contacting component with prolonged (>24 hours, < 30 days) contact
** For assessment of cytotoxicity risk from the Belt Strap, the testing data as well as use of the belt strap materials in US legally marketed devices were considered.

D. Sterility and Packaging

The Evoke SCS System components that are provided sterile are terminally sterilized using a 100% ethylene oxide (EO) sterilization cycle. Validation of the sterilization process demonstrates a Sterility Assurance Level (SAL) of 10^{-6} and complies 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 10993-7: 2008. *Biological Evaluation of Medical Devices – Part 7: Ethylene Oxide Sterilization Residuals*.

The product bacterial endotoxin limits were chosen based on FDA's *Guidance for Industry - Pyrogen and Endotoxins Testing: Questions and Answers (*June 2012) and were verified using Limulus Amoebocyte Lysate (LAL) testing.

Packaging and shelf- life validation tests were completed in compliance with ISO 11607:2006 *Packaging for Terminally Sterilized Medical Devices.* A shelf-life of two years has been established for the CLS and one year has been established for the other sterile system components.

E. Usability Testing

Patient and clinician usability testing were conducted per IEC 62366-1: 2015-02 *Medical Devices – Part 1: Application of usability Engineering to medical devices* to verify users' ability to perform those tasks for which failure to properly perform them could lead to death or serious injury. Usability aspects of tasks required for the overall safe and effective use of the device, but not posing serious risk to the user was also performed by patients and health care providers. System usability testing was completed successfully with no critical user errors identified in any of the use environments.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the Evoke System for treatment of chronic, intractable pain of the trunk and/or limbs in the US under Investigational Device Exemption (IDE) #G150266. A summary of the clinical study is presented below.

Additionally, long-term safety and effectiveness of the Evoke System is supported by a clinical study performed in Australia (Avalon study) and is summarized in section XI.A.

A. Study Design

The Evoke pivotal clinical study was a prospective, multicenter, randomized, double-blind, clinical trial. The study was designed to compare the use of ECAP-controlled, closed-loop stimulation to open-loop stimulation. The Evoke System open-loop stimulation mode is equivalent to other commercially available SCS systems. Because the Evoke System additionally features the ability to measure ECAPs in both open- and closed-loop stimulation modes, use of the Evoke System in both treatment groups allowed for a more direct comparison of spinal cord activation between groups. Thus, the study population was randomized to either the Evoke System closed-loop stimulation mode (Investigational group) or to open-loop stimulation (representative of treatment with commercially available SCS systems) using the Evoke System open-loop stimulation mode (Control group). Spinal cord activation was measured via ECAPs in both treatment groups.

Subjects, Investigators, and investigational site staff were blinded to the treatment assignment (double-blind). Subjects were randomized in a 1:1 ratio to the treatment arms and a frequentist statistical analysis was performed. The primary objective of the study was to demonstrate that outcomes related to chronic intractable trunk and/or limb pain were at least as good (non-inferior) when using closed-loop SCS compared to open-loop SCS. Additionally, if non-inferiority was established, the study was designed to further assess the potential superiority of closed-loop SCS for treatment of chronic intractable trunk and/or limb pain compared to open-loop SCS. The required sample size was 120 subjects total (60 subjects in each treatment group). To account for potential drop-out, a total of up to 134 subjects (67 subjects in each treatment group) could be randomized.

An independent, blinded Clinical Events Committee (CEC) reviewed and adjudicated all adverse events occurring in the study. An independent, blinded Medical Monitor provided guidance on the study.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the Evoke study was limited to patients who met the following inclusion criteria:

a. Subject is male or female between the ages of 18 and 80 years.

b. Have been diagnosed with chronic, intractable pain of the trunk and/or limbs, which has been refractory to conservative therapy for a minimum of 6 months.

c. VAS (visual analog scale) leg pain score ≥ 6 cm.

d. VAS back pain score ≥ 6 cm.

e. VAS overall trunk and limb pain score ≥ 6 cm.

f. Be an appropriate candidate for an SCS trial and the surgical procedures required in this study based on the clinical judgment of the Investigator.

g. Prescribed pain medications have been stable for at least 30 days prior to the baseline evaluation.

h. Owestry Disability Index (ODI) score of 41-80 (severely disabled or crippled) out of 100 at the baseline evaluation.

i. Be willing and capable of giving informed consent and able to comply with study-related requirements, procedures, and visits.

j. The subject's primary back pain is located such that lead placement will be in the thoracolumbar region.

Patients were not permitted to enroll in the Evoke study if they met any of the following exclusion criteria:

a. Have a medical condition or pain in other area(s), not intended to be treated with SCS, that could interfere with study procedures, accurate pain reporting, and/or confound evaluation of study endpoints, as determined by the Investigator.

b. Have evidence of an active disruptive psychological or psychiatric disorder or other known condition significant enough to impact perception of pain, compliance of intervention, and/or ability to evaluate treatment outcomes.

c. Are not a surgical candidate due to a diagnosis of an uncontrolled coagulation disorder, bleeding diathesis, progressive peripheral vascular disease, uncontrolled diabetes mellitus, or morbid obesity.

d. Have an existing drug pump and/or SCS system or another active implantable device such as a pacemaker, deep brain stimulator (DBS), or sacral nerve stimulator (SNS).

e. Have prior experience with SCS.

f. Have a condition currently requiring or likely to require the use of MRI or diathermy.

g. Have a life expectancy of less than 1 year.

h. Have an active systemic infection or local infection in the area of the surgical site.

i. Be allergic, or have shown hypersensitivity, to any materials of the neurostimulation system which come in contact with the body.

j. Be pregnant or nursing (if female and sexually active, subject must be using a reliable form of birth control, be surgically sterile, or be at least 2 years post-menopausal).

k. Have a documented history of substance abuse (narcotics, alcohol, etc.) or substance dependency in the 6 months prior to the baseline evaluation.

l. Be concomitantly participating in another clinical study.

m. Be involved in an injury claim under current litigation or have pending/approved worker's compensation claim.

n. Had surgery and/or interventional procedure to treat back and/or leg pain within 90 days (if surgery) and 30 days (if any other procedure) prior to the baseline evaluation.

o. Subject is a prisoner.

p. Being treated with electroconvulsive therapy (ECT) or transcranial magnetic stimulation (rTMS).

q. Subject is unwilling or unable to discontinue and remain off of any medication used to treat chronic pain that is not FDA approved for chronic pain.

r. Subject has pain due to peripheral vascular disease or angina.

s. Subject is on anticoagulation therapy that would preclude their ability to undergo the implant procedure.

2. Follow-up Schedule

All subjects first underwent a trial with the external trial stimulator to determine eligibility for the permanent implant. Randomization occurred following trial lead placement. Subjects who had at least a 50% reduction compared to baseline in overall trunk and limb pain as measured by a Visual Analog Scale (VAS) at the end of the trial were approved to receive a permanent implant. Other preoperative assessments are described in Table 7. All subjects were scheduled to return postoperatively at 1-, 3-, 6-, 9-, and 12-months after implantation and biannually thereafter for up to 3 years. Postoperative assessments are described in Table 8. Adverse events and complications were recorded at all visits. The key timepoints are shown below in the tables summarizing safety and effectiveness.

Table 7. Pre- and Intraoperative Visit Schedule (Baseline through Implant Procedure)

Assessment	Screening/ Baseline	Trial Procedure	Trial End (≤30 days)	Implant Procedure (Day 0)
Informed Consent	X			
Inclusion/Exclusion	X			
Baseline Evaluation (Demographics, Medical History, Physical Exam, Psychological Evaluation)	X			
Pain Medication/ Therapies	X	X	X	X
Procedure/X-rays		X	[X]	X
Programming		X		X
Pain Assessment (Visual Analog Scale (VAS) & Pain Map)	X		X	
Pain Diary	X			
Oswestry Disability Index (ODI)	X			
Short Form Health Survey (SF-12)	X			
EuroQoL (EQ-5D-5L)	X			
Profile of Mood States (POMS)	X			
Pittsburgh Sleep Quality Index (PSQI)	X			
Adverse Event Monitoring	X	X	X	X
Study Exit			X[1]	

[X] = Optional
[1]A Study Exit form was completed for all enrolled (i.e., randomized) subjects at the time of study exit (i.e., study completion or early withdrawal).

Table 8. Postoperative Visit Schedule (Follow-up)

Assessment	1 Month[1]	3 Month[1]	6 Month[1]	9 Month[1]	12 Month[1]	18, 24, 30, & 36 Month[1]
Telephone Follow-up	X	X	X	X	X	X
Pain Medication/ Therapies	X	X	X	X	X	X
Procedure/X-rays	[X]	[X]	[X]	[X]	[X]	[X]
Programming	[X]	[X]	[X]	[X]	[X]	[X]
Pain Assessment (Visual Analog Scale (VAS) & Pain Map)	X	X	X	X	X	X
Pain Diary	X	X	X		X	X
Oswestry Disability Index (ODI)	X	X	X		X	X
Short Form Health Survey (SF-12)	X	X	X		X	X
EQ-5D-5L	X	X	X		X	X
Profile of Mood States (POMS)	X	X	X		X	X
Pittsburgh Sleep Quality Index (PSQI)	X	X	X		X	X
Patient Global Impression of Change (PGIC) & Patient Satisfaction	X	X	X		X	X
Posture Change Assessment	X	X	X		X	X
Stimulation Characteristics		X			X	X
Blinding Assessments		X			X	
Adverse Event Monitoring	X	X	X	X	X	X
Study Exit						X[2]

[X] = Optional
[1]Visit Windows: 1-Month (30 days ± 14 days), 3-Month (90 days ± 14 days), 6-Month (180 days ± 30 days), 9-Month (270 days ± 30 days), 12-Month (365 days ± 30 days), 18-month (545±90 days), 24-month (730±90 days), 30-month (910±90 days), and 36-month (1095±90 days)
[2]A Study Exit form was completed for all enrolled (i.e., randomized) subjects at the time of study exit (i.e., study completion or early withdrawal).

3. Clinical Endpoints

Primary Effectiveness Endpoint

The primary endpoint was a composite of the percentage of subjects that experienced a 50% or greater reduction in average overall trunk and limb pain at the primary endpoint visit (3-month) and had no increase in baseline pain medications within 4 weeks of the primary endpoint visit.

The primary analysis was conducted at the 3-month follow-up and an additional pre-defined analysis was completed at the 12-month follow-up.

Individual Subject Success

An individual subject was considered a primary composite endpoint success if the subject:

- Experienced at least 50% pain relief in average overall trunk and limb pain as measured by a 100 mm Visual Analogue Scale (VAS) at 3-month visit; and

- No increase in baseline pain medications within 4 weeks of the primary endpoint visit.

  Subjects who increase their baseline pain medications under the following conditions were considered a failure for this component of the primary endpoint:
  - An increase in morphine equivalent units (MEU) of a baseline opioid within 4 weeks of primary endpoint visit.
    - Exceptions: temporary increase to treat post-procedure pain or an acute co-morbidity unrelated to the study indication that was not expected to respond to SCS.
  - An increase from baseline in non-opiate pain medication used to treat their study indication pain for a duration of greater than 5 days that was not stopped within 4 weeks of primary endpoint visit.
    - Exceptions: Tylenol/rescue medication was allowed up to two weeks prior to the primary endpoint visit.

Study Success

Study success was defined as the percentage of subjects who met the criteria for Individual Subject Success in the closed-loop (Investigational) group compared to the open-loop (Control) group, using a 10% non-inferiority margin. If non-inferiority was achieved at a one-sided alpha of 0.05, a two-sided superiority test was performed at the significance level of 0.05.

Hierarchical Secondary Effectiveness Endpoints

If non-inferiority was met in the testing of the primary composite endpoint, the following secondary endpoints were successively evaluated (hierarchical test approach) in the order shown using a 10% non-inferiority margin with a 0.05 significance level until statistical significance was not achieved. All four secondary endpoints were initially tested at 3 months. If all four secondary endpoints passed non-inferiority at the 3-month analysis, hierarchical testing continued at 12 months in the same order specified below until a hypothesis test failed. All secondary endpoints that passed their non-inferiority test were tested for superiority, first at 3-months and then at 12-months. P-values adjusted for multiple comparisons (via the Hochberg method) are provided for the tests of superiority.

a. Comparison of percentage change from baseline in average leg pain (as assessed by VAS) between Investigational and Control groups at the primary endpoint visit.

b. Comparison of percentage change from baseline in average back pain (as assessed by VAS) between Investigational and Control groups at the primary endpoint visit.

c. Comparison of incidence of ≥80% reduction in average overall trunk and limb pain (as assessed by VAS) between Investigational and Control groups at the primary endpoint visit.

d. Comparison of incidence of ≥50% reduction in average back pain (as assessed by VAS) between Investigational and Control groups at the primary endpoint visit.

