Clinical Study Protocol

Evoke Study: A prospective, multicenter, randomized double-blind study examining the safety and efficacy of using the Evoke™ Spinal Cord Stimulator (SCS) System with feedback to treat patients with chronic pain of the trunk and/or limbs.

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1 CLINICAL PROTOCOL SUMMARY

Title	A prospective, multicenter, randomized, double-blind study examining the safety and efficacy of using the Evoke™ Spinal Cord Stimulator (SCS) System with feedback to treat patients with chronic pain of the trunk and/or limbs. (Evoke Study)
Investigational Device	Evoke Spinal Cord Stimulator (SCS) System
Treatment Groups	Investigational: Evoke SCS with feedback (closed-loop stimulation) The feedback control uses Evoked Compound Action Potential (ECAP) measurements to provide consistent stimulation based on the subjects neural response during physiological changes and movement by automatically adjusting the level of stimulation current required to meet the subject's requested target level. Control: Evoke SCS without feedback (conventional open-loop stimulation)
Randomization	1:1
Study Purpose	This study will evaluate the safety and efficacy of the Saluda Medical Evoke SCS System with feedback control to treat chronic pain of the trunk and/or limbs.
Targeted Indication For Use	The 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.
Study Design	This study is a prospective, multicenter, randomized, double-blind clinical trial designed to assess the safety and efficacy of the Saluda Medical Evoke SCS System for the treatment of subjects suffering from chronic, intractable pain of the trunk and/or limbs. This study will compare the Saluda Medical Evoke SCS System with feedback (Investigational) to Saluda Medical Evoke SCS System without feedback (Control).
Sample Size	The Sponsor assumes that the true success rate associated with the Investigational arm for the primary composite endpoint is at least 57%, and that the success rate in the Control arm may be up to 45%. In order to have at least 80% power to determine that Investigational stimulation is non-inferior to Control stimulation at a one-sided significance level of 0.05 and a non-inferiority margin (δ) of 10%, a minimum of 60 subjects per group are required with known primary endpoint status or who are presumed non-responders. In order to account for potential subject loss post-randomization of up to 10%, 134 subjects will be randomized in order to obtain at least 120 subjects with known primary endpoint status or who are presumed non-responders.
Analysis Populations	The primary analysis population is the Intent to Treat subgroup (ITT), which will include all randomized subjects that either have known endpoint status or are presumed non-responders. Subjects will be analyzed according to their randomization assignment. Two additional analysis populations will also be assessed for a subset of analyses: • The Permanent Implant Subset (PIS) will include all subjects who received a permanent implant. • The Per Protocol (PP) analysis population will include all subjects who received a permanent implant with evaluable primary endpoint data and no major deviations.

Study Sites	Up to 20 US sites.
Study Duration	• 3 month follow-up for primary and secondary endpoints • 12 month follow-up for secondary endpoints • Up to 3 years follow-up, if required Subjects will be enrolled in this study for up to 3 years. The primary analysis and submission of the Premarket Approval (PMA) supplement will occur after the last subject reaches their 3 month follow-up.
Primary Objective	The primary objective is to demonstrate non-inferiority of the Investigational mode of stimulation to Control stimulation in the primary composite endpoint for the treatment of subjects suffering from chronic, intractable pain of the trunk and/or limbs.
Study Success Criteria	The study will be deemed successful in the event that non-inferiority is found in testing of the composite primary endpoint at a one-sided 0.05 level of significance against a clinical non-inferiority margin of 10%. In the event non-inferiority is found, superiority of the Investigational arm will be assessed at a two-sided significance level of 0.05. Superiority does not need to be found in order to determine that the trial is successful.
Primary Endpoint	The primary endpoint is a composite endpoint, where a subject is deemed a success if: • They experience a 50% reduction in overall trunk and limb pain as determined by the Visual Analog Scale (VAS) at the 3-month visit, AND • They have no increase in baseline pain medications within 4 weeks of the 3-month visit
Secondary Endpoints for Hierarchical Testing	A number of secondary endpoints are pre-defined for hierarchical testing in order that all endpoints achieving statistical significance under the closed statistical testing procedure will be reported in the clinical study report. If the primary endpoint is met, the following secondary endpoints will be tested in order: • Percentage change in VAS leg pain at 3 months • Percentage change in VAS back pain at 3 months • Incidence of ≥80% reduction in VAS overall trunk and limb pain at 3 months • Incidence of ≥50% reduction in VAS back pain at 3 months • Percentage change in VAS overall trunk and limb pain at 12 months • Percentage change in VAS leg pain at 12 months • Percentage change in VAS back pain at 12 months
Other Secondary Endpoints	A number of additional secondary endpoints will also be collected and assessed across study visits. These endpoints include the following: • Comprehensive summary of all adverse events (AEs) • Change, percent change, incidence of 50% and ≥80% reduction, and cumulative proportion of responders in VAS pain scores • EQ-5D-5L • Oswestry Disability Index (ODI) • Pain diary • Pain map • Stimulation characteristics • Posture change assessment • Patient Global Impression of Change (PGIC) • Patient satisfaction • Pittsburgh Sleep Quality Index (PSQI) • Profile of Mood States (POMS) • 12 Item Short Form Survey (SF-12) • Programming and neurophysiologic properties

Inclusion Criteria	Subjects enrolled in this study must meet the following inclusion criteria, as determined by the Investigator: 1. Subject is male or female between the ages of 18 and 80 years. 2. 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. 3. VAS leg pain score ≥ 6 cm. 4. VAS back pain score ≥ 6 cm. 5. VAS overall trunk and limb pain score ≥ 6 cm. 6. Be an appropriate candidate for an SCS trial and the surgical procedures required in this study based on the clinical judgment of the Investigator. 7. Prescribed pain medications have been stable for at least 30 days prior to the baseline evaluation. 8. ODI score of 41-80 (severely disabled or crippled) out of 100 at the baseline evaluation. 9. Be willing and capable of giving informed consent and able to comply with study-related requirements, procedures, and visits. 10. The subject's primary back pain is located such that lead placement will be in the thoracolumbar region.
Exclusion Criteria	Subjects enrolled in this study must not meet the following exclusion criteria, as determined by the Investigator: 1. 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. 2. 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. 3. 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. 4. 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). 5. Have prior experience with SCS. 6. Have a condition currently requiring or likely to require the use of MRI or diathermy. 7. Have a life expectancy of less than 1 year. 8. Have an active systemic infection or local infection in the area of the surgical site. 9. Be allergic, or have shown hypersensitivity, to any materials of the neurostimulation system which come in contact with the body. 10. 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). 11. Have a documented history of substance abuse (narcotics, alcohol, etc.) or substance dependency in the 6 months prior to the baseline evaluation. 12. Be concomitantly participating in another clinical study. 13. Be involved in an injury claim under current litigation or have pending/approved worker's compensation claim.

	14. 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. 15. Subject is a prisoner. 16. Being treated with electroconvulsive therapy (ECT) or transcranial magnetic stimulation (rTMS). 17. 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. 18. Subject has pain due to peripheral vascular disease or angina. 19. Subject is on anticoagulation therapy that would preclude their ability to undergo the implant procedure.

2 BACKGROUND

2.1 Disease and Current Treatment

Spinal cord stimulation (SCS) is indicated for the treatment of chronic, intractable pain of the trunk and/or limbs. Pain is a sensation produced by the nervous system in response to injury or illness. It helps to identify a region of injury and protect it from further insult. It typically lasts until the injury has resolved. In certain circumstances pain may last beyond the period of healing. When this occurs, it is referred to as chronic pain (1). For the purposes of studying chronic pain, the International Association for the Study of Pain (IASP) has defined chronic pain as pain that lasts more than six months beyond the normal time of healing.

Chronic pain can be the result of several different conditions; the origin of the pain is often used as a means of classification. Some of the more common classifications for chronic pain include: neuropathic pain, failed back surgery syndrome (FBSS), low back and leg pain, complex regional pain syndrome (CRPS) I and II, and ischemic pain.

A recent cross-sectional internet-based survey found that the prevalence of pain (lasting more than 6 months) occurred in 30.7% of the US adult population. This overall prevalence was found to increase with age (2). Chronic pain impairs a patient's ability to perform physical activities, reduces their ability to perform their work and family responsibilities, and is the cause of mental health issues (3). In addition to the physical and emotional burden it brings, the financial cost to society is tremendous. In the US alone it is estimated to cost in the order of $560 to $635 billion per year with an added loss of productivity in the range of $299 to $335 billion (4). It was concluded that the annual cost of chronic pain is greater than the annual cost of heart disease, cancer, and diabetes combined.

The current treatment for chronic pain disorders such as those listed above is medical management and occurs on a continuum with less invasive therapies prescribed first. First line treatment strategies are generally conservative including; exercise programs, rehabilitation programs (physical therapy, occupational therapy, or massage therapy), cognitive and behavioral modifications, transcutaneous electrical nerve stimulation (TENS), biofeedback, and over the counter pain medications. Second line treatments become more intensive and involve the use of interventional techniques such as nerve blocks (local anesthetic or steroids) and spinal injections. They can also include more powerful pain medications such as systemic opioids. The last line of treatment involves more advanced therapies that require surgical interventions. These include surgery to repair an anatomical issue responsible for the pain, surgical techniques that permanently block pathways to the brain such as cordotomy, rhizotomy and thalamotomy, and implantation of systems such as intrathecal drug delivery (IDD) systems or spinal cord stimulators.

Recent guidelines and literature reviews of the treatment for chronic pain of the trunk and/or limbs demonstrate that each of these surgical interventions have the potential to be effective in managing pain, increasing patient activity, and to result in high patient satisfaction when conservative treatment modalities have failed. The risk profile for SCS therapy has advantages to surgical revision and

neuroablation due to the fact it is reversible. In addition, SCS therapy has the advantage of not having drug side effects, including respiratory distress, as compared to IDD systems.

In SCS, electrical stimulation generated from a pulse generator is delivered to the dorsal columns in the spinal cord via leads implanted in the epidural space. Over the last 40 years there have been many advances in SCS therapy; from a better understanding of the target patient population to improvements in device technology. The technology has evolved from large profile, single channel, non-rechargeable implantable pulse generators (IPG) and monopolar leads to smaller profile, multichannel, rechargeable IPGs and multiple contact leads with varied electrode arrays.

With the technological advances there has been a reduction in the number and severity of complications associated with SCS systems. However, the complications associated with the natural movement of the electrode with respect to the dorsal columns such as overstimulation or other unwanted changes in stimulation is still an issue and can result in patients being unsatisfied with the device.