Additional Secondary Endpoints

A number of additional secondary endpoints were also collected and assessed across study visits. These endpoints include the following:

a. Comprehensive summary of all Adverse Events (AEs)

b. Change, percent change, incidence of ≥50% ("responders") and ≥80% ("high responders") reduction, and cumulative proportion of responders analysis in VAS pain scores

c. Pain Map

Data were collected by asking subjects to shade in the areas where they were experiencing pain on a body map drawing. These data were used to record the location of the pain being treated with the SCS system.

d. Pain Diary

Data on pain variability were collected through subject completion of a pain diary.

e. Oswestry Disability Index (ODI)

f. Short Form Health Survey (SF-12)

g. EQ-5D-5L

h. Profile of Mood States Brief (POMS)

i. Pittsburgh Sleep Quality Index (PSQI)

j. Patient Global Impression of Change (PGIC)

Data on patient global impression of change were collected as a single item measure of global improvement with treatment using a 7-point rating scale containing the options "very much improved", "much improved", "minimally improved", "no change", "minimally worse", "much worse", and "very much worse".

k. Patient Satisfaction

Data on subject satisfaction with the therapy and pain relief ("very satisfied," "satisfied," "neither satisfied nor unsatisfied," "unsatisfied," and "very unsatisfied") along with likelihood of recommending the therapy ("strongly recommend," "recommend," "neutral," "not recommend," and "definitely not recommend") were collected.

l. Posture Change Assessment

Data on spinal cord (SC) activation (ECAP amplitude) and the subjects' perception of stimulation intensity (11-point numeric scale, from 0 representing "No Feeling" to 10 "Very Intense" based on a published paresthesia intensity rating scale (3)) were collected in different postures in-clinic to mimic activities of daily living (i.e., coughing, lying down, and sitting).

m. Stimulation Characteristics

Data on subjects' general stimulation sensation and experience, including usage, perception of paresthesia, stimulation management strategies, and interaction with the device, were collected.

n. Programming and Neurophysiologic Properties

Programming parameters collected for each program during programming sessions included:

- Frequency (Hz)
- Pulse Width (μs)
- Stimulation Current Amplitude (mA)
- Measured Sensitivity (i.e., rate of change of the ECAP amplitude per unit input current (μV/mA))

Neurophysiological properties collected during programming sessions included:

- ECAP waveform features: ECAP amplitude, width, slope, and shape.
- Conduction Velocity: the speed at which an ECAP propagates along a neural pathway (m/s).
- Rheobase: the minimum stimulus current needed for neural activation at an infinitely long pulse width (mA).
- Chronaxie: the minimum pulse width needed for neural activation at twice the rheobase current (μs).
- Late Responses: neural responses resulting from dorsal root activation.

The ECAP amplitude is representative of the number of spinal cord (SC) fibers activated by stimulation (4). The Evoke System produces an ECAP amplitude for each stimulus and stores the ECAP amplitudes as histogram data. The ECAP amplitude histograms are an objective measure of the SC activation in response to spinal cord stimulation over time. The ECAP amplitude histograms were characterized by some key statistics to elucidate any differences in SC activation between closed-loop (Investigational) and open-loop (Control) stimulation. These include:

- Mode ECAP Amplitude: is a measure of the most frequent SC activation level for a given histogram period.
- Ratio of the Mode ECAP Amplitude to the Comfort Level ECAP Amplitude (mode/comfort level): is a measure of how close the most frequent SC activation level is to the comfort level. A value closer to 1 is indicative of SC activation near or at the comfort level.
- Ratio of the Interdecile ECAP Amplitude Range to the Median ECAP Amplitude ($(90^{th}$ percentile – 10^{th} percentile)/median): is a measure of the spread of the ECAP amplitude histogram where lower values mean that the spread of the distribution is tighter around the median.

The therapeutic range of SC activation is defined by the ECAP amplitudes between patient perception threshold and maximum (i.e., therapeutic window).

- Patient Perception Threshold: the SC activation level the patient first feels a change in sensation (e.g., paresthesia, pain relief).
- Comfort Level: the SC activation level perceived as comfortable by the patient.
- Maximum Level: the SC activation level the patient can withstand (or tolerate) for approximately one minute.

The percent time the subjects' SC activation was within the therapeutic window was calculated. Refer to Figure 2 for theoretical examples of ECAP amplitude represented as histogram data (normal and non-normal distribution) and how statistical measures from these histograms may be used to describe SC activation for a patient.

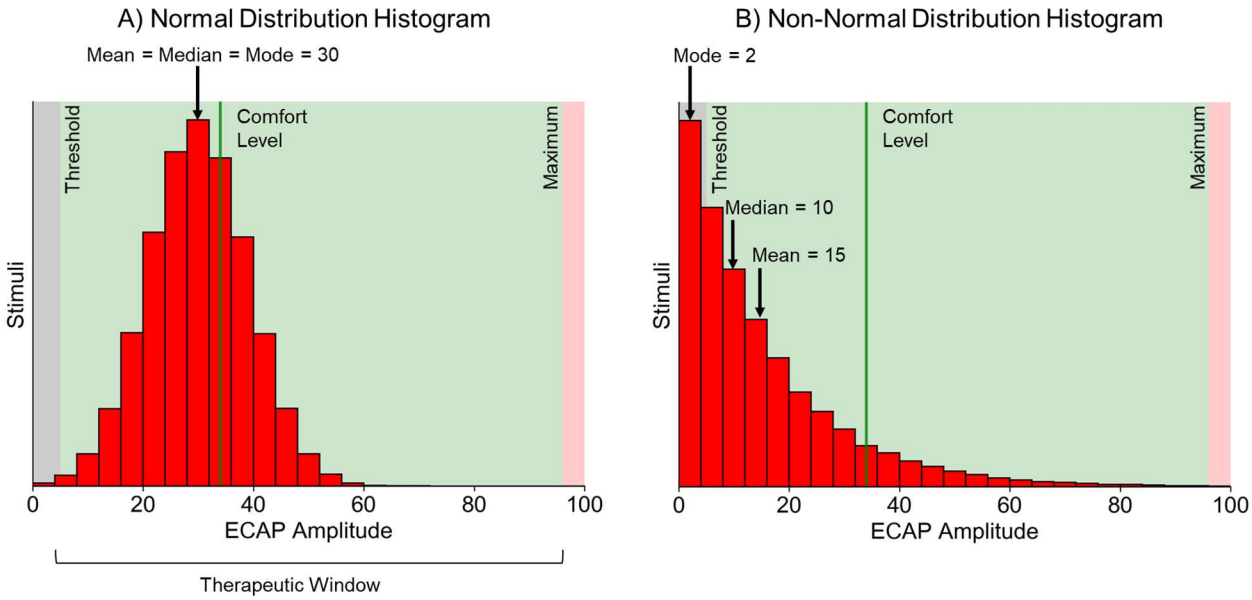

Figure 2. Theoretical Examples of ECAP Amplitude Histogram Statistics

Safety Endpoint

The incidence and characteristics of all adverse events were evaluated for the entire study population and also compared between treatment groups.

Analysis Populations

The primary analysis population, as prespecified in the Statistical Analysis Plan (SAP) was the Intention-To-Treat (ITT) analysis dataset, which included all randomized subjects with known endpoint status or classified as a presumed non-responder.

Additionally, the SAP prespecified an additional analysis population to assess study outcomes. The Permanent Implant Subset (PIS), a subset of the ITT analysis dataset, included the subjects in the ITT population who received a permanent implant.

The following events eliciting missing data at 3 months caused a subject to be classified as a presumed non-responder:

- Failure of the trial stimulation phase (<50% improvement in average overall trunk and limb pain VAS).
- Subject voluntary withdrawal due to an AE adjudicated as related to the device or stimulation.

- Investigator withdrawal due to an AE adjudicated as related to the device or stimulation.

Additionally, a subject was considered a presumed non-responder after 3 months if they withdrew due to lack of efficacy.

Presumed non-responders were analyzed as failures for the primary endpoint, hierarchical secondary endpoint, and other secondary endpoint VAS incidence measures. For hierarchical secondary endpoint and other secondary endpoint in-clinic VAS continuous measures, subjects with missing data categorized as presumed non-responders utilized a last-value carried forward imputation methodology. Subjects that failed the medication component of the primary endpoint had a change from baseline value of "0" imputed for the hierarchical secondary endpoint calculations.

B. Accountability of PMA Cohort

Patients were enrolled and randomized in the Evoke study between February 21, 2017 and February 20, 2018. The database for this PMA reflected data collected through April 1, 2019 and included 134 subjects (67 Investigational subjects, 67 Control subjects) from 13 investigational sites. All patients had passed through the 12-month window, and the study was in follow-up. The ITT population included 125 subjects (62 Investigational subjects, 63 Control subjects) at 3 months (timing of primary endpoint analysis) that were randomized and had known endpoint status (58 Investigational, 53 Control) or were classified as a presumed non-responder (4 Investigational, 10 Control), and 118 subjects at 12 months that were randomized and had known endpoint status (55 Investigational subjects, 48 Control subjects) or were classified as a presumed non-responder (4 Investigational subjects, 11 Control subjects).

Of the 125 subjects in the ITT population, 111 subjects (58 Investigational subjects, 53 Control subjects) received a permanent implant and were included in the PIS analysis set at 3 months. Fourteen randomized subjects failed the trial procedure (4 Investigational subjects, 10 Control subjects) and were therefore excluded from the PIS analysis dataset. At 12 months, there were 104 subjects (55 Investigational subjects, 49 Control subjects) in the PIS analysis dataset.

See Figure 3 for a flow diagram of subject accountability.

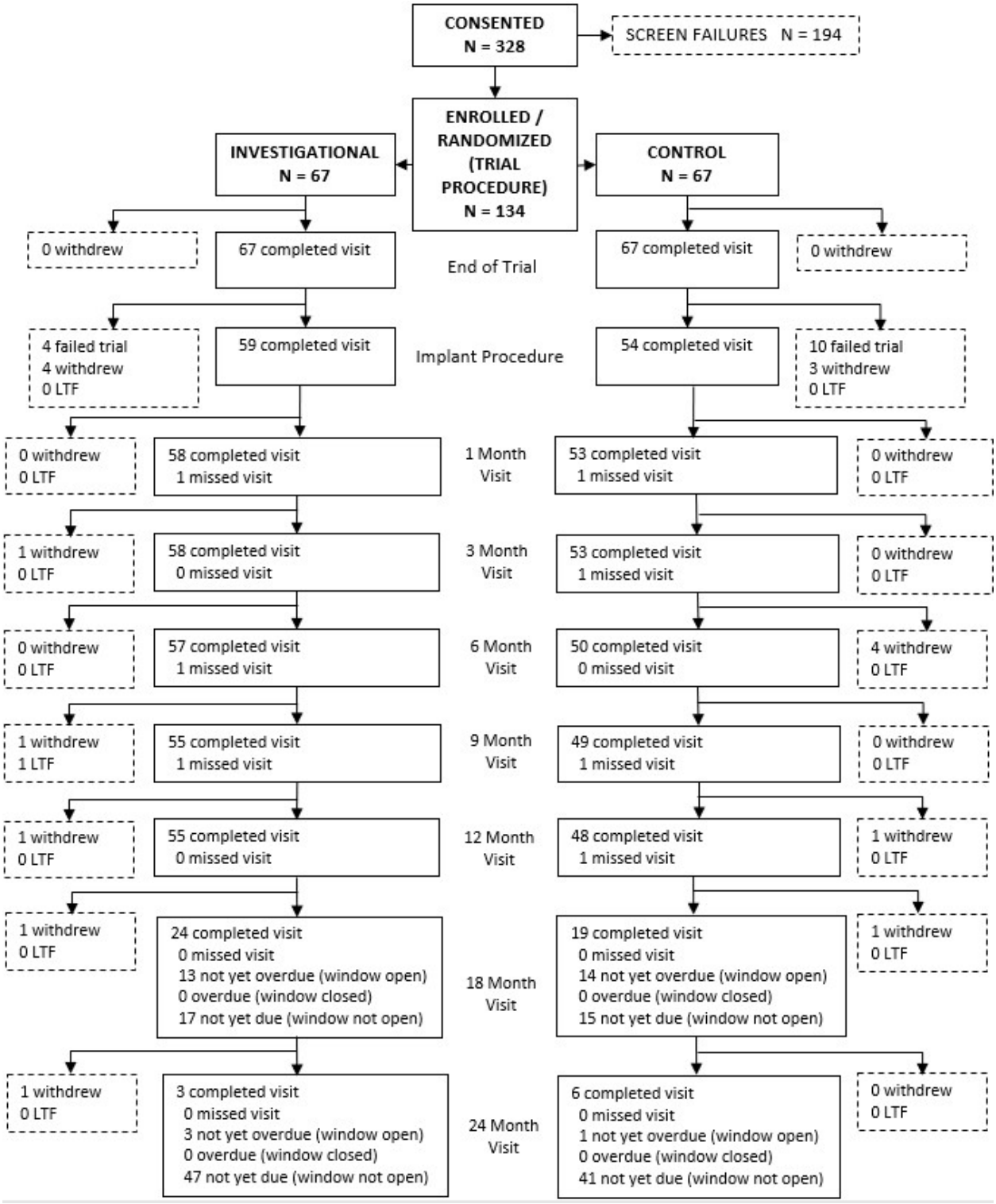

Figure 3. Subject Accountability

C. Study Population Demographics and Baseline Parameters

Table 9 presents information on key baseline demographics and characteristics. There were no statistically significant differences in baseline demographics and characteristics between treatment groups, indicating that the randomization resulted in balanced groups, supporting the validity of comparisons between the groups. The demographics of the study population are typical for a study of this type performed in the US.

Table 9. Baseline Demographics and Characteristics – Randomized

Characteristic	Investigational N=67 Subjects	Control N=67 Subjects	P-value
Age (years)			
Mean (SD)	54.6 (9.7)	55.9 (11.6)	0.490
Min., Max.	28.7, 80.1	24.8, 80.8	
Gender (n (%))			
Male	34 (50.7%)	35 (52.2%)	1.000
Female	33 (49.3%)	32 (47.8%)	
Race (not mutually exclusive) (n (%))			
American Indian or Alaska Native	1 (1.5%)	2 (3.0%)	
Asian	0 (0.0%)	0 (0.0%)	
Black or African American	2 (3.0%)	6 (9.0%)	
Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	
White	63 (94.0%)	59 (88.1%)	0.365[1]
Other[2]	0 (0.0%)	2 (3.0%)	
Ethnicity (n (%))			
Hispanic/Latino	3 (4.5%)	6 (9.0%)	0.492
Non-Hispanic/Latino	64 (95.5%)	61 (91.0%)	
BMI (kg/m^2)			
Mean (SD)	31.3 (5.7)	32.4 (6.8)	0.335
Min., Max.	18.3, 46.2	17.5, 48.5	

Characteristic	Investigational N=67 Subjects	Control N=67 Subjects	P-value
Duration of Pain (years)			
Mean (SD)	13.6 (9.6)	11.2 (9.9)	0.151
Min., Max.	0.5, 41.4	0.7, 46.0	
Pain Location (n (%))			
Chronic Intractable Back Pain	67 (100%)	67 (100%)	
Chronic Intractable Leg Pain	67 (100%)	67 (100%)	
Unilateral	24 (35.8%)	28 (41.8%)	0.595[3]
Bilateral	43 (64.2%)	39 (58.2%)	
Pain Etiology (not mutually exclusive) (n (%))			
Arachnoiditis	0 (0.0%)	2 (3.0%)	0.496
Complex Regional Pain Syndrome (CRPS) I	0 (0.0%)	1 (1.5%)	1.000
Degenerative Disc Disease	33 (49.3%)	42 (62.7%)	0.164
Failed Back Surgery Syndrome (FBSS)	38 (56.7%)	41 (61.2%)	0.726
Internal Disc Disruption or Tear / Discogenic Pain	7 (10.4%)	10 (14.9%)	0.605
Lumbar Facet-Mediated Pain	8 (11.9%)	8 (11.9%)	1.000
Mild-Moderate Spinal Stenosis	26 (38.8%)	27 (40.3%)	1.000
Neuropathic Pain	1 (1.5%)	1 (1.5%)	1.000
Radiculopathy	61 (91.0%)	59 (88.1%)	0.779
Sacroiliac Joint-Mediated Pain	9 (13.4%)	5 (7.5%)	0.398
Spondylolisthesis	6 (9.0%)	5 (7.5%)	1.000
Spondylosis with Myelopathy	2 (3.0%)	3 (4.5%)	1.000
Spondylosis without Myelopathy	26 (38.8%)	24 (35.8%)	0.858
Other Chronic Pain	6 (9.0%)	3 (4.5%)	0.492
Baseline Pain Medication Usage	63 (94.0%)	59 (88.1%)	0.365

Characteristic	Investigational N=67 Subjects	Control N=67 Subjects	P-value
Opioids	41 (61.2%)	40 (59.7%)	1.000
Non-opioids[4]	51 (76.1%)	52 (77.6%)	1.000
Previous Non-Invasive Therapies[5]	65 (97.0%)	64 (95.5%)	1.000
Previous Interventional Procedure[6]	63 (94.0%)	62 (92.5%)	1.000
Previous Back Surgery[7]	39 (58.2%)	41 (61.2%)	0.860

Two-sample t-test between treatment groups for continuous variables; Fisher's exact test between treatment groups for categorical variables.
[1]Comparison of white versus non-white races.
[2]The 'Other' races included Middle Eastern (1) and Latino (1).
[3]Comparison of unilateral versus bilateral leg pain.
[4]Non-opioid pain medication classes include: anticonvulsant, antidepressant, local anesthetic, muscle relaxant, and NSAIDs
[5]Non-invasive therapies include: acupuncture, aquatherapy, assistive device, biofeedback, chiropractic care, exercise therapy, massage therapy, psychotherapy, physical therapy, transcutaneous electro-nerve stimulator (TENS)
[6]Interventional procedures include: ankle surgery, benign cyst removal, block/injection – other, epidural steroid injection, facet joint injection, intradiscal procedure (e.g., Intradiscal Electrothermal Therapy (IDET)), lumbar rhizotomy, lumbar sympathetic block, medial branch block, radiofrequency denervation, sacroiliac joint injection, trigger point injection
[7]Back surgeries include: artificial disc replacement, discectomy or microdiscectomy, foraminotomy, kyphoplasty and vertebroplasty, laminectomy, nucleoplasty (e.g., disc decompression, laser surgery), spinal fusion, back surgery – not otherwise specified, back surgery – other

1. Study Execution

Aside from the difference in stimulation mode, subjects in both treatment groups received the same care, with the device, implant procedure, and programming process being the same for both groups. There were no statistically significant differences between groups in procedure duration or lead placement for the trial or permanent implant procedures. All programming parameters were chosen using the process outlined in the Evoke Clinical Manual. Programming in both groups utilized ECAP measurement in addition to subject feedback to optimize patient outcomes. The only difference in programming was enabling (Investigational) or disabling (Control) the feedback loop. There were no statistically significant differences between groups in the frequency of programming visits, programming duration, and programming parameters (Table 10). Both treatment groups used the device the majority of the time with no statistically significant differences in usage between groups.

Table 10. Summary of Programming Parameters – ITT

Parameter	Investigational	Control	P-value
Stimulation Frequency (Hz)			
Mean (SD)	41.7 (16.6)	42.3 (13.6)	0.850

Parameter	Investigational	Control	P-value
Min., Max.	10.0, 180.0	10.0, 90.0	
Pulse Width (µs)			
Mean (SD)	308.9 (83.2)	296.9 (76.8)	0.660
Min., Max.	80.0, 740.0	100.0, 800.0	
Processing Offset (µs)			
Mean (SD)	182.9 (117.9)	176.7 (80.2)	0.662
Min., Max.	61.0, 2441.0	61.0, 610.0	
Filter Frequency (Hz)			
Mean (SD)	951.1 (135.9)	970.9 (182.8)	0.147
Min., Max.	565.0, 1928.0	565.0, 1928.0	
Patient Sensitivity* (µV/mA)			
Mean (SD)	98.9 (111.5)	--	--
Min., Max.	6.0, 1000.0	--	
Target Amplitude† (µV)			
Mean (SD)	49.5 (59.4)	--	--
Min., Max.	0.0, 348.1	--	

Repeated measures mixed model for difference between groups.
**Patient Sensitivity is used to set up the loop for the closed-loop (Investigational) therapy; is not relevant to the open-loop (Control) therapy.*
†Target Amplitude is set to the preferred level using the EPC during daily use by the patient for closed-loop (Investigational) therapy; is not relevant to the open-loop (Control) therapy. It is represented here by the Mode of the ECAP amplitude histogram collected prior to the 12-month visit.

Furthermore, at 3 and 12 months the subjects' electrophysiological measurements in both groups were statistically equivalent, demonstrating the ability of stimulation to recruit nerve fibers and produce action potentials (ECAP amplitude and other features), activate the same fiber types (conduction velocity), and produce comparable axonal excitability (rheobase) and membrane time constant (chronaxie) (Table 11). These data indicate that the randomization generated directly comparable treatment groups with respect to neurophysiology. On average, the conduction velocity was approximately 60 m/s in both treatment groups, which is within the literature reported range for Aβ sensory fibers (5).

Table 11. Summary of Neurophysiological Property Measurements at 3 and 12 Months – ITT

	3 Month			12 Month		
	Investigational	**Control**	**P-value**	**Investigational**	**Control**	**P-value**
Conduction Velocity (m/s)						
Median	57.3	58.9	0.430	60.2	58.9	0.996
Min., Max.	45.1, 93.2	42.0, 82.9		43.3, 84.2	45.2, 86.2	
Chronaxie (µs)						
Median	359.5	311.0	0.181	306.6	236.2	0.259
Min., Max.	75.7, 684.0	78.0, 866.7		116.9, 609.0	89.4, 633.4	
Rheobase (mA)						
Median	2.8	2.9	0.676	2.9	2.8	0.725
Min., Max.	0.7, 6.0	1.0, 9.9		1.1, 6.8	1.0, 6.9	

Kruskal-Wallis test between treatment groups.

Lastly, the double-blind design was maintained with no deviations in blinding, reducing the potential of data being systematically distorted by knowledge of the treatment received. The extent to which the characteristics of the treatment arms are statistically comparable and the robustness with which the study was executed and operationalized supports the strength of the study conclusions.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on all randomized subjects (134 subjects total; 67 Investigational subjects, 67 Control subjects), and included all adverse events reported and adjudicated as of database lock. On average, Investigational subjects had a permanent implant for 16.3 (±3.8) months and Control subjects had a permanent implant for 16.2 (±4.8) months (mean ± SD). The cumulative implant months of experience for subjects that received a permanent implant was 959.0 months (79.8 years) in the Investigational group and 874.9 months (72.8 years) in the Control group.

Key safety outcomes are presented below in **Error! Reference source not found.** through Table 17.
As all subjects received the same investigational device, underwent the same trial and permanent implant procedures, and received active stimulation. The characteristics of the adverse events are presented by treatment group and treatment groups combined (total) (**Error! Reference source not found.**), and by treatment groups combined only for the incidence of adverse event types (Table 13 through Table 17). Adverse events are reported according to the CEC adjudication. An adverse event was classified as 'study-related' if it was possibly or definitely related to the procedure, device, or stimulation therapy. The Clinical Events Committee guidelines were used to determine if an adverse event was definitely related, possibly related, or unrelated to the study.

The characteristics of all adverse events occurring in the study are presented by treatment group and by treatment groups combined (total) in **Error! Reference source not found.**. The type, nature, and severity of adverse events were similar between groups. No unanticipated serious adverse device effects (UADEs) occurred in this study as of database lock. There has been one death (cardiac arrest), unrelated to the study.