Despite the many technological advances, SCS is still largely performed using an open-loop configuration with patient feedback as the only means for stimulation control. Recently there has been an interest in developing devices that incorporate feedback, enabling a closed-loop system. The first product on the market that has attempted to incorporate feedback is the Medtronic RestoreSensor. This device incorporates a 3-axis accelerometer to provide position-adaptive stimulation. A paper by Schultz et al. (5) described a study that compared position-adaptive stimulation to conventional manual programming. They found that 86.5% of patients achieved improved pain relief with no loss of convenience or improved convenience with no loss of pain relief when using position-adaptive stimulation. They also found that 80.3% reported improved comfort during position changes, 69% reported improved activity, and 47.9% reported improved sleep. Despite the improvement in convenience, subjects in the position-adaptive arm still reported undesirable changes in stimulation 13% of the time. In addition, subjects in the same arm pressed 18.2 buttons per day on average to adjust stimulation. This study provides evidence for the need for a closed-loop device capable of automatically adjusting to not only changes in posture but also other conditions that affect the level of stimulation such as blood pressure, coughing, and movement of the lead.

The Saluda Medical SCS feedback control system measures the electrical response from the neural tissue (Evoked Compound Action Potential (ECAP)), in response to electrical stimulation, and uses this signal to adjust the stimulus amplitude from the stimulator. By maintaining the neural response within a narrow range the patient no longer feels abrupt changes in stimulation and can move around without over or under stimulation.

2.2 Summary of Prior Preclinical and Clinical Experience

Saluda Medical has conducted a number of feasibility and observational studies on the neurophysiology of SCS and feedback control of SCS. The purpose of these studies was to provide information for device design, basic understanding of the neurophysiology of SCS, and to establish the feasibility of using ECAP measurements for feedback control of SCS. All studies were approved by the institutions' ethics committees. The animal studies were non-GLP (Good Laboratory Practice; 21 CFR Part 58) studies.

Saluda Medical's experience with human subjects and with sheep have demonstrated that:

- When the neural tissue in the spinal cord is electrically stimulated, it produces an ECAP. The ECAP can be measured with suitably designed electronics.
- The threshold for measurement of the ECAP corresponds closely to the patient's perception threshold.
- Above threshold the ECAP amplitude increases approximately linearly with stimulation current.
- ECAP amplitude is proportional to the coverage of the patient's painful area.
- The slope of the linear increase in ECAP amplitude with current is called the patient sensitivity and is measured in μV/mA.
- The ECAP threshold and sensitivity vary with the patient's posture.
- If the current is automatically adjusted to maintain a constant ECAP amplitude, then the patient reports a constant percept.

2.2.1 Recording and Measurement of Evoked Spinal Cord Potentials in Ovine: An Acute Study – NTDS01

The purpose of this study was to determine if the evoked response could be used to adjust the stimulation parameters for a spinal cord stimulator. A total of 6 sheep were evaluated in this study. Sheep were chosen as an appropriate large animal since the canal size is large enough to insert a human sized SCS lead. 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. Signals could also be detected in response to stimulating the sciatic nerve. 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 fibers activated during SCS in sheep.

2.2.2 Recording and Measurement of Evoked Spinal Cord Potentials in Humans – NTDH02

This study was the first in-human study performed. The study was performed to record signal responses (neural response) from the spinal cord due to electrical stimulation in an adjacent area of the spinal cord with electrodes on the same electrode array. A total of 5 subjects diagnosed with chronic pain and undergoing the implantation of a trial SCS lead to determine their suitability for SCS to treat their pain were enrolled from one site in Australia. After lead implantation, electrical stimulation parameters were chosen post-operative by routine adjustment method with verbal feedback from the subject. The electrodes were then connected via a custom fabricated connector box 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. No serious or non-serious adverse events (AEs) were reported. This study established that ECAPs can be recorded in humans with chronic pain and that the fibers being recruited during SCS are Aβ sensory nerve fibers. In addition, the amplitude of the ECAP signal was found to correlate with the degree of coverage of the painful area. The results of this study are published in Parker et al. (2012) (6).

2.2.3 Recording and Measurement of Evoked Spinal Cord Potentials in Ovine: An Acute Study – NMCSS03

The purpose of this study was to further characterize the neurophysiological properties of dorsal column fibers and to evaluate a custom stimulator and recording system (NICTA Multi-channel stimulation and recording system). Conduction velocities, rheobase, chronaxie, and refractory periods were measured. Twenty-seven sheep were evaluated acutely under this protocol. Sheep were chosen as an appropriate large animal due to the size of their epidural space. This study demonstrated the ability to measure ECAPs with the NICTA system in sheep and characterized the neurophysiological properties of nerve fibers activated during SCS in sheep. The results of this study are published in Parker et al. (2013) (7).

2.2.4 Automatic Control of Spinal Cord Stimulation in Humans – NMCSH04

The purpose of this study was to collect ECAP data from subjects implanted with externalized commercial SCS leads. This data was used to determine the feasibility of reliably recording ECAPs and using those signals as a control variable in a closed-loop feedback controlled system. The stimulation and recording was performed using a Multi-Channel System (MTS) or Body-Worn System (BWS) (NICTA Implant Systems/Saluda Medical, Sydney Australia). A total of 39 subjects were examined from one site in Australia. No serious device-related AEs were reported.

There were 3 non-serious AEs related to transient uncomfortable over-stimulation. All events were resolved without sequela. In all cases, the subject had transient discomfort, requiring no treatment and proceeded with the study. One subject experienced the accidental disconnection of the recording electrodes resulting in a sudden increase in stimulation. Stimulation was turned off and the electrodes were reconnected. An impedance check was added to the hardware to allow detection of a disconnected

lead. In another subject, over-stimulation occurred after incorrectly setting up electrodes. This has been resolved by emphasizing electrode selection in programming procedures and training of users. The third AE occurred with starting stimulation at a previous current when the intention was to start at 0mA. This issue was resolved by amending the controlling device software to ensure no changes could be made to the current while stimulation is off.

This study established the ability to measure ECAPs with the NICTA/Saluda Medical system in subjects with chronic pain. Additional key findings from this study include:

- Characterized neurophysiological properties of nerve fibers activated during SCS in subjects with chronic pain.
- Characterized the variability of ECAP size and paresthesia strength with posture changes, cough and heartbeat.
- Demonstrated the use of feedback control to reduce paresthesia variability.
- Established methods and procedures to reliably measure ECAPs and set feedback parameters
- Demonstrated the influence of electrode position on ECAP size during trial SCS lead placement.

2.2.5 A Feasibility Study Evaluating the Saluda Medical SCS System Incorporating Feedback Control Using Evoked Compound Action Potentials to Aid in the Accurate Positioning of Spinal Cord Stimulation Leads in Humans – SMCSH10

The primary objective of this study was to demonstrate the feasibility of using intraoperative feedback control as an aid in the accurate positioning of a percutaneous SCS lead. The data was also used to evaluate the safety of using intraoperative feedback control as an aid in the implantation of an SCS lead; implant procedure time; the feasibility of using intraoperative ECAP measurements to predict the ability to set feedback control post-operatively; the use of feedback and non-feedback SCS in an acute setting; and changes in various outcome measures such as pain scales, subject satisfaction, quality of life, paresthesia descriptors. The stimulation and recording was performed using a MTS or BWS (NICTA Implant Systems/Saluda Medical, Sydney Australia). A total of 20 subjects were enrolled from two sites in Australia.

No serious device-related AEs were reported. There was one non-serious AE related to transient uncomfortable overstimulation. This event occurred as the result of incorrectly setting up the electrodes. Stimulation was disconnected within 5 seconds of the overstimulation. This issue was resolved by emphasizing electrode selection in programming procedures and through the training of users.

This study further demonstrated the influence of electrode position on ECAP size during trial SCS percutaneous lead placement. Feedback control during lead placement was not attempted due to limited intraoperative time. In addition, this study demonstrated the use of feedback control to improve pain relief, reduce paresthesia variability, and reduce stimulation side-effects.

2.2.6 A Feasibility Study Evaluating the NICTA SCS System Incorporating Feedback Control Using Evoked Compound Action Potentials to Aid in the Accurate Positioning of Paddle Spinal Cord Stimulation Leads in Humans – NMCSH11

The primary objective of this study was to examine the properties of the dorsal column axons by measuring ECAPs during SCS. The study also sought to determine the feasibility of using ECAPs to aid in the positioning of SCS paddle leads.. A total of 15 subjects were enrolled in this study from one site in the US. No device-related AEs were reported. This study demonstrated the influence of electrode position on ECAP size during SCS paddle lead placement. Measurement of ECAP amplitude to determine lead orientation was shown to be a potential intraoperative aid during SCS surgery.

2.2.7 A Prospective, Multicenter, Randomized Double-Blind Crossover Study Examining the Safety and Effectiveness of Using Spinal Cord Stimulation Incorporating Feedback to Treat Patients with Chronic Pain of the Trunk and/or Limbs in an Extended Trial – SBWSH1302

This prospective, multicenter, randomized, double-blind crossover study was conducted under a United States (US) Food and Drug Administration (FDA) Investigational Device Exemption (IDE) approval (IDE Number: G140024). The purpose of this study was to evaluate the feasibility of using the Saluda Medical External Trial System (ETS) to provide feedback during a trial of SCS. The ETS was investigated to support the design, development, safety and performance of the implantable device. The primary objective of the study was to compare the effectiveness of feedback to non-feedback SCS in subjects with chronic pain of the trunk and/or limbs with regard to pain relief and stimulation side effects in an extended trial.

In this cross-over study design, subjects were evaluated in both feedback and non-feedback (i.e., conventional open-loop stimulation) stimulation modes of the Saluda Medical ETS, but were blinded to their treatment. Following successful response to a 3 to 5-day trial with a commercial SCS system subjects were randomized to receive either feedback first or non-feedback first. They were then followed for 10 days in each treatment arm; assessments were performed mid-way and at the end of each treatment arm.

A total of 69 subjects were enrolled (i.e., signed informed consent and met inclusion/exclusion criteria) across 10 sites in the US. Of the 69 enrolled subjects, 37 were ultimately randomized, and a total of 22 subjects provided analyzable data and were included in the final efficacy analysis. In order to be considered analyzable, a subject had to complete treatment, provide follow-up data with both stimulation modalities, and have had both stimulation modalities provided as intended.

Fourteen of the twenty-two analyzable subjects (63.6%) met the primary endpoint which required that subjects report either less pain or fewer stimulation-related side effects, with no increase in either (based on 5-point Likert scales for each assessment) in the feedback arm compared to the non-feedback arm. Of the 69 enrolled subjects, there were no unanticipated adverse effects (UADEs) or serious device-related AEs. Two serious adverse events (SAEs) were reported due to hospitalization, and were not related to the device. One SAE occurred when a subject felt chill and had a fever and was subsequently hospitalized; the subject was diagnosed with cancer. Another SAE occurred when a subject was admitted to the hospital with edema of the lower extremities; the subject was treated with medication and continued in the study. There were 51 non-serious AEs reported in the study, which included shocking/intensity changes, stimulation in unwanted location, loss of stimulation, lead migration, pain, drainage at wound site, gastrointestinal virus, hives, and incontinence.

This study met its primary objective, and demonstrated that ECAPs could be captured and closed-loop control applied using the ETS in an extended trial. In addition, no safety concerns were identified.