Table 12. Characteristics of All Adverse Events – Randomized

	Investigational N=67 Subjects		**Control N=67 Subjects**		**TOTAL N=134 Subjects**	
Characteristic	**Events n**	**Subjects n (%)**	**Events n**	**Subjects n (%)**	**Events n**	**Subjects n (%)**
Total Adverse Events	**150**	**45 (67.2%)**	**104**	**45 (67.2%)**	**254**	**90 (67.2%)**
Adverse Event (AE)	134	42 (62.7%)	93	43 (64.2%)	227	85 (63.4%)
Study-related*	22	12 (17.9%)	9	9 (13.4%)	31	21 (15.7%)
Serious Adverse Event (SAE)	16	10 (14.9%)	11	8 (11.9%)	27	18 (13.4%)
Study-related*	1	1 (1.5%)	2	2 (3.0%)	3	3 (2.2%)
Relation to Device						
Unrelated	143	45 (67.2%)	99	44 (65.7%)	242	89 (66.4%)

	Investigational N=67 Subjects		Control N=67 Subjects		TOTAL N=134 Subjects	
Characteristic	**Events n**	**Subjects n (%)**	**Events n**	**Subjects n (%)**	**Events n**	**Subjects n (%)**
Possible	4	4 (6.0%)	3	3 (4.5%)	7	7 (5.2%)
Definite	3	3 (4.5%)	2	2 (3.0%)	5	5 (3.7%)
Relation to Procedure						
Unrelated	133	44 (65.7%)	96	41 (61.2%)	229	85 (63.4%)
Possible	4	3 (4.5%)	3	3 (4.5%)	7	6 (4.5%)
Definite	13	9 (13.4%)	5	5 (7.5%)	18	14 (10.4%)
Relation to Stimulation Therapy						
Unrelated	145	44 (65.7%)	101	43 (64.2%)	246	87 (64.9%)
Possible	4	3 (4.5%)	2	2 (3.0%)	6	5 (3.7%)
Definite	1	1 (1.5%)	1	1 (1.5%)	2	2 (1.5%)
Severity						
Mild	41	27 (40.3%)	32	24 (35.8%)	73	51 (38.1%)
Moderate	87	37 (55.2%)	59	34 (50.7%)	146	71 (53.0%)
Severe	22	14 (20.9%)	13	9 (13.4%)	35	23 (17.2%)
Phase at Onset						
Prior to Trial	5	5 (7.5%)	3	3 (4.5%)	8	8 (6.0%)
Trial Period	1	1 (1.5%)	2	2 (3.0%)	3	3 (2.2%)
End of Trial to Implant	7	6 (9.0%)	6	5 (7.5%)	13	11 (8.2%)

	Investigational N=67 Subjects		Control N=67 Subjects		TOTAL N=134 Subjects	
Characteristic	**Events n**	**Subjects n (%)**	**Events n**	**Subjects n (%)**	**Events n**	**Subjects n (%)**
Implant to 30 Days	12	11 (16.4%)	9	7 (10.4%)	21	18 (13.4%)
>30 days to 90 Days	26	17 (25.4%)	20	19 (28.4%)	46	36 (26.9%)
>90 Days to 365 Days	68	33 (49.3%)	51	29 (43.3%)	119	62 (46.3%)
>365 Days	31	16 (23.9%)	13	11 (16.4%)	44	27 (20.1%)
Outcome						
Ongoing	36	22 (32.8%)	28	21 (31.3%)	64	43 (32.1%)
Resolved without sequelae	99	35 (52.2%)	62	33 (49.3%)	161	68 (50.7%)
Resolved with sequelae	15	10 (14.9%)	14	9 (13.4%)	29	19 (14.2%)
Unanticipated Adverse Device Effect (UADE)[1]	**0**	**0 (0.0%)**	**0**	**0 (0.0%)**	**0**	**0 (0.0%)**

[1]An unanticipated adverse device effect (UADE) was defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

** An adverse event was classified as 'study-related' if it was possibly or definitely related to the procedure, device, or stimulation therapy.*

Serious Adverse Events

Table 13 presents the study-related serious adverse events by treatment groups combined (total). Three serious adverse events in three subjects (1 Investigational and 2 Control) were study-related (2.2%); none were stimulation related. All three serious study-related serious adverse events occurred within 30 days of the procedure. These events included wound infection, epidural abscess, and lead breakage/fracture.

Table 13. Summary of Study-Related Serious Adverse Events – Randomized

	Total N=134 Subjects	
Preferred Term	**Events n**	**Subjects n (%)**
Total Adverse Events	**3**	**3 (2.2%)**
Epidural Abscess	1	1 (0.7%)
Lead Breakage/Fracture	1	1 (0.7%)
Wound Infection	1	1 (0.7%)

Table 14 presents the serious adverse events by treatment groups combined (total). Among the 134 randomized subjects, a total of 27 serious adverse events (SAEs) in 18 subjects (13.4%) were reported (16 SAEs, 14.9% Investigational subjects; 11 SAEs, 11.9% Control subjects). Eighteen of the 27 (66.7%) serious adverse events were classified as severe. At the time of database lock three SAEs were still ongoing (3/27 = 11.1%).

Table 14. Summary of Serious Adverse Events – Randomized

	Total N=134 Subjects	
Preferred Term	**Events n**	**Subjects n (%)**
Total Adverse Events	**27**	**18 (13.4%)**
Cellulitis	3	2 (1.5%)
Arrhythmia and Irregularities	2	2 (1.5%)
Abdominal Pain	1	1 (0.7%)
Anxiety Disorders	1	1 (0.7%)
Arthritis	1	1 (0.7%)
Benign Prostatic Hypertrophy	1	1 (0.7%)
Cardiac Chest Pain	1	1 (0.7%)
Cholecystitis	1	1 (0.7%)
Coronary Artery or Heart Disease	1	1 (0.7%)

	Total N=134 Subjects	
Preferred Term	**Events n**	**Subjects n (%)**
Dehydration	1	1 (0.7%)
Diverticulitis	1	1 (0.7%)
Epidural Abscess	1	1 (0.7%)
Facet Cyst	1	1 (0.7%)
Fall or Trip or Slip or Twist	1	1 (0.7%)
Lead Breakage/Fracture	1	1 (0.7%)
Liver Abscess	1	1 (0.7%)
MRSA	1	1 (0.7%)
Myocardial Infarct or Heart Attack	1	1 (0.7%)
Peripheral Vascular Disease	1	1 (0.7%)
Prostate Cancer	1	1 (0.7%)
Renal Insufficiency	1	1 (0.7%)
Suicidal Ideation or Attempt	1	1 (0.7%)
Transient Ischemic Attack	1	1 (0.7%)
Wound Infection	1	1 (0.7%)

All Adverse Events

Table 15 presents the study-related adverse events by treatment groups combined (total). There were no differences between treatment groups in study-related (device, procedure and/or stimulation therapy) adverse events. As both treatment groups received the same device and underwent the same procedure, as expected there were no differences between groups in device- and procedure-related adverse events. Importantly, there were no differences in stimulation therapy-related adverse events.

Among the 134 randomized subjects, a total of 34 study-related adverse events (AEs) in 24 subjects (17.9%) were reported. The Investigational group had 23 study-related adverse events in 13 subjects (19.4%; 95% CI: 10.8, 30.9) and the Control group had 11 study-related adverse events in 11 subjects (16.4%; 95% CI:

8.5, 27.5). The most frequently reported study-related adverse events in both treatment groups were lead migrations (6.7%), IPG pocket pain (3.7%), and muscle spasm or cramp (2.2%). There were five stimulation therapy-related events in four Investigational subjects (6.0%; 95% CI: 1.7, 14.6) and three stimulation therapy-related events in three Control subjects (4.5%; 95% CI: 0.9, 12.5).

Table 15. Summary of Study-Related Adverse Events – Randomized

	Total N=134 Subjects	
Preferred Term	**Events n**	**Subjects n (%)**
Total Adverse Events	**34**	**24 (17.9%)**
Lead Migration	10	9 (6.7%)
IPG Pocket Pain	5	5 (3.7%)
Muscle Spasm or Muscle Cramp	3	3 (2.2%)
Dural Puncture or Tear	2	2 (1.5%)
IPG Malfunction due to Electrocautery	2	2 (1.5%)
Unwanted Stimulation Location	2	2 (1.5%)
Wound Infection	2	2 (1.5%)
Dysesthesia - Lower Extremity	1	1 (0.7%)
Epidural Abscess	1	1 (0.7%)
Inadequate Lead Placement	1	1 (0.7%)
Lead Breakage/Fracture	1	1 (0.7%)
Low Back Pain	1	1 (0.7%)
Nausea and/or vomiting	1	1 (0.7%)
Skin Irritation or Redness	1	1 (0.7%)
Wound Dehiscence	1	1 (0.7%)

Table 16 presents all adverse events for treatment groups combined (total). Among the 134 randomized subjects, a total of 254 adverse events (AEs) in 90 subjects (67.2%) were reported (150 AEs, 67.2% Investigational subjects; 104

AEs, 67.2% Control subjects). The majority of all adverse events (219/254 = 86.2%) were classified as mild or moderate in severity with only 13.8% (35/254) being considered severe for 23 subjects (17.2%). At the time of database lock, of the 254 adverse events, 64 were still ongoing (25.2%), and 190 AEs were resolved (74.8%).

Table 16. Summary of All Adverse Events – Randomized

	Total N=134 Subjects	
Preferred Term	**Events n**	**Subjects n (%)**
Total Adverse Events	**254**	**90 (67.2%)**
Fall or Trip or Slip or Twist	22	18 (13.4%)
Upper Respiratory Symptoms or Upper Respiratory Tract Infection	18	14 (10.4%)
Lead Migration	10	9 (6.7%)
Bronchitis	6	5 (3.7%)
IPG Pocket Pain	5	5 (3.7%)
Bursitis	5	4 (3.0%)
Cellulitis	5	4 (3.0%)
Motor Vehicle Accident	5	4 (3.0%)
Sinus Infection or Sinusitis	5	4 (3.0%)
Anxiety Disorders	4	4 (3.0%)
Ear Infection	4	4 (3.0%)
Unilateral Leg Pain	4	4 (3.0%)
Nausea and/or vomiting	4	3 (2.2%)
Abdominal Pain	3	3 (2.2%)
Arrhythmia and Irregularities	3	3 (2.2%)
Arthritis	3	3 (2.2%)
Hip Joint Pain	3	3 (2.2%)
Muscle Spasm or Muscle Cramp	3	3 (2.2%)

	Total N=134 Subjects	
Preferred Term	**Events n**	**Subjects n (%)**
Peripheral Neuropathy - Lower Extremity	3	3 (2.2%)
Radiculopathy - Lower Extremity	3	3 (2.2%)
Upper Extremity Pain	3	3 (2.2%)
Activities of Daily Living (ADL) Injury	3	2 (1.5%)
Knee Pain	3	2 (1.5%)
Abnormal Blood Chemistry	2	2 (1.5%)
Bladder Infection	2	2 (1.5%)
Bone Fracture	2	2 (1.5%)
Bone Spur	2	2 (1.5%)
Cardiac Chest Pain	2	2 (1.5%)
Dental Issues	2	2 (1.5%)
Diarrhea	2	2 (1.5%)
Disc Bulge or Protrusion	2	2 (1.5%)
Dural Puncture or Tear	2	2 (1.5%)
Dysesthesia - Lower Extremity	2	2 (1.5%)
Facet joint deterioration	2	2 (1.5%)
Foot Pain	2	2 (1.5%)
Gastroenteritis	2	2 (1.5%)
Headache	2	2 (1.5%)
IPG Malfunction due to Electrocautery	2	2 (1.5%)
Neck or Cervical Pain	2	2 (1.5%)
Peripheral Vascular Disease	2	2 (1.5%)
Prostate Cancer	2	2 (1.5%)
Pulled or Strained Muscle	2	2 (1.5%)

	Total N=134 Subjects	
Preferred Term	**Events n**	**Subjects n (%)**
Restless Leg Syndrome	2	2 (1.5%)
SI Joint Pain	2	2 (1.5%)
Sacroiliitis	2	2 (1.5%)
Skin Infection	2	2 (1.5%)
Skin Rash	2	2 (1.5%)
Spinal Stenosis	2	2 (1.5%)
Syncope or Fainting	2	2 (1.5%)
Tremor - Upper Extremity	2	2 (1.5%)
Trigger Finger or Stenosing Tenosynovitis	2	2 (1.5%)
Unwanted Stimulation Location	2	2 (1.5%)
Wound Infection	2	2 (1.5%)
Back Pain and Bilateral Radiation into Legs	2	1 (0.7%)
MRSA	2	1 (0.7%)
Abnormal Uterine Bleeding	1	1 (0.7%)
Acne	1	1 (0.7%)
Adrenal Nodule	1	1 (0.7%)
Alopecia	1	1 (0.7%)
Ankylosing Spondylitis	1	1 (0.7%)
Back Pain	1	1 (0.7%)
Back and Upper Extremities Pain	1	1 (0.7%)
Benign Prostatic Hypertrophy	1	1 (0.7%)
COPD (Chronic Obstructive Pulmonary Disease)	1	1 (0.7%)
Cholecystitis	1	1 (0.7%)
Chronic Pain Syndrome	1	1 (0.7%)

	Total N=134 Subjects	
Preferred Term	**Events n**	**Subjects n (%)**
Cirrhosis or Fatty Liver	1	1 (0.7%)
Coccydynia	1	1 (0.7%)
Coronary Artery or Heart Disease	1	1 (0.7%)
Dehydration	1	1 (0.7%)
Diverticulitis	1	1 (0.7%)
Diverticulosis	1	1 (0.7%)
Edema - Lower Extremities	1	1 (0.7%)
Epidural Abscess	1	1 (0.7%)
Erythema	1	1 (0.7%)
Eye Infection	1	1 (0.7%)
Eye Injury or Pain	1	1 (0.7%)
Facet Cyst	1	1 (0.7%)
Fibromyalgia	1	1 (0.7%)
Forgetfulness or Memory Loss	1	1 (0.7%)
Gastritis	1	1 (0.7%)
Hypertension	1	1 (0.7%)
Impaired Balance	1	1 (0.7%)
Inadequate Lead Placement	1	1 (0.7%)
Incontinence	1	1 (0.7%)
Joint Disorders or Injury	1	1 (0.7%)
Kidney Stone	1	1 (0.7%)
Lead Breakage/Fracture	1	1 (0.7%)
Leukemia	1	1 (0.7%)
Liver Abscess	1	1 (0.7%)

	Total N=134 Subjects	
Preferred Term	**Events n**	**Subjects n (%)**
Low Back Pain	1	1 (0.7%)
Lytic Lesion(s)	1	1 (0.7%)
Macromastia	1	1 (0.7%)
Migraine	1	1 (0.7%)
Myocardial Infarct or Heart Attack	1	1 (0.7%)
Myofascial Pain Syndrome	1	1 (0.7%)
Osteoporosis	1	1 (0.7%)
Overdose	1	1 (0.7%)
Peripheral Neuropathy - Upper Extremity	1	1 (0.7%)
Plantar fasciitis	1	1 (0.7%)
Pneumonia	1	1 (0.7%)
Radiculopathy - Upper Extremity	1	1 (0.7%)
Renal Cyst	1	1 (0.7%)
Renal Insufficiency	1	1 (0.7%)
Shingles	1	1 (0.7%)
Sinus Problems - Other	1	1 (0.7%)
Skin Irritation or Redness	1	1 (0.7%)
Strep Throat	1	1 (0.7%)
Stroke	1	1 (0.7%)
Suicidal Ideation or Attempt	1	1 (0.7%)
Throat Adenoma NOS	1	1 (0.7%)
Thryoid Adenoma	1	1 (0.7%)
Tinnitis	1	1 (0.7%)
Tooth Infection	1	1 (0.7%)

	Total N=134 Subjects	
Preferred Term	**Events n**	**Subjects n (%)**
Transient Ischemic Attack	1	1 (0.7%)
Weakness - Lower Extremity	1	1 (0.7%)
Weakness - Upper Extremity	1	1 (0.7%)
Wound Dehiscence	1	1 (0.7%)

Subsequent Surgical Procedures

Table 17 presents a summary of implanted device replacements, revisions, and explants by treatment groups combined (total). There were a total of 22 subsequent surgical procedures; 13 procedures in nine Investigational subjects and nine procedures in eight Control subjects. Four Investigational subjects and five Control subjects underwent system explants. All nine subjects exited the study following explant.

Table 17. Subsequent Revision, Replacement, or Explant Procedures – Randomized

	Total N=134 subjects	
Subsequent Procedure	**Events N**	**Subjects n (%)**
Revision - Implant Phase		
Lead(s)	1	1 (0.7%)
CLS	1	1 (0.7%)
System	1	1 (0.7%)
Replacement - Implant Phase		
Lead(s)	7	7 (5.2%)
CLS	2	2 (1.5%)
System	1	1 (0.7%)

	Total N=134 subjects	
Subsequent Procedure	**Events N**	**Subjects n (%)**
System Explant - Implant Phase[1]	**9**	**9 (6.7%)**

[1]Reasons for system explant included: wound infection, epidural abscess, lead migration resulting in physician order to replace with paddle lead (Saluda Medical paddle lead not yet available), required MRI, lack of efficacy, and patient request.

2. Effectiveness Results

The analysis of effectiveness was based on the ITT population. The primary analysis occurred at 3 months and included 125 subjects total (62 Investigational subjects, 63 Control subjects). An additional analysis was completed at 12 months and included 118 subjects total (59 Investigational subjects, 59 control subjects). Key effectiveness outcomes are presented below in Table 18 through Table 24.

Primary Composite Endpoint Primary (ITT) Analysis

The primary composite endpoint, which assessed pain improvement without increase in baseline pain medications, successfully demonstrated non-inferiority (prespecified 10% non-inferiority margin; p-value < 0.001) of closed-loop stimulation (Investigational) to open-loop stimulation (Control) (Table 18 and Figure 4) at 3 and 12 months. In total, 82.3% of Investigational subjects compared to 60.3% of the Control subjects at 3 months, and 83.1% of Investigational subjects compared to 61.0% of Control subjects at 12 months, met the criteria for Individual Subject Success. As non-inferiority was successfully established, superiority was also evaluated. The results of the study successfully demonstrated that closed-loop stimulation was superior to open-loop stimulation at 3 months (p-value = 0.005) and 12 months (p-value = 0.006).

Table 18. Primary Composite Endpoint Treatment Success at 3 and 12 Months - ITT

	3 Month		12 Month	
Primary Endpoint Component	**Investigational**	**Control**	**Investigational**	**Control**
Number of Subjects - ITT	**62**	**63**	**59**	**59**
Overall Primary Endpoint Success				
n/N (%)	51/62 (82.3%)	38/63 (60.3%)	49/59 (83.1%)	36/59 (61.0%)

	3 Month		12 Month	
Primary Endpoint Component	**Investigational**	**Control**	**Investigational**	**Control**
95% CI	(72.7%, 91.8%)	(48.2%, 72.4%)	(73.5%, 92.6%)	(48.6%, 73.5%)
Success rate difference (%) and 95% CI	21.9% (6.6%, 37.3%)		22.0% (6.3%, 37.7%)	
P-value (non-inferiority $\delta = 10\%$)	<0.001		<0.001	
P-value (superiority)	0.005		0.006	
Primary Endpoint Failures (n)	**11**	**25**	**10**	**23**
<50% overall trunk and limb pain relief at follow-up visit*	7	14	4	9
Increase in baseline pain medications within 4 weeks of the follow-up visit*	0	3	2	6
Presumed non-responders	4	10	4	11

**Not mutually exclusive.*
Normal approximation to binomial test.

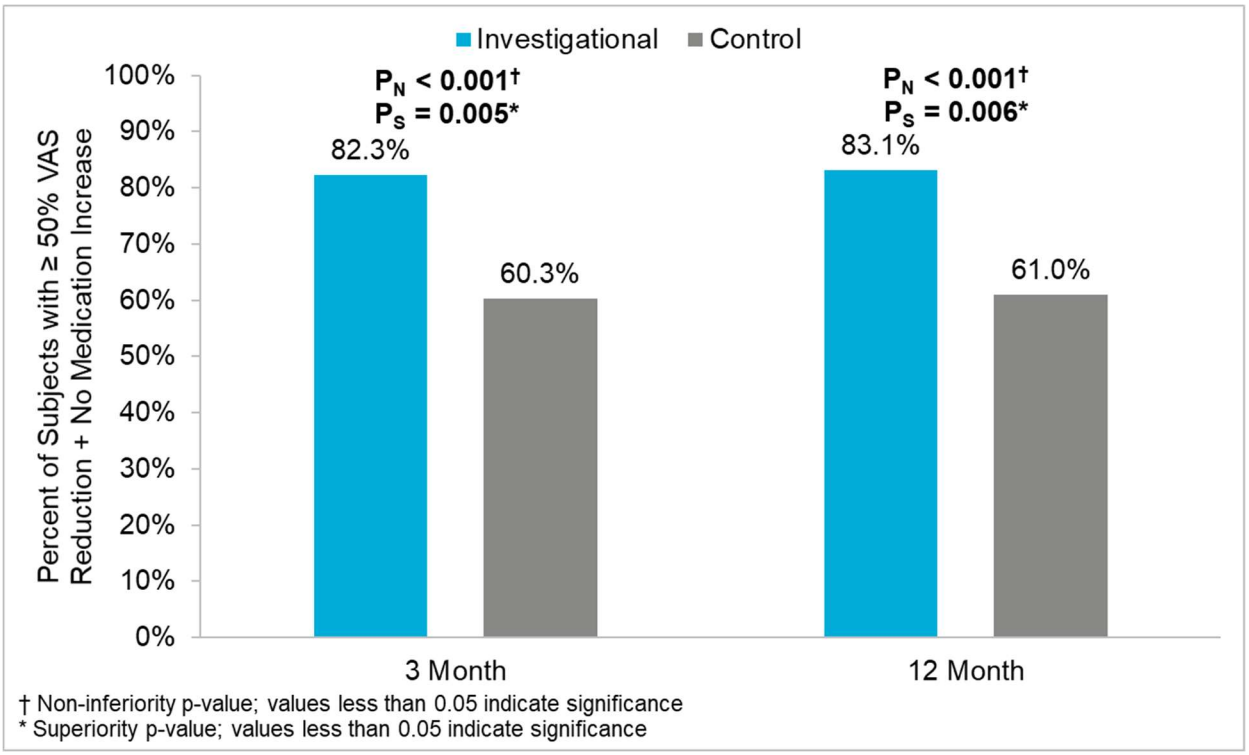

Figure 4. Primary Composite Endpoint Treatment Success at 3 and 12 Months – ITT

Primary Composite Endpoint PIS Analysis

As noted above, the primary composite endpoint was also assessed in the PIS analysis population. This analysis allowed for a more specific assessment of the performance of closed-loop stimulation in the group of study subjects who actually received the permanent implant and underwent the full course of treatment. In the PIS analysis population, 87.9% of Investigational subjects compared to 71.7% of Control subjects at 3 months, and 89.1% of Investigational subjects compared to 73.5% of Control subjects at 12 months, met the Individual Subject Success criteria (Table 19). These results successfully demonstrated both non-inferiority (prespecified 10% non-inferiority margin; p-value <0.001) and superiority (3 months: p-value = 0.031; 12 months: p-value = 0.039) of closed-loop stimulation (Investigational) to open-loop stimulation (Control) at 3 and 12 months. The consistency of the outcomes of the primary endpoint analysis using the ITT population and the PIS population confirms the robustness of the study conclusions.

Table 19. Primary Composite Endpoint Treatment Success at 3 and 12 Months - PIS

	3 Month		12 Month	
Primary Endpoint Component	**Investigational**	**Control**	**Investigational**	**Control**
Number of Subjects - PIS	**58**	**53**	**55**	**49**
Overall Primary Endpoint Success				
n/N (%)	51/58 (87.9%)	38/53 (71.7%)	49/55 (89.1%)	36/49 (73.5%)
95% CI	(79.5%, 96.3%)	(59.6%, 83.8%)	(80.9%, 97.3%)	(61.1%, 85.8%)
Success rate difference (%) and 95% CI	16.2% (1.5%, 31.0%)		15.6% (0.8%, 30.5%)	
P-value (non-inferiority $\delta = 10\%$)	<0.001		<0.001	
P-value (superiority)	0.031		0.039	
Primary Endpoint Failures (n)	**7**	**15**	**6**	**13**
<50% overall trunk and limb pain relief at follow-up visit*	7	14	4	9
Increase in baseline pain medications within 4 weeks of the follow-up visit*	0	3	2	6
Presumed non-responders	0	0	0	1

**Not mutually exclusive.*
Normal approximation to binomial test.

Hierarchical Secondary Endpoints

All predefined, hierarchical secondary endpoints demonstrated non-inferiority of closed-loop (Investigational) to open-loop (Control) stimulation. While outcomes were also numerically better in the closed-loop group across all of these measures, closed-loop stimulation was statistically superior to open-loop stimulation in the percentage change in VAS average back pain at 3 months and the incidence of ≥50% reduction in VAS average back pain at 3 and 12 months. These results further support the robust pain improvements demonstrated by those treated with closed-loop stimulation, indicating that this form of stimulation provides a meaningful clinical benefit as compared to the existing, commercially available, SCS options.