2.3 Rationale for the Clinical Study

There is a high demand for safe and effective treatments for chronic pain. Traditional open-loop SCS has a long-standing history with well-characterized clinical safety and performance in treating chronic intractable pain of the trunk and/or limbs. There is a recognized need for the development of a closed-loop system that incorporates a feedback mechanism to try to alleviate unwanted changes in stimulation occurring with movement. The Evoke SCS System has a feedback mechanism that uses ECAP measurement and closed-loop control to provide consistent stimulation based on the subjects neural response during changes in body position by automatically adjusting the level of stimulation current required. The feedback system measures the ECAP for every stimulus and compares this to a target, the ECAP amplitude at which the stimulation is most comfortable. The stimulation current is then adjusted proportionally to the difference between the ECAP and the target. The results from the prior preclinical and clinical studies support the initial safety and performance of the Evoke SCS System. This clinical study has been designed as a pivotal study of the Evoke SCS System to support a US FDA

Premarket Approval (PMA) supplement for the feedback feature for the Evoke SCS System. The study will evaluate the safety and efficacy of the Saluda Medical Evoke SCS System with feedback control to treat chronic pain of the trunk and/or limbs incorporating feedback control.

3 DEVICE DESCRIPTION AND INDICATION FOR USE

3.1 Device Description

3.1.1 Investigational Device

The Investigational device is the Evoke™ Spinal Cord Stimulator (SCS) System. It consists of a stimulator (implantable and external), leads, accessories, and surgical tools. Please refer to the current Evoke IFUs (Surgical Guide, Clinical Manual, User Manual and supporting materials) for the most up-to-date description of the System and Accessory Components.

The Evoke SCS system is substantially equivalent to other spinal cord stimulators on the market, except for one new feature – the Feedback Mechanism. The Feedback Mechanism uses ECAP measurement and closed-loop control to provide consistent stimulation based on the subject's neural response during physiological changes and movement by automatically adjusting the level of stimulation current required to meet the subject's requested target level. In the feedback-controlled stimulation mode the magnitude of the nerves' response to the stimulus (i.e., ECAP) is measured and then compared to a set point (i.e., comfortable target level determined by the patient) in a feedback algorithm which calculates a new stimulus amplitude to present. This process is repeated for every stimulus and the net result is that the current is continuously adjusted in order to maintain constant ECAP amplitude (Figure 1). The Feedback Mechanism will be used in the Investigational treatment group.

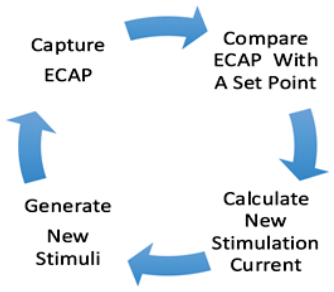

Figure 1: Feedback Mechanism

To optimise ECAP measurement for the Feedback Mechanism, the Evoke System may use a triphasic stimulation pulse. Traditionally, SCS achieves charge-balanced stimulation by following the active cathodic (negative) pulse with an anodic (positive) pulse of equal charge. This anodic pulse may be rectangular and symmetric with the cathodic pulse, or it may be a decaying exponential that is several times longer duration than the cathodic pulse. For triphasic stimulation the anodic pulse is split into two rectangular pulses, one before and one after the cathodic pulse, with the charge of the two anodic pulses equal to the cathodic pulse. In SCS, cathodic pulses activate the dorsal column axons to deliver therapy. The anodic pulses do not deliver therapy, so the arrangement and shape of the anodic pulses, whether biphasic or triphasic, rectangular or exponential, does not affect the therapy or safety of SCS.

3.1.2 Control Device

The Control device used in this study is the same as the Investigational device; however, stimulation programming differs between the two study arms. In the control arm, the new feature of the device (Feedback Mechanism) will not be used. In this mode, the Control device will deliver therapy equivalent to conventional open-loop FDA-approved SCS systems.

3.2 Target Indication for Use

The 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.

4 STUDY PURPOSE AND OBJECTIVES

4.1 Study Purpose

This is a pivotal study being conducted to support a PMA supplement for the feedback feature of the Evoke SCS System. This study will evaluate the safety and efficacy of the Saluda Medical Evoke SCS System with feedback control to treat chronic pain of the trunk and/or limbs.

4.2 Primary Objective

The primary study objective is to demonstrate non-inferiority of the Investigational mode of stimulation to the Control mode of stimulation in the primary composite endpoint at the 3-month visit (i.e., 50% reduction in VAS overall trunk and limb pain and no increase in baseline pain medications within 4 weeks of the visit) for the treatment of subjects suffering from chronic, intractable pain of the trunk and/or limbs.

4.3 Secondary Objectives

The secondary objectives are intended to characterize the treatment effect of Investigational vs. Control stimulation modes with respect to the following outcome measures:

- AEs
- Visual Analog Scale (VAS) pain scores
- EQ-5D-5L
- Oswestry Disability Index (ODI)
- Pain diary
- Pain map
- Stimulation characteristics
- Posture change assessment
- Patient Global Impression of Change (PGIC)
- Patient satisfaction
- Pittsburgh Sleep Quality Index (PSQI)
- Profile of Mood States (POMS)
- 12 Item Short Form Survey (SF-12)
- Programming and neurophysiologic properties

5 STUDY DESIGN

5.1 Overview

This study is a prospective, multicenter, randomized, double-blind, parallel-group clinical trial designed to assess the safety and efficacy of the Saluda Medical Evoke SCS System for the treatment of subjects suffering from chronic, intractable pain of the trunk and/or limbs.

Subjects with chronic, intractable pain of the trunk and/or limbs that has been refractory to conservative therapy for a minimum of 6 months will be screened for participation in this study. Subjects who provide informed consent and meet the study eligibility criteria will be randomized in a 1:1 fashion to either the Saluda Medical Evoke SCS System with feedback or the Saluda Medical Evoke SCS System without feedback.

Subjects will first undergo a trial period with the external trial stimulator for up to 30 days (typically 1 week) to determine if the subject will be eligible for the permanent implant. Subjects who have at least

a 50% reduction compared to baseline in overall trunk and limb pain as measured by the VAS will be approved to receive a permanent implant of the Evoke SCS System.

Subjects will be followed up at 1-, 3-, 6-, 9-, and 12-months following the permanent implant. Subjects will be followed up for a minimum of 12 months and biannually thereafter for up to a maximum of 3 years. The primary analysis and submission for PMA supplement approval will occur after the last subject reaches their 3-month follow-up.

Figure 2 provides a diagram of the study design and follow-up schedule.

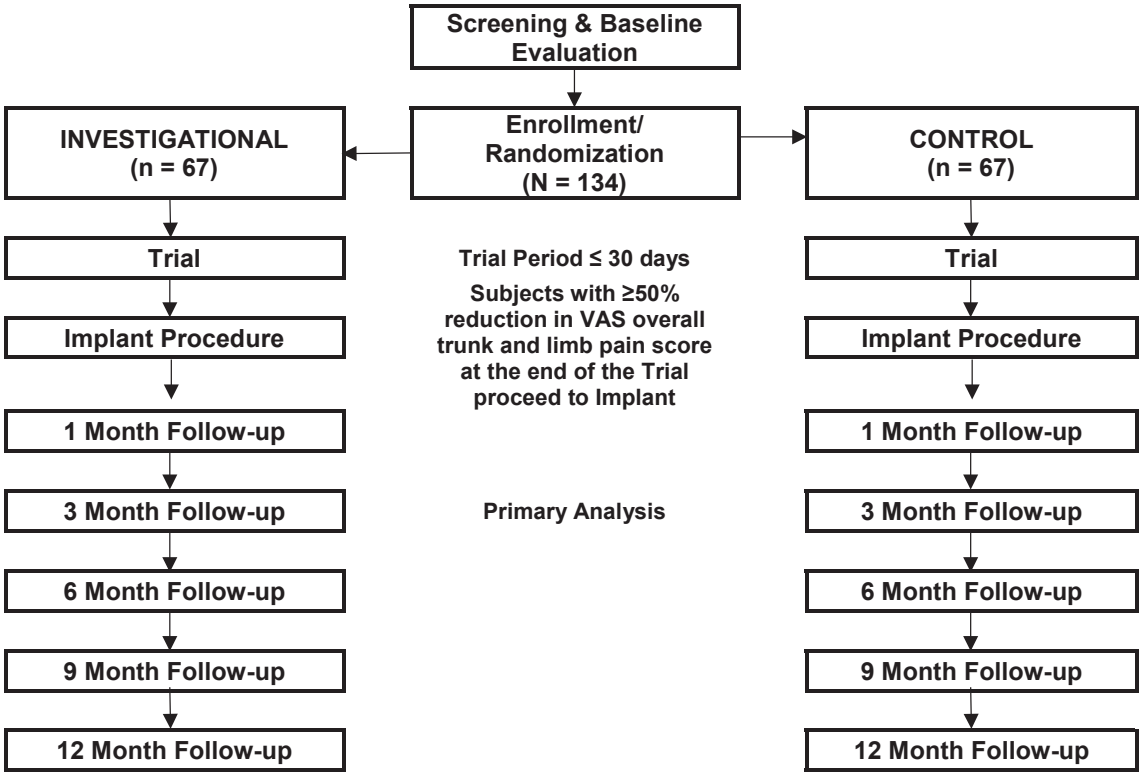

Figure 2: Study Design and Follow-up Schedule

5.2 Randomization

Subjects will be randomly assigned in a 1:1 fashion to receive either Investigational or Control stimulation. The randomization will be generated utilizing permuted blocks, stratified by study site to ensure within-site balance. Randomization will occur at the time of the trial stimulation procedure following informed consent and verification of study eligibility.

5.3 Blinding

This is a double-blind study. Neither the subjects nor the Investigator or their staff, will be informed which treatment group a subject has been assigned to. In addition, the independent adjudication committee will be blinded to the subjects' treatment assignments. Measures will be taken to improve the likelihood of maintaining the blind throughout the course of the study (e.g., wording in the informed consent, communication, and interaction). A blinding assessment will be performed to assess maintenance of subject and Investigator blinding. Subjects will be asked what treatment group they think they are in and

Investigators will be asked what treatment group they think the subjects are in, and they each will be asked why they believe their answer.

The Investigator may determine it is necessary to unblind to manage an AE. Unblinding will only occur in circumstances where there is a risk to subject health or safety. Every attempt shall be made to keep the subject blinded to the treatment assignment, unless the Investigator believes that the subject shall be made aware in order to manage the AE.

5.4 Minimization of Bias

Several measures have been incorporated into the study design to help minimize bias. The study will be randomized in order to increase the likelihood of having comparable treatment groups with respect to baseline characteristics and to remove Investigator bias in allocation of the treatment assignment. In addition, the study will be double-blind in that the treatment allocation will be concealed from the study subjects and the Investigators and their staff to reduce the potential of data being systematically distorted by knowledge of the treatment received. Furthermore, the independent adjudication committee responsible for adjudicating all AEs will be blinded to the subjects' treatment assignments.