The first hierarchical secondary endpoint, percentage change in VAS average leg pain, successfully demonstrated non-inferiority of closed-loop stimulation (Investigational) to open-loop stimulation (Control) at 3 and 12 months (prespecified 10% non-inferiority margin; p-value < 0.001) (Table 20). Mean percentage change in VAS average leg pain was 76.8% in the Investigational group compared to 67.8% in the Control group at 3 months, and 72.9% in the Investigational group compared to 62.1% in the Control group at 12 months.

Table 20. Percentage Change in VAS Average Leg Pain at 3 and 12 Months – ITT

	3 Month		12 Month	
Hierarchal Secondary Endpoint	**Investigational**	**Control**	**Investigational**	**Control**
Number of Subjects - ITT	**62**	**63**	**59**	**59**
Percent Reduction in VAS Leg Pain				
Mean (SD)	76.8 (28.3)	67.8 (35.5)	72.9 (31.0)	62.1 (37.5)
Median	87.9	81.7	85.6	75.4
Min., Max.	-10.4, 100.0	-9.1, 100.0	-10.4, 100.0	-6.4, 100.0
Difference between means and 95% CI	9.0 (-2.4, 20.4)		10.7 (-1.8, 23.3)	
P-value (non-inferiority δ = 10%)	<0.001		<0.001	
P-value (superiority, adjusted*)	0.119		0.093	

**Hochberg procedure.*
two-sample t-test

The second hierarchical secondary endpoint, percentage change in VAS average back pain, successfully demonstrated non-inferiority at 3 and 12 months (prespecified 10% non-inferiority margin; p-value < 0.001) and superiority at 3 months (p-value = 0.045) of closed-loop stimulation (Investigational) to open-loop stimulation (Control) (Table 21). Mean percentage change in VAS average back pain was 72.1% in the Investigational group compared to 57.5% in the Control group at 3 months, and 69.4% in the Investigational group compared to 54.0% in the Control group at 12 months.

Table 21. Percentage Change in VAS Average Back Pain at 3 and 12 Months – ITT

	3 Month		12 Month	
Hierarchal Secondary Endpoint	**Investigational**	**Control**	**Investigational**	**Control**
Number of Subjects - ITT	**62**	**63**	**59**	**59**
Percent Reduction in VAS Back Pain				
Mean (SD)	72.1 (29.4)	57.5 (36.4)	69.4 (30.6)	54.0 (39.5)
Median	85.4	64.9	81.1	62.7
Min., Max.	-4.2, 100.0	-16.2, 100.0	-4.2, 100.0	-16.2, 100.0
Difference between means and 95% CI	14.6 (2.9, 26.3)		15.4 (2.5, 28.3)	
P-value (non-inferiority $\delta = 10\%$)	<0.001		<0.001	
P-value (superiority, adjusted*)	0.045		0.059	

**Hochberg procedure.*
two-sample t-test

The third hierarchical secondary endpoint, incidence of ≥80% reduction (prespecified in the study protocol as high responders) in VAS average overall trunk and limb pain, successfully demonstrated non-inferiority of closed-loop stimulation (Investigational) to open-loop stimulation (Control) at 3 and 12 months (prespecified 10% non-inferiority margin; 3 months: p-value = 0.002; 12-months: p-value < 0.001) (Table 22, Figure 5, and Figure 6). 58.1% of Investigational subjects compared to 42.9% of Control subjects met the endpoint at 3 months, and 55.9% of Investigational subjects compared to 37.3% of Control subjects met the endpoint at 12 months.

Table 22. Incidence of ≥80% Reduction in VAS Average Overall Trunk and Limb Pain at 3 and 12 Months – ITT

	3 Month		12 Month	
Hierarchal Secondary Endpoint	**Investigational**	**Control**	**Investigational**	**Control**
Number of Subjects - ITT	**62**	**63**	**59**	**59**

	3 Month		12 Month	
Hierarchal Secondary Endpoint	**Investigational**	**Control**	**Investigational**	**Control**
Incidence of ≥ 80% Reduction in VAS Overall Trunk and Limb Pain				
n/N (%)	36/62 (58.1%)	27/63 (42.9%)	33/59 (55.9%)	22/59 (37.3%)
95% CI	(45.8%, 70.3%)	(30.6%, 55.1%)	(43.3%, 68.6%)	(24.9%, 49.6%)
Success rate difference (%) and 95% CI	15.2% (-2.1%, 32.5%)		18.6% (1.0%, 36.3%)	
P-value (non-inferiority $\delta = 10\%$)	0.002		<0.001	
P-value (superiority, adjusted*)	0.119		0.078	

**Hochberg procedure.*
normal approximation to binomial test

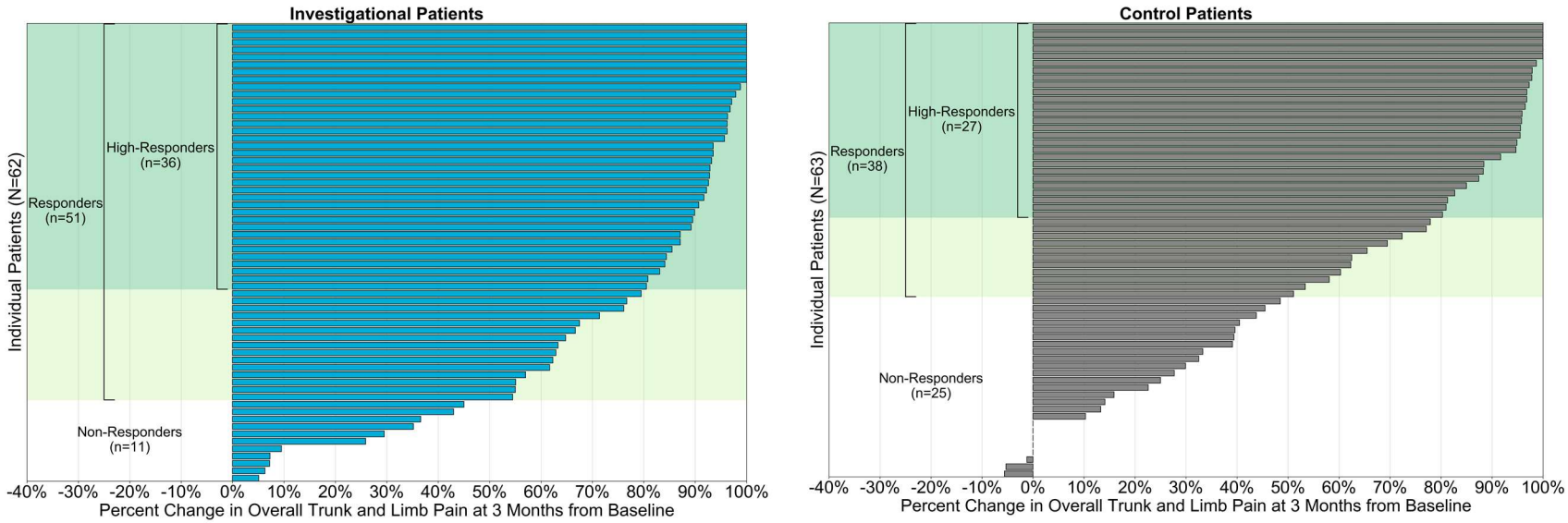

Figure 5. Individual Percent Change from Baseline in In-Clinic VAS Average Overall Trunk and Limb Pain Scores at 3 Months – ITT

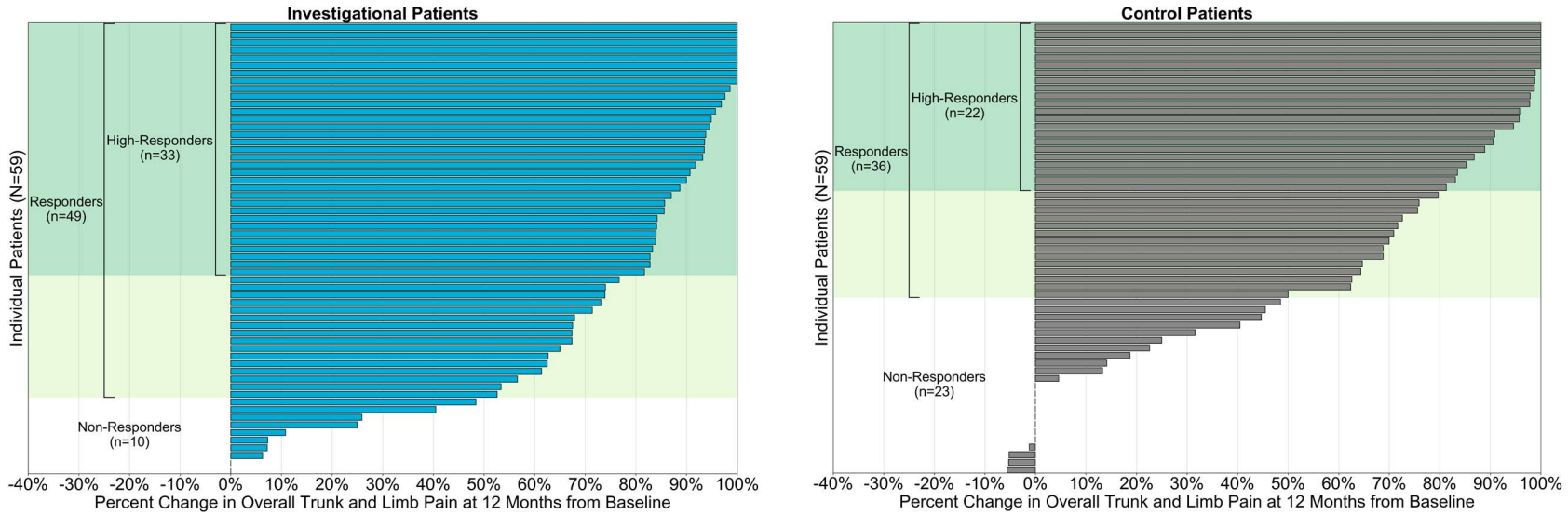

Figure 6. Individual Percent Change from Baseline in In-Clinic VAS Average Overall Trunk and Limb Pain Scores at 12 Months - ITT

The fourth hierarchical secondary endpoint, incidence of ≥50% reduction (responder) in VAS average back pain, successfully demonstrated non-inferiority (prespecified 10% non-inferiority margin; p-value < 0.001) and superiority (3 months: p-value = 0.013; 12 months: p-value = 0.032) of closed-loop stimulation (Investigational) to open-loop stimulation (Control) at 3 and 12 months (Table 23). 80.6% of Investigational subjects compared to 57.1% of Control subjects met the endpoint at 3 months, and 79.7% of Investigational subjects compared to 57.6% of Control subjects met the endpoint at 12 months.

Table 23. Incidence of ≥50% Reduction in VAS Average Back Pain at 3 and 12 Months – ITT

	3 Month		12 Month	
Hierarchal Secondary Endpoint	**Investigational**	**Control**	**Investigational**	**Control**
Number of Subjects - ITT	**62**	**63**	**59**	**59**
Incidence of ≥ 50% Reduction in VAS Back Pain				
n/N (%)	50/62 (80.6%)	36/63 (57.1%)	47/59 (79.7%)	34/59 (57.6%)
95% CI	(70.8%, 90.5%)	(44.9%, 69.4%)	(69.4%, 89.9%)	(45.0%, 70.2%)
Success rate difference (%) and 95% CI	23.5% (7.8%, 39.2%)		22.0% (5.8%, 38.3%)	
P-value (non-inferiority δ = 10%)	<0.001		<0.001	
P-value (superiority, adjusted*)	0.013		0.032	

**Hochberg procedure.*
normal approximation to binomial test

Additional Secondary Endpoints

A number of additional secondary endpoints were assessed and collectively provide increased evidence in support of the determination of effectiveness drawn from the assessment of the primary and hierarchical secondary endpoints. Table 24 provides a summary of the additional secondary endpoint analyses of patient reported outcome (PRO) measures collected in the Evoke study per the recommendations of IMMPACT (6,7) including pain intensity measured by VAS, functional disability measured by ODI, quality of life measured by SF-12 and EQ-5D-5L, emotional functioning measured by POMS, sleep measured by PSQI, impression of change measured by PGIC, and patient satisfaction. Numerically greater improvements

were observed across these measures in the Investigational group, further supporting the conclusion of efficacy for the closed-loop treatment.