The subjects, Investigators and their staff will not have access to the randomization assignment. The same device is being used in the Investigational and Control groups; however, the stimulation setting will differ between the groups according to the randomization assignment (i.e., feedback vs. no feedback). The Field Clinical Engineer (FCE) will allocate the treatment assignment. All FCEs will be Sponsor representatives (employees or contractors) and they will be responsible, with the oversight of the Investigator, for programming both the Investigational and Control devices throughout the study. In order to maintain consistency in therapy delivery (and reduce bias), the FCEs will follow the procedures in the Evoke Clinical Manual to program all subjects, which will be the equivalent in both study arms with the exception of enabling/disabling the feedback mechanism.

- Lead placement by the Investigator will be equivalent in both study arms per the Evoke Surgical Manual.
- Intraoperative programming will be completed in an equivalent manner in both study arms.
- Subjects will be programmed and optimized for paresthesia coverage of painful areas. There will be no difference in the methods of programming.
- In the Investigational arm, the feedback mechanism will be turned on, and in the Control arm, the feedback mechanism will be disabled.

In addition, FCEs will not contact study subjects directly; subjects may contact the site at any time if they are having issues with their device or to optimize stimulation. The site staff will determine if the subject needs to come in for reprogramming or troubleshooting, and will schedule a phone call or visit with the subject, FCE, and Investigator as needed.

Finally, a number of analyses are planned to assess the balance achieved between study groups in baseline measurements, the consistency of results achieved between study sites, and to help understand the robustness of the results in the presence of incomplete data. These analyses are detailed in Section 11.4.

6 STUDY POPULATION

6.1 Study Sites

Study subjects will be enrolled at up to 20 US sites.

6.2 Inclusion Criteria

Subjects enrolled in this study must meet the following inclusion criteria, as determined by the Investigator:

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

2. 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.

3. VAS leg pain score ≥ 6 cm.

4. VAS back pain score ≥ 6 cm.

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

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

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

8. ODI score of 41-80 (severely disabled or crippled) out of 100 at the baseline evaluation.

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

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

6.3 Exclusion Criteria

Subjects enrolled in this study must not meet the following exclusion criteria, as determined by the Investigator:

1. 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.

2. 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.

3. 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.

4. 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).

5. Have prior experience with SCS.

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

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

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

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

10. 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).

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

12. Be concomitantly participating in another clinical study.

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

14. 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.

15. Subject is a prisoner.

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

17. 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.

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

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

7 STUDY ASSESSMENTS

7.1 Visual Analog Scale (VAS) for Pain

The Visual Analogue Scale (VAS) is a subjective measure of pain. It consists of a 10 cm line with two end-points representing "no pain" and "worst pain imaginable". Subjects are asked to rate their pain by placing a mark on the line corresponding to their level of pain. The distance along the line from the "no pain" end to the subject's mark is measured. The VAS will be completed for the subjects' study indication pain for which the SCS system is treating.

7.2 EQ-5D-5L

The EQ-5D-5L is a standardized instrument for measuring health-related quality of life states and consists of the EQ-5D descriptive system and the EQ Visual Analog Scale (EQ VAS). The EQ-5D-5L descriptive system comprises five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). The responses to each of the questions indicate five levels of severity (no problems/slight problems/moderate problems/severe problems/extreme problems), and result in a single country-specific index value (an index score of 1 correlates to the highest quality of life on this scale) that may be used to calculate quality-adjusted life years (QALYs). The EQ VAS records the respondent's self-rated health on a 20 cm vertical VAS, where endpoints are labelled "Best imaginable health state" and "Worst Imaginable health state." This provides a quantitative measure of health as judged by the individual respondents.

7.3 Oswestry Disability Index (ODI)

The Oswestry Disability Index (ODI) is a measure of disability in patients with back or leg pain. The questionnaire contains ten sections related to daily living activities including intensity of pain, lifting, ability to care for oneself, ability to walk, ability to sit, sexual function, ability to stand, social life, sleep quality, and ability to travel. Each section contains six statements describing different potential scenarios relating

to the section topic. The subject chooses the statement which most closely resembles their current situation. Higher scores correspond with greater disability.

7.4 Pain Diary

Data on pain variability will be collected through subject completion of a pain diary. The subjects will record their worst, least, and average pain. The pain diary will be completed for the subjects' study indication pain for which the SCS system is treating.

7.5 Pain Map

Data on the area of pain will be collected by asking subjects to shade in the areas where they are experiencing pain on a body map drawing. The pain map will be completed for the subjects' study indication pain for which the SCS system is treating.

7.6 Stimulation Characteristics

Data on subjects' experience with stimulation will be collected by asking subjects questions about device usage, stimulation adjustments, and paresthesia.

7.7 Posture Change Assessment

Data on stimulation intensity in different postures will be collected by asking subjects to rate the stimulation intensity on an 11-point numeric rating scale (0 equals "no feeling" and 10 equals "very intense") while upright, coughing (in an upright position), and supine with neural properties recorded.

7.8 Patient Global Impression of Change (PGIC) and Patient Satisfaction

Patient Global Impression of Change (PGIC) is a single item measure of global improvement with treatment. The subject is presented with 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".

Subject recommendation of and satisfaction with the therapy and pain relief will also be collected. Satisfaction options include "very satisfied," "satisfied," "neither satisfied nor unsatisfied," "unsatisfied," and "very unsatisfied."

7.9 Pittsburgh Sleep Quality Index (PSQI)

The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire that measures sleep quality and disturbances over a 1-month time interval. Nineteen individual items generate seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of the scores for these seven components yields one global score, with a score of zero equating to the best sleep quality and 21 to the worst sleep quality

7.10 Profile of Mood States (POMS) Brief Form

The Profile of Mood States (POMS) Brief Form is a 30 item, 5-point Likert scale that measures mood states overall (Total Mood Disturbance) as well as for six domains: Tension, Depression, Anger, Vigor, Fatigue, and Confusion. Higher scores indicate more negative mood states except for the Vigor domain where higher scores indicate increased Vigor.

7.11 12 Item Short Form Survey (SF-12) – Quality of Life

The 12 Item Short Form Survey (SF-12) is a self-reported health-related quality of life scale with 12 questions that yield scores on eight dimensions of quality of life including: physical functioning, role-

physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. These eight dimensions may be combined to provide two summary scales for physical health (physical composite score (PCS)) and mental health (mental composite score (MCS)). Improvements on the SF-12 scale are represented by higher scores.

7.12 Programming and Neurophysiologic Properties

Programming parameters will be recorded during programming sessions. Neurophysiologic properties may also be recorded.

8 STUDY PROCEDURES

8.1 Visit Schedule

Table 1a: Visit Schedule

Procedure	Screening/ Baseline	Trial Procedure	Trial End (≤30 days)	Implant Procedure (Day 0)	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, 24, 30, & 36 Month[1]
Informed Consent	X									
Inclusion/Exclusion	X									
Baseline Evaluation (Demographics, Medical History, Physical Exam, Psychological Evaluation)	X									
Pain Medication/ Therapies	X	X	X	X	X	X	X	X	X	X
Procedure/X-rays[2]		X	X[7]	X						
Programming[3]		X		X	X	X	X	X	X	X
Pain Assessment (VAS & Pain Map)	X		X		X	X	X	X	X	X
Stimulation Characteristics						X			X	X
Posture Change Assessment					X	X	X		X	X
EQ-5D-5L	X				X	X	X		X	X
ODI	X				X	X	X		X	X
Pain Diary[8]	X				X	X	X		X	X
PSQI	X				X	X	X		X	X
POMS	X				X	X	X		X	X
SF-12	X				X	X	X		X	X
Telephone FU[4]					X	X	X	X	X	X

PGIC & Patient Satisfaction					X	X	X		X	X
Blinding Assessments						X			X	
Adverse Event	X[5]	X	X	X	X	X	X	X	X	X
Study Exit		X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]

[1] Visit Windows: 18-month (545±90 days), 24-month (730±90 days), 30-month (910±90 days), and 36-month (1095±90 days)
[2] X-rays are required (AP and lateral) for the trial and implant procedures. In addition, X-rays will be obtained for any lead revision/replacement procedure (when possible). X-rays are optional at any time during the study in order to evaluate potential AEs, as needed and determined by the physician. Fluoroscopy may substitute for X-ray.
[3] Programming may occur as needed/optional throughout the study.
[4] Telephone Follow-up to occur ideally two weeks prior to the next scheduled follow-up visit to determine the need for reprogramming or troubleshooting; no window is given, but the phone call should be completed prior to the follow-up visit.
[5] All adverse events occurring following subject informed consent will be collected.
[6] A Study Exit form will be completed for all enrolled (i.e., randomized) subjects at the time of study exit (i.e., study completion or early withdrawal).
[7] End of trial (lead pull procedure).
[8] Subjects will be asked to complete a pain diary for seven consecutive days; deviations will be required if at least one full day was not recorded. At follow-up, the diary should be completed prior to their scheduled visit.

Table 1b: Self-Selected Crossover Schedule

If a subject decides to crossover, the following schedule should be followed between the 24-month and 30-month visit windows. The crossover schedule does not change/affect the 30- or 36-month visits/windows. The crossover phase shall be completed prior to the 30-month visit.

Procedure	Post 24 Month Assessments	Initial Crossover, Prior to device being turned back on	1 Month Post Crossover (PC) (30 days ± 14 days)[4]	3 Month Post Crossover (PC) (90 days ± 14 days)[4]
Informed Consent	X[1]			
Crossover Participation Decision	X[2]			
Pain Assessment		X[5]	X[6]	X
Crossover 1M and 3M Follow-Up			X[6]	X
Posture Change Assessment, Stimulation Characteristics, PGIC & Patient Satisfaction, EQ-5D-5L, ODI, PSQI, POMS, SF-12			X	X
Telephone FU[3]			X	X

[1]Informed consent requirements per IRB approval. Consent may occur any time prior to crossover activities.
[2]If the subject elects not to participate in the crossover phase, no further action is required following crossover participation decision documentation. Subject maintains protocol schedule (30- and 36-month visits).
[3]Telephone Follow-up to occur prior to the next scheduled follow-up visit to determine the need for reprogramming or troubleshooting; no window is given.
[4]The visit window is based on the crossover participation decision date.
[5]Subjects selecting to crossover will be programmed in the crossover stimulation mode and then the device will be turned off. The subject will be given a pain assessment form and asked to not turn stimulation on until pain returns. When their pain returns, they are asked to complete the pain assessment form documenting their pain and then may turn stimulation on.
[6]If a subject crosses back to their original mode prior to the 3-month post-crossover visit (i.e., 1 month post crossover), they will resume the original protocol schedule and their next visit is the 30-month visit.

8.2 Screening/Baseline Evaluation

Potential study subjects will be identified and informed of the study. Subjects who provide informed consent for study participation (refer to section 13.2.2) will undergo a number of baseline evaluations to determine their eligibility for study participation. These include:

- Demographics
- Medical history
- Physical examination
- Psychological evaluation
- Utilization of pain medication/therapies
- Pregnancy test (as applicable)
- Pain assessment (VAS and Pain Map)
- Pain diary
- Health-related quality of life (SF-12 and EQ-5D-5L)
- Functional disability (ODI)
- Emotional functioning (POMS)
- Sleep quality (PSQI)
- Imaging will be obtained only if required, in the Investigator's opinion, to confirm eligibility (not required per protocol)

8.3 Randomization and Enrollment

Subjects who provide informed consent and meet eligibility criteria will be randomized, at which point they will be considered enrolled in the study. Randomization will occur at the time of the trial procedure/programming to minimize loss of subjects between randomization and the trial procedure. Reasons for screen failures will be documented.

8.4 Trial Phase

Before permanent implant of the Evoke system, subjects will undergo a trial stimulation phase with the external stimulator attached to up to two Evoke leads. The procedure will be performed in accordance with the Evoke Surgical Guide. The lead(s) will be inserted into the epidural space and advanced to the vertebral level associated with the subject's pain. The externalized lead(s) will be connected to the external stimulator. The device will be programmed for pain coverage in accordance with the Evoke Clinical Manual and set to either feedback on or feedback off by the FCE according to the subjects' randomization assignment. Timing of post-procedure programming will occur at the discretion of the Investigator.

The trial will last up to 30 days (typically 1 week) to determine if the subject will proceed to the permanent implant. Subjects may have multiple visits during the trial phase in order to optimize stimulation settings. The following data will be collected during the trial phase:

Trial Procedure/Trial Phase:

- Trial procedure data
- X-ray/fluoroscopy images
- Device programming parameters
- Utilization of pain medication/therapies
- AEs

End of Trial:

- Pain assessment (VAS and Pain Map)
- End of Trial (lead pull procedure)
- Utilization of pain medication/therapies
- AEs

8.5 Implant Procedure Phase

Subjects will be approved to undergo implantation of the Evoke SCS system if the subjects' trial was successful (i.e., VAS overall trunk and limb pain score at the end of trial was reduced by 50% or more compared to the baseline measurement).

The permanent implant will involve the implantation of the Evoke stimulator and one or two Evoke leads. The implant procedure will be performed in accordance with the Evoke Surgical Guide, and programming will be performed in accordance with the Evoke Clinical Manual. Timing of post-procedure programming will occur at the discretion of the Investigator. The device will be set to either feedback on or feedback off by the FCE according to the subjects' randomization assignment.

The following data will be collected during the implant procedure phase:

- Implant procedure data
- X-ray/fluoroscopy images
- Device programming parameters
- Utilization of pain medication/therapies
- AEs

8.6 Follow-up Visits

Subjects will be followed-up at 1 month (30±14 days), 3 months (90±14 days), 6 months (180±30 days), 9 months (270±30 days), and 12 months (365±30 days), and biannually thereafter for up to 3 years following the implant procedure. Subjects may have their device reprogrammed throughout follow-up. The following data will be collected during follow-up:

All Follow-up Visits:

- Device programming parameters
- Pain assessment (VAS and Pain Map)
- Utilization of pain medication/therapies
- AEs

Additional Data Collected at the 1-, 3-, 6- and 12-Month Visits Only:

- Pain Diary
- Posture change assessment
- Health-related quality of life (SF-12 and EQ-5D-5L)
- Functional disability (ODI)
- Emotional functioning (POMS)
- Sleep quality (PSQI)
- Impression of change (PGIC) and patient satisfaction

Additional Data Collected at the 3- and 12-Month Visits Only:

- Stimulation characteristics
- Assessment of blinding (Investigator and subject)

The same data collected at the 12-month follow-up visit (except for the Blinding Assessment) will be collected at the 18-month (545±90 days), 24-month (730±90 days), 30-month (910±90 days), and 36-month (1095±90 days) follow-up visits, if required.

Self-selected Crossover Option:

Subjects will be consented and given the option to cross over to the other stimulation mode following completion of 24-month visit assessments (and prior to the 30-month visit). Neither the site nor subject will be unblinded at this time (i.e., double-blind maintained).

If the subject decides not to crossover, their decision will be documented, and they will continue to be followed at their scheduled 30- and 36-month visits.

If the subject decides to crossover, up to two additional scheduled visits will be required and the following will occur. At the time of the crossover participation decision, subjects selecting to crossover will be programmed in the crossover stimulation mode and the device will be turned off. The subject will be provided with a pain assessment form and asked to leave stimulation off until their pain returns. When their pain returns, they are asked to complete the pain assessment form documenting their pain and then may turn stimulation on. A subject is required to come into the clinic for a 1-month post-crossover visit (30 days ± 14 days after the crossover participation decision date). If the subject chooses to go back to their original stimulation mode, they may do so at this point. If the subject stays in the crossover mode, they will have another scheduled visit at 3-months post-crossover (90 days ± 14 days after the crossover participation decision date). At the 3-month post-crossover visit, the subject will decide to either return to their original stimulation mode or stay with the new stimulation mode (crossover mode) for the remainder of the study (i.e., 30- and 36-month visits). Telephone Follow-ups prior to the scheduled crossover visits will be required. Interim or unscheduled programming visits may occur as needed to optimize the new stimulation mode for the subject. It is expected that the crossover protocol schedule be followed; however, due to the exploratory nature of the crossover, no schedule-related protocol deviations will be required to be reported in the study database for the crossover period. The crossover shall be completed prior to the 30-month visit.

Data Collection during the Crossover phase includes:

- Crossover Participation Decision
- Programming and neurophysiological properties
- Pain assessment (VAS and Pain Map)
- Posture change assessment
- Health-related quality of life (SF-12 and EQ-5D-5L)
- Functional disability (ODI)
- Emotional functioning (POMS)
- Sleep quality (PSQI)
- Impression of change (PGIC) and patient satisfaction
- Stimulation characteristics
- Crossover 1M and 3M assessment
- Utilization of pain medication/therapies
- AEs

8.7 Telephone Follow-up

Approximately two weeks prior to the scheduled follow-up visits (no window is given, but should be completed prior to the follow-up visit), the site will contact subjects to determine if the subject is receiving appropriate pain coverage, if the stimulation system is functioning as expected, and whether they have any concerns or questions about the stimulation. Based on this call, additional training or troubleshooting may be provided over the phone or the subject may be asked to come into the clinic prior to their scheduled follow-up visit for reprogramming or troubleshooting.

8.8 Programming Sessions

Device programming will initially occur following the trial and implant procedures. Programming adjustments may occur as many times after initial programming (for either the trial or the permanent implant) in order to optimize treatment. Programming will be performed in accordance with the Clinical Manual by the FCE with the oversight of the Investigator.

8.9 Revisions, Replacements, and Explants

During the course of the study subjects may require a device revision, replacement or explant. The following data will be collected for revisions, replacements, and explants:

- Revision/replacement/explant procedure data
- X-ray/fluoroscopy images for lead revisions and replacements
- AEs

8.10 Study Exit – Completion and Withdrawal

At the end of the subjects' study participation, either due to study completion or early withdrawal, a study exit form will be completed documenting the date and reason for study exit. The study exit form is only required for enrolled/randomized subjects. For those subjects who miss a scheduled study visit, the site shall attempt to contact the subject at least three times, with at least one attempt being a certified letter, prior to considering the subject lost to follow-up (LTF). For subjects who withdraw from the study early, all attempts will be made to collect the primary and secondary endpoint data, including safety data.

8.11 Concomitant Pain Medications and Therapies

Pain medications and therapies will be collected at baseline and changes will be tracked throughout the subjects' participation in the study. Subjects will be asked not to change their baseline pain medications or therapies or increase/decrease their dosage or frequency through the 3-Month visit. Subjects will be permitted to take up to 2 grams of Tylenol daily as a rescue drug regimen. Pain medications/therapies may be taken for post-operative pain or AEs as needed.

9 ADVERSE EVENTS

9.1 Adverse Event Definitions

9.1.1 Adverse Event

An **adverse event (AE)** is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs in subjects, whether or not related to the investigational medical device.

9.1.2 Serious Adverse Event

A **serious adverse event (SAE)** is defined as an AE that

- Led to death,
- Led to serious deterioration in the health of the subject, and that either resulted in:
  1. a life-threatening illness or injury, or
  2. a permanent impairment of a body structure or a body function, or
  3. prolonged hospitalization, or
  4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- Led to fetal distress, fetal death, or congenital anomaly or birth defect.

Note: Planned hospitalization for a pre-existing condition or a procedure required by the protocol (e.g., the index implant procedure, or device replacement due to normal battery depletion or lead migration), or a hospitalization without serious deterioration in health, is not considered an SAE.

9.1.3 Unanticipated Adverse Device Effects

An **unanticipated adverse device effect (UADE)** means 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 event will not be considered a UADE if it is a known consequence of the underlying disease or condition under investigation, surgery, or other events that commonly occur in the study population independent of the investigational device.

The final determination of whether an AE meets the definition of a UADE will be made by the independent adjudication committee for this study.

9.2 Adverse Event Recording and Reporting

9.2.1 Adverse Event Recording

Investigators are responsible for providing a description of all AEs, including the clinical outcome for the subject. Investigators will evaluate each event for seriousness, severity, and relatedness to the procedure, device, or stimulation therapy. Investigators must supply the Sponsor with any additional information related to safety reporting of a particular event.

9.2.2 Adverse Event Reporting

Investigators are required to report all AEs during the course of the study (except as outlined below). If an AE leads to multiple outcomes that sequentially worsen, only the worst AE will be reported.

Investigators shall report AEs to the Sponsor, and to their reviewing IRB per the IRB's reporting requirements. Investigators are required to report UADEs to the Sponsor and their reviewing IRB as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect, per 21 CFR 812.150 (refer to section 13.7.2 for Investigator reporting requirements).

AE reporting exceptions:

- AEs that would be reasonably expected to be associated with any surgical procedure (e.g., anesthesia associated symptoms, surgical site pain, post-procedure pain) will not be required to be reported as AEs unless, in the opinion of the Investigator, the nature and/or severity is outside of what is typical for SCS procedures and recovery.

- Lack of efficacy, by itself, does not constitute an AE since failure to receive therapeutic benefit is an issue of efficacy, not safety.

- Loss of therapy/stimulation does not constitute an AE unless an untoward medical occurrence results.

- A subject's perception of the stimulation induced feeling of stimulation sensation is called paresthesia. There are well-known challenges associated with optimizing SCS such as changes in stimulation intensity and stimulation in unwanted areas. This study aims to actively capture the subjects' stimulation sensations by using a structured process (i.e., Stimulation Characteristics, Posture Change Assessment) that will be more sensitive and more informative than passive capture or general inquiries. Negative stimulation or paresthesia sensations will not be reported as AEs unless the Investigator determines the nature and/or severity is outside what is typical for neurostimulation.