Table 24. Summary Patient Reported Outcome (PRO) Measurements at 3 and 12 Months – ITT

	3 Month		12 Month	
	Investigational	**Control**	**Investigational**	**Control**
Responder Rates (% subjects)				
VAS Back Pain ≥80% Reduction	56.5%	36.5%	50.8%	35.6%
VAS Leg Pain ≥50% Reduction	80.6%	68.3%	83.1%	61.0%
VAS Leg Pain ≥80% Reduction	66.1%	54.0%	55.9%	47.5%
Percent Change from Baseline (mean (SD))[1]				
VAS Overall Pain	73.8 (28.0)	59.4 (35.8)	72.3 (29.0)	56.2 (38.5)
Change from Baseline (mean (SD))[1]				
ODI	30.3 (16.4)	26.5 (15.5)	28.0 (16.3)	26.1 (14.5)
SF-12 PCS	13.9 (9.8)	11.5 (9.4)	11.7 (10.6)	11.6 (9.6)
SF-12 MCS	8.9 (10.4)	1.9 (10.2)	7.4 (12.2)	-0.8 (10.0)
EQ-5D-5L Index Score	0.269 (0.172)	0.256 (0.162)	0.245 (0.194)	0.226 (0.170)
EQ VAS	28.3 (22.7)	22.0 (23.1)	27.1 (23.4)	20.3 (20.7)
POMS TMD	20.2 (21.2)	10.1 (14.1)	21.7 (19.8)	8.9 (14.6)
PSQI	5.7 (4.6)	4.5 (4.0)	5.7 (4.2)	4.5 (4.7)
Clinically Important Change (% subjects)				
ODI[2]	81.0%	79.2%	78.2%	77.1%
SF-12 PCS[3]	81.0%	66.0%	72.7%	72.9%

	3 Month		12 Month	
	Investigational	**Control**	**Investigational**	**Control**
SF-12 MCS[3]	55.2%	28.3%	50.9%	20.8%
EQ-5D-5L Index Score[4]	89.7%	86.8%	85.5%	79.2%
POMS TMD[5]	69.0%	41.5%	70.9%	45.8%
PSQI[6]	75.9%	66.0%	76.4%	62.5%
Other (% subjects)				
ODI Percent Minimal to Moderate Disability[2]	84.5%	77.4%	80.0%	70.8%
Change from Baseline from PSQI Poor to Good Sleep Quality[7,8]	31.6%	28.8%	29.6%	27.7%
PGIC (% much improved or very much improved)	89.7%	81.1%	81.8%	75.0%
Subject Satisfaction with Therapy (% satisfied or very satisfied)	94.8%	86.8%	90.9%	85.4%

Abbreviations: MCS = Mental Component Summary; ODI = Oswestry Disability Index; PCS = Physical Component Summary; PGIC = Patient Global Impression of Change; POMS = Profile of Mood States; PSQI = Pittsburgh Sleep Quality Index; SF-12 = Short Form Health Survey; TMD = Total Mood Disturbance; VAS = Visual Analog Scale

1 Positive change is better.

2 Roland M, Fairbank J. The Roland-Morris Disability Questionnaire and the Oswestry Disability Questionnaire. Spine. 2000 Dec 15;25(24):3115-24.

3 Maruish, M. E. (Ed.). (2012). User's manual for the SF-12v2 Health Survey (3rd ed.). Lincoln, RI: QualityMetric Incorporated.

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8 Does not include subjects who did not qualify for the Baseline condition or who did not have a follow-up.

3. Subgroup Analyses

High Responder Rate (≥80% VAS Pain Score Reduction)

The Evoke Study identified, a priori as a hierarchical secondary endpoint, a high responder threshold of ≥80% for VAS overall trunk and limb pain percent reduction as a way to evaluate high responders who achieved a particularly low level of pain following intervention. The results of that secondary endpoint, described above, demonstrated statistically comparable (i.e., non-inferior) results between groups at 3 and 12 months. Although statistical superiority was not demonstrated, there was a numerically greater percentage of subjects in the closed-loop group that experienced this level of pain relief compared to the control group. Given these results, a post-hoc analysis of the Evoke study data was conducted to evaluate the

clinical meaningfulness of the high responder rate of ≥80% compared to the well-recognized substantial responder rate of ≥50% defined by IMMPACT. Pain relief as well as other domains considered important by chronic pain patients and the clinician/researcher recommended outcome domains identified by IMMPACT were compared between subjects with responder rates ≥50% and <80% ("responders") versus ≥80% ("high responders") at 3 and 12 months (6,7).

Refer to Table 25 for a summary of the statistically significant differences (p-value < 0.05) in patient reported outcome (PRO) measures between responders and high responders (treatment groups combined). As seen in the table, on the PRO measures evaluated (ODI, POMS, and PSQI) at 3 and 12 months, the high responder group had statistically significantly greater improvements in mean scores from baseline and statistically significantly higher proportions of subjects with clinically meaningful changes, as applicable.

This post-hoc analysis is not without limitations. Since it was not pre-specified, the study was not powered to show a difference between these subgroups (i.e., subjects with VAS overall trunk and limb pain reduction ≥50% and <80% vs. ≥80%). However, the majority of the Evoke study ITT population at 3 (90/111 = 81.1%) and 12 months (90/103 = 87.4%) was included in this subgroup analysis. In addition, for all clinically relevant PROs evaluated, high responders showed statistically significantly better results for several of the summary measures supporting the robustness of the conclusions for this sub-analysis.

Table 25. Differences in Patient Reported Outcomes between Responders and High Responders at 3 and 12 Months

	3 Months		12 Months	
Clinically Meaningful and Normal Population Comparisons	**VAS ≥50% and <80%**	**VAS ≥80%**	**VAS ≥50% and <80%**	**VAS ≥80%**
Oswestry Disability Index (ODI) Score				
ODI Mean (SD) Change from Baseline	23.5 (10.5)	36.4 (13.1)	22.9 (16.1)	31.3 (14.4)
ODI Percent Minimal Disability[1,2]	6/27 (22.2%)	41/63 (65.1%)	7/32 (21.9%)	28/58 (48.3%)
Profile of Mood States (POMS) Brief Total Mood Disturbance (TMD) Score[3]				
POMS TMD Mean (SD) Change from Baseline	9.7 (10.0)	20.5 (20.4)	10.3 (17.5)	20.9 (18.4)
POMS TMD Clinically Important Change from Baseline[4]	8/27 (29.6%)	37/63 (58.7%)	12/32 (37.5%)	35/58 (60.3%)
Pittsburgh Sleep Quality Index (PSQI) Score				

	3 Months		12 Months	
Clinically Meaningful and Normal Population Comparisons	**VAS ≥50% and <80%**	**VAS ≥80%**	**VAS ≥50% and <80%**	**VAS ≥80%**
PSQI Mean (SD) Change from Baseline	3.7 (3.6)	6.2 (4.8)	4.4 (4.1)	6.4 (4.4)
PSQI Remission (Good Sleep Quality and Clinically Significant Change)[5]	2/27 (7.4%)	29/63 (46.0%)	4/32 (12.5%)	23/58 (39.7%)
PSQI Change from Baseline from Poor to Good Sleep Quality[6,7]	2/27 (7.4%)	29/61 (47.5%)	5/31 (16.1%)	23/57 (40.4%)
PSQI Change from Non-Normal at Baseline to Normal at Follow-up[7,8]	4/27 (14.8%)	32/61 (52.5%)	5/30 (16.7%)	26/57 (45.6%)

1 Mapi Research Trust. Oswestry Disability Index Scoring Instructions.

2 Evoke Study eligibility criteria required subjects have severe to crippled disability at baseline.

3 POMS Brief normal values are not available.

4 Dworkin, R. H. et al. Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations. J Pain 9, 105–121 (2008).

5 Buysse, D. J. et al. Efficacy of brief behavioral treatment for chronic insomnia in older adults. Arch. Intern. Med. 171, 887–895 (2011).

6 Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R. & Kupfer, D. J. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 28, 193–213 (1989).

7 Does not include subjects who did not qualify for the Baseline condition or who did not have a follow-up.

8 Buysse, D. J. et al. Relationships Between the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and Clinical/Polysomnographic Measures in a Community Sample. J. Clin. Sleep. Med. 4, 563–71 (2008).

Two-sample t-test for continuous variables; Fisher's exact test for categorical variables. P-value < 0.05 indicated statistical significance.

4. Pediatric Extrapolation

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

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 one investigator which was a full-time or part-time employee of the sponsor and 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: one

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

A. Long-term Study Results from an Australian Prospective Study of the Evoke System (Avalon Study)

The Avalon study (ANZCTR Identifier: ACTRN12615000713594) is a prospective, multicenter, single-arm study designed to assess the safety and performance of the Saluda Medical Evoke System closed-loop stimulation for the treatment of chronic, intractable pain of the trunk and/or limbs. This study was approved by each of the four participating centers' ethics committees and performed in accordance with ISO 14155, Declaration of Helsinki, International Conference of Harmonisation (ICH) GCP, and Therapeutic Goods Administration (TGA) applicable regulations and/or guidelines. Subjects who provided informed consent and met the study eligibility criteria underwent a trial with the external trial stimulator to determine if the subject was eligible for the permanent implant. Subjects who had at least a 40% reduction in pain compared to baseline as measured by VAS were approved to receive a permanent implant of the Evoke SCS System. Subjects were followed up at 1-, 3-, 6-, and 12-months following the permanent implant, and quarterly thereafter through 24-months if subjects consented to extended follow-up.

The baseline demographics and characteristics of the Avalon study population were similar to those for the Evoke study population. The mean age of subjects enrolled in the Avalon study was 56.3 years and 50% of subjects were male. The mean body mass index (BMI) at baseline was 30.3 kg/m^2. The mean duration of chronic pain for enrolled subjects was 14.3 years. The predominate primary diagnosis of enrolled subjects was Failed Back Surgery Syndrome/Failed Neck Surgery Syndrome (FBSS/FNSS) (Note: none of the subjects' primary area of pain was the neck or upper extremities), followed by radiculopathy.

Subject enrollment, the primary endpoint analysis, and 24-month follow-up are complete. The first subject was enrolled (i.e., had a trial procedure) in the Avalon study on August 25, 2015 and the first permanent implant occurred on October 13, 2015. There were 70 trial procedures and 50 permanent implant procedures. On average, subjects had a permanent implant for 21.0 months (range, 0.5 to 25.8 months). The cumulative implant months of experience for the subjects that received a permanent implant was 1052.3 months (87.6 years). Of the 50 subjects who received the permanent implant, 49 completed the 1 Month visit, 45 the 3 Month visit, 46 the 6 Month visit, 43 the 12 Month visit, 37 the 15 Month visit, 39 the 18 Month visit, 38 the 21 Month visit, and 38 the 24 Month visit.

This study demonstrated sustained high rates of VAS overall pain reduction through 24 months, with percent reduction from baseline ranging from 71.2% to 81.2%, responder rates (≥50% reduction) ranging from 78.3% to 89.5%, and high responder rates (≥80% reduction) ranging from 42.2% to 69.2% throughout follow-up (Table 26).

The type, rate, nature, and severity of adverse events that have occurred in the Avalon study were consistent and comparable to the Evoke study and to reported adverse events in the literature and from available market data for other SCS systems.