9.3 Independent Adjudication Committee

A blinded independent adjudication committee will be responsible for the review, evaluation, categorization, and adjudication of all AEs that occur during the clinical study. AEs will be reported based on the adjudication committee determination.

10 DEVICE DEFICIENCIES

10.1 Device Deficiency Definitions

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labelling.

10.2 Device Deficiency Reporting

The Investigator shall report all suspected device deficiencies to the Sponsor. Device deficiencies will not necessarily result in an AE. However, if an AE is associated with a device deficiency, the AE shall be documented and reported.

11 STATISTICAL ANALYSIS

The most up-to-date description of the analysis resides in the Statistical Analysis Plan (SAP).

11.1 Timing of Analyses

The primary composite endpoint will be tested after the final subject completes their 3-month follow-up. If the primary endpoint is successfully met, the PMA report will be submitted in support of product approval and include analyses of the primary composite endpoint and testing of the subset of hierarchical secondary endpoints defined at 3-months. Additionally, all data collected up to the point of data lock will be submitted for approval.

An additional analysis will be completed assessing all defined endpoints when the final subject completes their 12-month follow-up. Additional annual reporting will be completed as required.

11.2 Study Endpoints

11.2.1 Primary Composite Endpoint

The primary endpoint is a composite endpoint, where a subject is deemed a success if:

- They experience a 50% reduction in overall trunk and limb pain as determined by VAS at the 3-month visit, AND
- They have no increase in baseline pain medications within 4 weeks of the 3-month visit

The efficacy component of the primary endpoint will be determined using the in-clinic subject-completed VAS for overall trunk and limb pain. The VAS assessment of pain is a validated measure, and a 50% reduction from baseline is clinically accepted as a subject success (8, 9).

Subjects who increase their baseline pain medications under the following conditions will be 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 is 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 has not stopped within 4 weeks of primary endpoint visit.
    - Exceptions: Tylenol/rescue medication will be allowed up to two weeks prior to the primary endpoint visit.

11.2.2 Secondary Endpoints for Hierarchical Testing

A number of secondary endpoints are pre-defined for hierarchical testing, so that all endpoints achieving statistical significance under the closed statistical testing procedure will be reported in the final clinical study report. The secondary endpoints for hierarchical testing will be determined using the in-clinic subject-completed VAS. The following secondary endpoints will be tested in order if the primary endpoint is met:

- Percentage change in VAS leg pain at 3 months
- Percentage change in VAS back pain at 3 months
- Incidence of ≥80% reduction in VAS overall trunk and limb pain at 3 months
- Incidence of ≥50% reduction in VAS back pain at 3 months

In addition, when the 12-month follow-up data are complete, an additional analysis will be performed to include:

- The Primary composite endpoint and;
- The Secondary Endpoints for hierarchical testing in the same specified order

11.2.3 Additional Secondary Endpoints

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

- Comprehensive summary of all Adverse Events (AEs)
- Change, percent change, incidence of ≥50% and ≥80% reduction, and cumulative proportion of responders analysis in VAS pain scores
- EQ-5D-5L
- ODI
- Pain diary
- Pain map
- Stimulation characteristics
- Posture change assessment
- PGIC
- Patient satisfaction
- PSQI
- POMS
- SF-12
- Programming and neurophysiologic properties

11.3 Sample Size

This study will randomize up to 134 subjects at up to 20 study sites. In order to help ensure the generalizability of the study results, no study site will randomize more than 26 subjects (20% of the total randomized).

11.3.1 Calculation

The Sponsor assumes that the true success rate associated with the Investigational stimulation for the primary composite endpoint is at least 57%, and that the success rate associated with Control stimulation may be as large as 45%.

Non-inferiority calculation
In order to have at least 80% power to determine that Investigational stimulation is non-inferior to Control stimulation at a one-sided significance level of 0.05 and a non-inferiority margin (δ) of 10%, a

minimum of 60 subjects per group (120 total) are required with known or presumed primary endpoint status (refer to section 11.4.4 for details on how presumed non-responders are classified). This calculation was performed in PASS 2013 and is based upon an unpooled z-test without continuity correction for a non-inferiority test of two proportions.

Adjustment for subject loss
In order to conservatively account for potential post-randomization subject loss of up to 10%, a total of 134 subjects will be randomized in order to obtain at least 120 subjects with known or presumed primary endpoint status.

11.4 General Statistical Procedures

The following general statistical methods will be employed to assess the study data:

- Standard summary statistics will be used to summarize key study variables. Categorical variables will be summarized via incidence and percent. Continuous variables will be summarized via mean, median, standard deviation, and range. 95% confidence intervals will also be included with summary statistics as appropriate.

- Standard two-group tests for significance will be employed, including two sample t-tests, chi-square tests and the normal approximation to the binomial two-sample z-test. Additional exploratory analyses for primary and secondary endpoints may be performed and include correlation analysis, ordinary least squares regression, logistic regression analyses, repeated measures analyses, and generalized estimating equation (GEE) analyses as appropriate.

- In the event planned parametric methods are found to be inappropriate based upon observed distributions of individual variables, appropriate non-parametric methods will be employed.

- Unless stated otherwise, statistical significance is defined as achieving a p-value less than 0.05. One-sided tests will be performed for assessments of non-inferiority and two-sided tests will be performed for assessments of superiority.

- For analysis of the primary composite and hierarchical secondary endpoints, all data obtained within 30 days of the target visit date will be included. This analysis window definition applies to all analysis sets. Data that falls outside this window will be assumed missing.

11.4.1 Assessment of Baseline Characteristics

Baseline characteristics of interest, including baseline pain measures and relevant medical conditions, will be summarized by treatment group and compared statistically to ensure balance between treatment groups. Comparisons between groups will be performed utilizing two sample t-tests for continuous variables and chi-square methods for categorical variables.

Any differences identified in baseline characteristics and measures will be investigated and elucidated in the clinical study reports. Supplementary regression analyses of the primary composite endpoint and the hierarchical secondary endpoints may be provided utilizing any baseline variables found to be unbalanced between treatment groups.

11.4.2 Assessment of Poolability

All study data will be pooled across all study sites to facilitate the testing of the primary composite and the hierarchical secondary endpoints. In the event major deviations within (a) study site(s) are identified during the course of the study, supplementary analyses will be provided showing the impact of both including and removing the offending study site(s) on the final study results.

Summary statistics of the primary composite endpoint and each hierarchical secondary endpoint will be presented by study site in order to assess visual differences in outcomes between study sites. In the

event marked visual differences are observed, they will be investigated and elucidated in the clinical study reports.

11.4.3 Analysis Populations

The primary analysis population is the Intent to Treat subgroup (ITT) in which all randomized subjects will be eligible for analysis. Subjects will be analyzed according to their randomization assignment and must either have known endpoint status or be classified as presumed non-responders as discussed below in section 11.4.4 in order to be included in the analysis. In order for the study to be deemed a success, the primary composite endpoint must pass in the evaluation of non-inferiority in the ITT analysis population. In addition, the secondary test of superiority on the primary composite endpoint must also pass in the ITT analysis population in order for superiority to be sought as a labeling claim. All testing of the hierarchical secondary endpoints in support of labeling claims will also be performed on the ITT analysis population.

Two additional analysis populations of interest are defined a priori and will be utilized to assess study outcomes. First, the Permanent Implant Subset (PIS) will include all subjects who received a permanent implant. Second, the Per Protocol (PP) analysis population will include all subjects who received a permanent implant, and who also have evaluable primary endpoint data and no major deviations.

It is not a requirement for study success that either the PIS or PP analysis elicit a successful test of the primary composite endpoint. However, any differences in inferences drawn between the three analysis populations will be investigated and elucidated in the clinical study reports.

11.4.4 Handling of Missing Data in Primary and Hierarchical Analyses

All randomized subjects will be eligible for inclusion in the ITT analyses of the primary and hierarchical secondary endpoints. The analysis set will be comprised of all subjects with complete data and those with missing data classified as presumed non-responders as described below.

Primary Composite Endpoint

The following events eliciting missing data at three months will cause the subject to be classified as a presumed non-responder and will be analyzed as a failure for the primary endpoint:

- Failure of the trial stimulation phase (<50% improvement in 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.

All other missing data will be classified as missing and no data imputations will be performed on these data for the primary endpoint analysis. The rate of missing is expected to be low and balanced between treatment groups. Events that will be categorized as missing include:

- Subject voluntary withdrawal for any reason other than a device or stimulation-related AE.
- Investigator withdrawal for any reason other than a device or stimulation-related AE.
- Subject fails to return for follow-up visits and 3 attempts to contact the subject are not successful.
- Subject returns for follow-up outside of the 30-day analysis window associated with the given visit.

Missing Data Sensitivity Analyses; Primary endpoint

A number of sensitivity analyses will be performed on the ITT analysis population to help understand the potential impact of missing data that will include, at a minimum:

- Best case scenario (all Investigational missing data assumed a success and all Control missing data assumed a failure).

- Worst case scenario (all Control missing data assumed a success and all Investigational missing data assumed a failure).
- Tipping point analysis (determine the point between best and worst case where the significance threshold is achieved).

Additional sensitivity analyses may be conducted in the event the above sensitivity analyses do not adequately assess the robustness of the study conclusions. In particular, multiple imputation may be utilized thereby allowing all randomized subjects to be included in the primary endpoint assessments.

The incidence of and reasons for missing primary endpoint data will be summarized and compared between the two study groups.

Hierarchical Secondary Endpoints

Missing data will be addressed as follows in the hypothesis testing for the hierarchical secondary endpoints:

- For incidence measures (e.g., incidence of ≥50% reduction in VAS scores), missing data will be managed in the same manner described above for the primary composite endpoint.
- For continuous measures (i.e. changes from baseline in VAS scores), subjects with missing data categorized as presumed non-responders will utilize a last-value carried forward imputation methodology.
- Subjects that fail the medication component of the primary endpoint will have a change from baseline value of “0” imputed.

Sensitivity analyses of the hierarchical secondary endpoints may be conducted in the event the above analyses provide borderline results. Analysis methods employed would be similar to those planned above for the testing of the primary composite endpoint.

11.5 Analysis of Study Endpoints

11.5.1 Primary Composite Endpoint

The primary composite endpoint will be analyzed via the normal approximation to the binomial distribution, utilizing an unpooled estimate of the standard error and no correction for continuity. Non-inferiority of Investigational relative to Control will be assessed against the clinical significance margin (δ) of 10% at a one-sided significance level (α) of 0.05.

If non-inferiority is met, then superiority will be tested at a two-sided significance level of 0.05.

11.5.2 Hierarchical Secondary Endpoints

Closed Testing Procedure

If non-inferiority is met in the testing of the primary composite endpoint, the hierarchical secondary endpoints will be tested in order. In the event all hierarchical secondary endpoints are met, secondary testing for superiority for each of the non-inferiority endpoints will also occur in the same order. All superiority testing will be performed at a two-sided α=0.05.