Table 26. Avalon Study VAS Overall Pain Reduction through 24 Months

Overall Pain	3 Month	6 Month	12 Month	15 Month	18 Month	21 Month	24 Month
Number of subjects	45	46	43	37	39	38	38
Mean (SD) Percent Reduction from Baseline	71.2 (27.0)	71.7 (30.5)	73.6 (28.0)	76.3 (28.5)	79.7 (23.1)	77.5 (27.1)	81.2 (24.0)
95% CI	(63.0-79.3)	(62.6-80.8)	(65.0-82.2)	(66.8-85.8)	(72.2-87.2)	(68.6-86.4)	(73.3-89.1)
Responders (≥50% reduction)	80.0%	78.3%	81.4%	81.1%	84.6%	81.6%	89.5%
High Responders (≥80% reduction)	42.2%	52.2%	53.5%	64.9%	69.2%	68.4%	68.4%

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

In accordance with the provisions of section 515(c)(2) 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 Evoke System was based on a double-blind, randomized, controlled, pivotal study (Evoke study) comparing ECAP-controlled, closed-loop SCS to open-loop SCS. The Evoke System is capable of operating either in the open-loop stimulation mode (equivalent to other commercially available SCS systems) or in the closed-loop stimulation mode. The device includes the ability to measure ECAP amplitude (SC activation) in both stimulation modes. Thus, the Evoke System was used in both study groups, facilitating a direct comparison of closed-loop stimulation to open-loop stimulation.

One-hundred and thirty-four (134) subjects were enrolled and randomized (67 in the Investigational [closed-loop] group and 67 in the Control [open-loop] group). Baseline assessments demonstrated treatment groups were well-matched with no statistical differences in demographic and baseline characteristics. Of the 134 subjects randomized, 125 subjects (62 Investigational subjects, 63 Control subjects) had known endpoint status or were classified as a presumed non-responder and were included in the ITT population at 3 months. At 12 months, 118 subjects (59 Investigational subjects, 59 Control subjects) had known endpoint status or were classified as a presumed non-responder and were included in the ITT population.

The results of the primary composite endpoint, which evaluated pain relief in combination with no increase in baseline pain medication, successfully demonstrated both non-inferiority (p-value < 0.001) and superiority (3 months: p-value $= 0.005$; 12 months: p-value $= 0.006$) of ECAP-controlled, closed-loop stimulation to open-loop stimulation. In total, greater than 82% (3 months: 82.3%; 12 months: 83.1%) of Investigational subjects met the primary endpoint individual success criteria compared to approximately 60% (3 months: 60.3%, 12 months: 61.0%) of Control subjects. Additionally, the analysis of the primary endpoint was performed in the PIS population, the subset of subjects in the ITT population with a permanent implant, and demonstrated both non-inferiority (p-value < 0.001) and superiority (3 months: p-value $= 0.031$; 12 months: p-value $= 0.039$) of closed-loop stimulation (3 months: 87.9%; 12 months: 89.1%) to open-loop stimulation (3 months: 71.7%; 12 months: 73.5%), confirming the robustness of the study conclusions. Thus, regardless of the methodology used to analyze the primary endpoint, the results consistently demonstrated superiority in clinical outcomes associated with closed-loop stimulation compared to open-loop stimulation.

Non-inferiority was demonstrated across all of the hierarchical secondary endpoints (p-values ≤ 0.002). In addition, numerically better improvement was consistently observed, with statistical superiority of closed-loop stimulation to open-loop stimulation in the percentage change in VAS average back pain at 3 months (72.1%

Investigational vs. 57.5% Control, p-value = 0.045) and incidence of ≥50% reduction in VAS average back pain at 3 and 12 months (3 months: 80.6% Investigational vs. 57.1% Control, p-value = 0.013; 12 months: 79.7% Investigational vs. 57.6% Control, p-value = 0.032).

Analysis was also conducted to evaluate the extent of SC activation during treatment in the two study groups. This analysis helps to assess the mechanism of action of SCS, providing the clinical explanation for the results observed in the primary and secondary study endpoints. That analysis showed statistically significant differences in spinal cord activation for closed-loop compared to open-loop SCS. The difference in the predefined endpoints between the closed-loop SCS and open-loop SCS appears to be due to the activation of the spinal cord, which can be explained by inhibition of the dorsal horn through modulation of the activity by dorsal column Aβ sensory fibers.

Additionally, long-term effectiveness has been demonstrated with the Evoke System in the Avalon study with VAS overall pain reduction ranging from 71.2% to 81.2%, responder rates (≥50% reduction) ranging from 78.3% to 89.5%, and high responder rates (≥80% reduction) ranging from 42.2% to 69.2% from 3 months to 24 months post-implant.

The results of the clinical studies demonstrate a clinically meaningful reduction in pain with the Evoke System for patients who suffer from chronic, intractable pain of the trunk and/or limbs. In addition, the available data successfully demonstrate that use of closed-loop therapy provides a meaningful clinical benefit and advantage compared to use of open-loop therapy. Given that currently available systems offer only open-loop therapy, the availability of the Evoke System provides an important clinical benefit.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies, as well as data collected in clinical studies conducted to support PMA approval as described above. The risks of the device were also compared to those for other similar commercially available SCS systems.

The type, nature, and severity of adverse events in the clinical studies of the Evoke System were consistent with the published data for other commercially available SCS systems. There have been no UADEs (Evoke study) or USADEs (Avalon study). The study-related adverse events that have been reported are known risks, and the severity and rate are not outside what is expected for SCS systems.

Among the 134 randomized subjects in the Evoke study, a total of 254 adverse events (AEs) in 90 subjects (67.2%) were reported (150 AEs, 67.2% Investigational

subjects; 104 AEs, 67.2% Control subjects). 13.4% of all adverse events were study-related, with 3.1% being related to the stimulation therapy. There were no differences between groups in study-related (device, procedure and/or stimulation therapy) adverse events, or stimulation therapy-related adverse events specifically.

A total of 27 serious adverse events (SAEs) in 18 subjects (13.4%) were reported (16 SAEs, 14.9% Investigational subjects; 11 SAEs, 11.9% Control subjects). None of the serious adverse events were classified as stimulation-related in either treatment group. There were three study-related serious adverse events in three subjects (1 Investigational and 2 Control) (2.2%) including wound infection, epidural abscess, and lead breakage/fracture. These are known risks, and the severity and rate are not outside what is expected for SCS systems.

Additionally, long-term safety has been demonstrated with the Evoke System in the Avalon study with follow-up out to 24 months. The type, rate, nature, and severity of adverse events that have occurred in the Avalon study were consistent and comparable to the Evoke study and to reported adverse events in the literature and from available market data for other SCS systems.

In the Evoke study, measurement of ECAPs was recorded successfully in all Investigational and Control subjects (N=103) and enablement of closed-loop was effective in all Investigational subjects (N=55) at 12 months. In addition, all subjects in the Avalon study who completed the 24-month visit (38 patients) were able to have their stimulator successfully programmed to measure ECAPs and stimulate with closed-loop enabled. There have been no reports of adverse events or discontinued stimulator use due to degradation of ECAP recordings.

C. Benefit-Risk Determination

The probable benefits and risks of the device are based on data collected in the clinical studies conducted to support PMA approval as described above.

Chronic pain is defined as pain that lasts more than three to six months beyond the normal time of healing (16). It results in significant morbidity with tremendous physical, mental, emotional, and financial burden to the individual persons, their families, and society as a whole.

Chronic pain is treated on a continuum, as mentioned above, with first line treatments including conservative care (e.g., physical therapy, acupuncture, biofeedback, non-opioid pain medications), second line treatments that are more intensive (e.g., systemic opioids, injections, nerve blocks), and last line treatments including surgical intervention (e.g., implantable SCS systems, intrathecal drug delivery (IDD) systems, surgical repair of anatomical issues, or surgical techniques to destroy nerve pathways). The risk profile for SCS therapy has advantages compared to reconstructive surgeries and neuroablation due to the fact it is

reversible as the device can be surgically removed. Furthermore, typically patients undergo a trial period with SCS, in which leads are temporarily placed in the epidural space and connected to an external trial stimulator, to assess tolerability (e.g., of the stimulation sensation and the device) and the degree of pain relief prior to being permanently implanted. In addition, SCS therapy has the advantage of not having drug side effects, including respiratory distress associated with IDD systems, and addictive properties and potential for overdose associated with opioid usage, which is currently of epidemic proportions in the US.

The Evoke SCS system is novel in that it is the first SCS system to have the ability to continuously measure in vivo human spinal cord activation in real-time during daily use. In addition to using this information to produce closed-loop stimulation to maintain consistent activation for this therapy, measurement of ECAPs can be used to confirm therapy is being received and to optimize programming (for both open-loop and closed-loop stimulation modes). As seen by the substantial improvements in outcomes in the Control group in the Evoke study, objective measurement of ECAPs during programming, in and of itself, may contribute to improved outcomes. Moreover, ECAP measurement may be used to gain insight into the mechanism of action of SCS and the condition of the spinal cord, as well as monitor the health of the spinal cord and the effects of treatment over time. This may be extended to other treatments that effect neural activation such as some types of pain medications (e.g., anticonvulsants and opioids), where measurement of ECAPs may be used to titrate and optimize dosing, as well as measure the interaction between these medications and SCS.

The benefit of the Evoke System was demonstrated in the Evoke study. High rates of substantial improvement (i.e., ≥50% reduction in back and leg pain (17)) with no increase in pain medications were observed in both closed- and open-loop stimulation using ECAP measurements to optimize therapy. Greater improvement of closed-loop compared to open-loop SCS was demonstrated by the robustness of the primary and hierarchical secondary endpoint outcomes. The primary endpoint and all hierarchical secondary endpoints successfully demonstrated non-inferiority. Additionally, closed-loop stimulation was statistically superior to open-loop stimulation with respect to the rate of at least 50% reduction in overall back and leg pain (primary endpoint; approximately 80% vs. 60%, respectively) and in back pain specifically (hierarchical secondary endpoint; approximately 80% vs. 57%, respectively). Additionally, the Avalon study has demonstrated sustained long-term rates of substantial improvement (i.e., ≥50% reduction) in VAS overall pain relief (≥78% of subjects) with the Evoke System. It would be expected that patients with chronic pain would experience a similar benefit.

As described above, the Evoke System was determined to be safe. The adverse events that were reported in both the Evoke and Avalon studies were consistent with the well-known safety profile of other similar commercially available SCS systems as reported in the published data.

Additional factors related to the Evoke study to be considered in determining probable risks and benefits for the Evoke System include study design and execution. The randomized, double-blind study design was developed to preserve objectivity and minimize unintentional bias. The randomization in this study produced well matched treatment groups with respect to baseline characteristics as well as neurophysiological properties, supporting the validity of the comparisons between groups. Subjects in both treatment groups received equal care, with the device, implant procedure, and programming (i.e., frequency of visits, duration of visits, and programming parameters) being the same for both groups. Programming in both groups utilized ECAP measurement in addition to subject feedback to optimize patient outcomes. As recommended by the FDA, Investigator oversight of the Field Clinical Engineers (FCEs) was documented to confirm comprehensive programming and optimization for all study subjects (18). Additionally, none of the subjects or Investigators were unblinded to the treatment assignment, reducing the potential of data being systematically distorted by knowledge of the treatment received.

In conclusion, the overall safety profile of the Evoke System appears to be very similar to that of other commercially available SCS options, while closed-loop stimulation demonstrated clinically meaningful advantage and superior outcomes compared with the type of open-loop therapy available from other commercial systems. Thus, the clinical benefits of the Evoke System clearly outweigh any associated risks.

1. Patient Perspective

Patient perspectives considered during the review included:

- Pain diary
- Patient Global Impression of Change (PGIC)
- Patient satisfaction

In conclusion, given the available information above, the data support that for the management of chronic intractable pain of the trunk and/or limbs the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the Evoke System when used in accordance with the indications for use in both open-loop and closed-loop mode. The results from the clinical studies support a reasonable assurance of the safety and efficacy of the Evoke System, as well as its long-term performance, when used in a manner consistent with its labeling and intended use. The evidence supporting the safety and effectiveness of the Evoke System is based on a non-inferiority/superiority pivotal study, a long-term prospective study, and over 30 years of clinical research and experience documented in the published data on fully implantable SCS systems and the

similarities of the Evoke System to commercially available implantable SCS systems. The results from comprehensive pre-clinical testing show that the Evoke System performs as intended. The analyses also support a clinical benefit to risk determination that is favorable.

XIV. CDRH DECISION

CDRH issued an approval order on February 28, 2022.

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.

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