Analyses

The incidence measures will be analyzed via the normal approximation to the binomial distribution, utilizing an unpooled estimate of standard deviation and no correction for continuity. The continuous hierarchical secondary endpoints will be assessed via two-sample t-tests.

11.5.3 Other Secondary Effectiveness Endpoints

The remaining secondary endpoints as well as observed relationships between endpoints will be assessed per the methods described above in Section 11.4. Findings of significance may be presented and include p-values and/or confidence intervals as appropriate. Standard methods will be utilized to compare statistics between study groups at time points of interest (e.g., two-sample t-test, normal approximation to the binomial).

11.5.4 Adverse Events

AEs will be summarized by treatment group. The incidence of all distinct AEs will be presented along with 95% confidence intervals on the ITT analysis population. AEs will also be summarized by seriousness, severity, and relatedness to the procedure, device, and/or stimulation. AEs will be reported based on the adjudication committee determination.

12 RISK ANALYSIS

12.1 Potential Risks

Risks associated with the Evoke SCS system are similar to those of other conventional open-loop SCS systems, which are generally minor. All medical procedures involve some risk of injury. Other anticipated risks associated with the Evoke SCS system are listed in this protocol or found in the literature, post-market surveillance data (e.g., FDA Manufacturer and User Facility Device Experience (MAUDE) database), and device labeling for SCS systems.

In addition to the general surgical risks, potential risks to subjects associated with implantation and use of the Evoke SCS system include, but are not limited to:

- Undesirable changes in stimulation sensation and/or location
- Uncomfortable changes in stimulation (over and/or under stimulation)
- Persistent post-surgical pain at hardware implantation sites
- CLS migration, which may result in pain or difficulty in charging
- Seroma or hematoma at surgery sites
- Epidural hemorrhage, spinal cord injury and possible paralysis
- Lead migration from the location chosen at initial implantation resulting in stimulation changes
- Breakage of the lead or failure of other system components, which may result in loss of stimulation
- Rejection of, or allergic reaction to, the implanted components
- Infection that may require hospitalization with intravenous antibiotic therapy
- Cerebrospinal fluid (CSF) leakage
- Inadequate pain relief following system implantation
- Erosion of the lead or CLS through the skin
- Weakness, clumsiness, numbness or pain below the level of lead implantation

Subjects may require surgery (including revision, explant, and replacement) as a result of any of the above.

12.2 Minimization of Risks

All predicable risks associated with the Evoke SCS System have been identified and mitigated, or minimised with residual risk disclosed within labelling.

Risks in this study will be minimized through the use of strict compliance with this protocol, and adherence to the guidelines for subject selection, site training, and close monitoring of the subject status. In addition, the product labeling details instructions for device use and warnings and precautions, which must be followed to minimize risk to subjects. Additionally, only licensed and qualified physicians

trained on the Evoke SCS System will implant the device, and device programming will be performed by a trained FCE with the oversight of the Investigator.

12.3 Potential Benefits

There are several potential benefits of the Evoke SCS system and specifically with regard to the feedback control to participating study subjects suffering from chronic, intractable pain of the trunk and/or limbs. These include:

- The Evoke SCS system may provide significant pain relief.
- The Evoke SCS system may allow patients to reduce their pain medications.
- The Evoke SCS system may improve patients' quality of life, sleep quality, emotional and/or physical functioning.
- The Evoke feedback control may reduce variation in stimulation intensity due to positional changes/activity.
- The Evoke feedback control stimulation may be more effective in providing pain relief compared to conventional open-loop stimulation.

12.4 Benefit-Risk Conclusions

SCS has been used for over 40 years to aid in the management of chronic pain of the trunk and limbs. The risks associated with participation in this study are outweighed by the potential benefits and value of the research. The Evoke system enables the treatment of chronic intractable pain of the trunk and/or limbs, which if left untreated, can lead to a poor quality of life and dependence on or serious harm from pain medication or other treatments. The evidence clearly indicates that although there are risks associated with the procedure and the device, the incidence rates are very low, and the majority of complications that can result from these risks can be treated. In addition, the procedure itself is completely reversible as the device, including the leads, can be removed.

13 STUDY ADMINISTRATION

13.1 Study Materials

13.1.1 Packaging and Labeling

In accordance with 21 CFR Part 812, the study device or its immediate package will bear a label with the following information: the name and place of business of the manufacturer, packer, or distributor (in accordance with 21 CFR Part 801), the quantity of contents, if appropriate, and the following statement: "CAUTION—Investigational device. Limited by Federal (or United States) law to investigational use." describing all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions are provided in the Instructions for Use (IFU).

13.1.2 Handling and Storage

The Investigator must ensure that the study devices are controlled and stored according to the IFU. All supplies are to be used only for this study protocol and not for any other purpose. Products are not to be used after the expiration date indicated on the label. The Investigator must not destroy any unused supply unless instructed by the Sponsor.

13.1.3 Product Administration

Study devices will be provided by the Sponsor. All implanting Investigators will be experienced with implanting SCS systems and sufficiently trained on appropriate use of the study device. Sponsor representatives will be on site during procedures and follow-ups for additional device support and programming.

13.1.4 Product Accountability

The Investigator is responsible for study device accountability, reconciliation, and record maintenance. The Investigator must maintain study device accountability records throughout the course of the study.

13.2 Ethics

13.2.1 Institutional Review Board Approval

The protocol, informed consent form (ICF) and authorization for the use and disclosure of health information per the Health Insurance Portability Accountability Act (HIPAA) must be approved by the study site's Institutional Review Board (IRB) before subject enrollment. Changes to the protocol must be approved in writing by the Sponsor and the IRB (as applicable) before the change is implemented.

Prior to subject enrollment, a copy of the IRB approval letter (and approved ICF and subject materials) must be submitted to the Sponsor. Investigators are responsible for submitting and obtaining initial approval and continuing approval of the study from the IRB and forwarding copies of the approval documentation to the Sponsor.

13.2.2 Informed Consent

The Investigator will prepare an ICF in accordance with this study protocol, regulatory requirements (21 CFR Part 50), Good Clinical Practices (GCP), and the ethical principles that have their origin in the Declaration of Helsinki using the sample ICF provided in Appendix A of this study protocol.

As part of the consent process, the subject will have ample time and opportunity to ask questions of, and receive answers from the personnel conducting the study, and to decide whether or not to participate in the study. The information that is given to the subject shall be in language understandable to them. Neither the Investigator nor the study site personnel shall coerce or unduly influence the subject to participate or continue to participate in the study.

All subjects must document their consent for study participation and authorization for use and disclosure of health information by signing the IRB-approved ICF. The Investigator will retain the original ICF signed by the subject and a copy of the ICF will be provided to the subject.

The Sponsor will inform the Investigator whenever information becomes available that may be relevant to the subject's consent, and will revise the ICF accordingly and provide it to the Investigator for approval by the IRB. The Investigator or his/her authorized designee shall inform the subject of this information. After approval by the IRB, a copy of this ICF must be provided to the participating subjects, and the informed consent process as described above repeated, in accordance with the IRB requirements.

13.2.3 Subject Confidentiality

The Sponsor and its designees will make every reasonable effort to protect the confidentiality of the subjects participating in the study. Only Sponsor personnel or contracted agents of the Sponsor will have access to these confidential files and will act in accordance with applicable regulations as required by HIPAA. The IRBs and FDA also have the right to inspect and copy all records pertinent to this study. All data used in the reporting of the study will eliminate any identifiable reference to the subjects.

13.3 Data and Quality Management

This study will be conducted in accordance with the regulatory requirements, GCP, and the ethical principles that have their origin in the Declaration of Helsinki. The study shall not begin until receipt of the required approval from the FDA and reviewing IRB. Any additional requirements imposed by the FDA or the IRB shall be followed as appropriate.

13.3.1 Data Collection and Management

Subject data will be collected and recorded on Case Report Forms (CRFs). An electronic data capture (EDC) system specifically created for this study in accordance with this study protocol, regulatory requirements (21 CFR Part 11), and GCP, will be used. The Investigator or his/her authorized designee will enter data from the source documents into the database. Data may be reviewed by the Sponsor using programmed or manual queries to ensure accuracy of the data entered and minimize the occurrence of missing data. Data management activities will be conducted in accordance with the Data Management Plan.

13.3.2 Monitoring

The study will be monitored to ensure the rights and well-being of human subjects are protected; the reported study data are accurate, complete, and verifiable from source documents; and the conduct of the study is in compliance with the study protocol, regulatory requirements, GCP, Declaration of Helsinki, and any conditions of approval imposed by the reviewing IRB and FDA. Monitors will be qualified by training and experience to monitor the study in accordance with these requirements. Monitoring activities will be conducted in accordance with the Monitoring Plan.

13.3.3 Audits/Inspections

Audits of the study sites may be performed by the Sponsor or designee, independent of and separate from routine monitoring or quality control functions, to evaluate study conduct and compliance with the study protocol, applicable regulatory requirements, GCP, Declaration of Helsinki, and any conditions of approval imposed by the reviewing IRB and FDA.

The FDA or other regulatory agencies may perform inspections of the study sites before, during, or after the conclusion of the study. The Investigator shall contact the Sponsor immediately upon notification of inspection, and must fully cooperate with the regulatory agency by permitting inspections at reasonable times and in a reasonable manner.

13.4 Access to Study Records

The Investigator must permit monitoring and auditing by the Sponsor or designee, and inspection by the appropriate regulatory authorities, and provide direct access all requested study-related records.

13.5 Study Site Training

All implanting Investigators will be trained on the device. All primary site personnel (Investigator(s) and core site staff) will be trained on the study protocol and the applicable Code of Federal Regulations. Support staff may be trained minimally based on delegated tasks.

13.6 Investigator Responsibilities

The Investigator is responsible for ensuring the study is conducted according to the signed Clinical Trial Agreement (CTA)/Investigator Agreement (IA), study protocol, regulatory requirements, GCP, Declaration of Helsinki, and any conditions of approval imposed by the reviewing IRB and FDA; for protecting the rights, safety, and welfare of subjects under the Investigator's care; and for the control of devices under investigation.

13.7 Investigator Agreement and Financial Disclosure

The Principal Investigator (PI) at each site will be required to sign the Investigator’s Agreement, as per 21 CFR Part 812.

In addition, in accordance with 21 CFR Part 54, all Investigators will be required to sign a Financial Disclosure form, which certifies or discloses the Investigator's and his/her immediate family's financial interests and arrangements with Saluda Medical. Investigators must inform the Sponsor of any changes to the information within the financial disclosure throughout the course of the study and for a period of two years after the device is approved by the FDA or the study is terminated, whichever is later.

13.7.1 Investigator Records

Records to be maintained by the investigator in the study site's essential study files for this study include, but are not limited to:

- Study protocol and all amendments
- Signed IA for the PI
- Signed Financial Disclosure for all Investigators
- IRB approval letter(s) including approved consent and HIPAA authorization form(s), and subject materials
- IRB Membership list(s) or Letter of Assurance
- All relevant correspondence relating to the study between the site and Sponsor, the site and IRB
- Curriculum Vitae (CV) for all Investigators
- Training documentation
- Delegation of Authority
- Investigational device accountability records including: date, quantity, lot/serial numbers of all devices, identification of all persons the device was used on and final disposition.

The following records must be maintained for each subject enrolled in the study:

- Signed ICF and Authorization for the Use and Disclosure of Health Information
- AEs and any supporting documentation
- Protocol deviations
- Source documentation: complete medical records, including procedure reports, professional notes, etc.

13.7.2 Investigator Reports

Investigators are required to prepare and submit the following complete, accurate, and timely reports:

- An Investigator shall submit to the Sponsor and to the reviewing IRB a report of any **UADE** occurring during an investigation as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect.

- An Investigator shall report to the Sponsor, within 5 working days, a **withdrawal of approval by the reviewing IRB** of the Investigator's part of an investigation.

- An Investigator shall submit **progress reports** on the investigation to the Sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.

- An Investigator shall notify the Sponsor and the reviewing IRB of any **deviation from the investigational plan** to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the Sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB in accordance with 812.35(a) also is required.

- If an **Investigator uses a device without obtaining informed consent**, the Investigator shall report such use to the Sponsor and the reviewing IRB within 5 working days after the use occurs.

- An Investigator shall, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a **final report** to the Sponsor and the reviewing IRB.

- An Investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

13.8 Sponsor Responsibilities

Saluda Medical Americas, Inc., a fully owned subsidiary of Saluda Medical Pty. Ltd., will serve as Sponsor of this clinical investigation and is responsible for selecting qualified Investigators and providing them with the information they need to conduct the investigation properly, ensuring proper monitoring of the investigation, ensuring that IRB review and approval are obtained, submitting an IDE application to FDA, ensuring that any reviewing IRB and FDA are promptly informed of significant new information about an investigation, as required in 21 CFR 812 Subpart C, and for Sponsor records and reports outlined in 21 CFR Part 812 Subpart G.

13.8.1 Sponsor Representatives

Sponsor representatives may participate in the conduct of the trial to the extent described in this protocol. Sponsor representatives will not be blinded in this study, particularly since Sponsor representatives are involved in device programming. Participation in the study will be limited to Sponsor personnel who are appropriately trained. Sponsor representatives will operate equipment during the procedures and follow-up, and interact with the subject to accomplish procedure and programming activities. Typical tasks may include:

- Interrogating and downloading the device data
- Programming device parameters
- Clarifying device behaviour, operation, or diagnostic output
- Assisting with the collection of study data from the device
- Entering data on study worksheets for procedures and programming
- Allocating the randomization assignments
- Recording any device deficiencies

At no point shall personnel from the Sponsor:

- Practice medicine
- Provide medical diagnosis or treatment to patients
- Discuss a subject’s condition or treatment with a subject without the oversight of a healthcare professional

13.9 Deviations to the Protocol

An Investigator is required to conduct this study in accordance with the signed CTA/IA, study protocol, regulatory requirements, GCP, Declaration of Helsinki, and any conditions of approval imposed by the reviewing IRB and FDA.

In accordance with FDA regulation 21 CFR Part 812.150(a)(4), the Investigator shall notify the Sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but no later than five working days after the emergency occurred.

All deviations from the study protocol must be reported to the Sponsor. Except in an emergency, prior approval by the Sponsor is required for an anticipated change in or deviation from the plan and, if these changes or deviations could affect the scientific soundness of the plan or the rights, safety or welfare of human subjects, prior FDA and IRB approval is also required in accordance with 21 CFR Part 812.35(a).

13.10 Amendments to the Protocol

Any amendments to the study protocol will be clearly documented and approved by the Sponsor and the IRB prior to implementation.

13.11 Completion, Early Termination, or Suspension of the Study

The Sponsor reserves the right to suspend or terminate the study at an individual study site or entirely at any time. Suspension or early termination of a study site may occur due to serious or repeated noncompliance on the part of an Investigator. Reasons for suspension or early termination of the entire study may include, but are not limited to, the following:

- The incidence and seriousness of AEs in this or other studies indicates a potential health hazard to subjects;
- New information on efficacy from this or other studies.

Subjects may continue to use the device following study closure, unless notified otherwise by the Sponsor (e.g., device does not receive regulatory approval). Subjects may be made aware of their treatment assignment at the completion of the study. They will be followed by their physician in accordance with established practice for SCS systems.

13.12 Record Retention

The Investigator and Sponsor shall maintain the required records during the investigation and for a period of two years after the latter of either the completion/termination of the study or the date the Evoke SCS System receives market approval for the indication being studied. An Investigator or Sponsor may withdraw from the responsibility to maintain records for the period required and transfer custody of the records to any other person who will accept responsibility for them.

The Investigator's study records may be discarded only upon approval from the Sponsor. The PI must contact the Sponsor before destroying any records pertaining to the study to ensure that they no longer need to be retained.

13.13 Clinical Trials Registry/Database (ClinicalTrials.gov)

This clinical study will be registered on www.ClinicalTrials.gov. Study results will be submitted as required. Per the requirements of 21 CFR Part 50, the ICF will contain a statement that clinical trial information will be entered into this clinical trials registry/database.

13.14 Publication

Publication of clinical data from this trial will be in accordance with the fully executed clinical trial agreements with the PIs. Publication of all data will conform to standards set forth in peer-reviewed journals and the Uniform Requirements for Manuscripts Submitted to Biomedical Journals published by the International Committee of Medical Journal Editors (ICMJE).

REVISION HISTORY

Revision	Description
1.00	Initial release submitted in the IDE (G150266).
2.00	Revision submitted in an amendment to the IDE (G150266_A001).
3.00	Revision submitted in an amendment to the IDE (G150266_A002). All subjects were enrolled and completed their primary endpoint visits under this protocol.
4.00	Revision submitted in an amendment to the IDE (G150266_S014) to allow for a self-selected crossover and to update the statistical analysis section to refer to the FDA approved SAP.

ABBREVIATIONS AND ACRONYMS

Abbreviation/Acronym	Term
AE	Adverse Event
BWS	Body-Worn System
CFR	Code of Federal Regulations
CLS	Closed Loop Stimulator
CTA	Clinical Trial Agreement
ECAP	Evoked Compound Action Potential
ETS	External Trial System
FBSS	Failed Back Surgery Syndrome
FCE	Field Clinical Engineer
FDA	Food and Drug Administration
GCP	Good Clinical Practice (For the purposes of this study, this means compliance with FDA regulations for IDEs.)
HIPAA	Health Insurance Portability Accountability Act
IA	Investigator Agreement
ICF	Informed Consent Form
IDD	Intrathecal Drug Delivery
IDE	Investigational Device Exemption
IFU	Instructions for Use (Surgical Guide, User Manual, Clinical Manual, and supporting materials)
IPG	Implantable Pulse Generator
IRB	Institutional Review Board
ITT	Intent to Treat
LTF	Lost to Follow-up
MRI	Magnetic Resonance Imaging
MTS	Multi-Channel System
ODI	Oswestry Disability Index
PGIC	Patient Global Impression of Change
PI	Principal Investigator
PIS	Permanent Implant Subset
PMA	Premarket Approval
POMS	Profile of Mood States
PP	Per Protocol
PSQI	Pittsburgh Sleep Quality Index
SAE	Serious Adverse Event
SCS	Spinal Cord Stimulator, or Spinal Cord Stimulation
SF-12	12 Item Short Form Survey
UADE	Unanticipated Adverse Device Effect
US	United States
VAS	Visual Analog Scale
WPI	World Precision Instruments

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APPENDIX A: SAMPLE INFORMED CONSENT TEMPLATE

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE: A prospective, multicenter, randomized double-blind study examining the safety and efficacy of using the Evoke™ Spinal Cord Stimulator (SCS) System with feedback to treat patients with chronic pain of the trunk and/or limbs.

PROTOCOL NO.: SCLSH1503

SPONSOR: Saluda Medical Americas, Inc.

INVESTIGATOR: Name
Address
City, State, Zip Code
Country

STUDY-RELATED PHONE NUMBER(S): Name
Phone Number(s)

INTRODUCTION

You are being asked to be in a research study because you have chronic pain in your trunk (back) and lower limbs (legs) and your study doctor, [indicate investigator], feels you may be a suitable candidate for neurostimulation therapy. The purpose of this consent form is to help you decide if you want to be in the research study.

You may take home an unsigned copy of this consent form to think about or discuss with family and friends before making your decision. You are free to ask questions about this study at any time. You should not join this research study until all of your questions are answered. If you agree to take part in this study, you will be asked to sign this consent form. After you sign the form, you will be given a copy. An additional copy will remain in your medical chart.

Before you learn about the study, it is important that you know the following:

- Your participation is entirely your choice
- You may or may not benefit from taking part in this study, but knowledge gained from your participation may help others
- You may decide not to take part or to stop being in the study at any time without losing the benefits of your usual medical care
- A description of this clinical trial will be available on http:// www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

This study is sponsored by Saluda Medical, a company that is testing a new investigational device for the treatment of chronic pain. If you have any questions, please ask.

PURPOSE OF THE STUDY

The purpose of this research is to show whether the study device, the Evoke™ Spinal Cord Stimulator System, is safe and works to treat chronic pain. This study will provide information that may help make this device more widely available to other people with chronic pain. The medical device is made by Saluda Medical.

The Evoke System is designed to stimulate your spinal cord to potentially relieve your pain. The study device has two parts that are placed surgically (implanted): 1) the stimulator (battery pack) that is placed under the skin in the buttocks or abdomen, and 2) up to 2 leads (wires) that are inserted next to your spinal cord and connected to the stimulator. This is an investigational (experimental) device. An investigational device is one that has not been approved by the U.S. Food & Drug Administration (FDA).

WHAT HAPPENS IF I AGREE TO BE IN THE STUDY?

If you decide you want to be in this study you must sign this consent. Your participation in the study will require one or more screening/baseline visits, participation in a trial stimulation phase and then, if you qualify, participation in the implant phase. Following the implant phase, you will enter a follow-up phase. Each of these phases are described in detail below.

While you are participating in this study, you may not participate in another study without notifying the study doctor and getting the written permission of the sponsor (Saluda Medical) to participate in the other study.

Screening/Baseline Assessment Phase

You will have one or more visits to complete study required tests before your study doctor decides if you qualify for the study. These are called screening or baseline visits and will be done before you are approved to be a participant in the study. The tests and information collected will include:

- A physical and psychological examination
- You will be asked questions about your health, physical and emotional well-being, pain symptoms, medications, and treatment.
- You will complete questionnaires that ask you about your health, physical and emotional well-being, quality of life, daily activities, sleep, and any limitations due to your pain.
- A pregnancy test (if you are female and if applicable).
- Imaging (MRI or CT) may be necessary, but will be determined by the study doctor

During the screening visits for the study, your study doctor will review all the test results and may find that you do not qualify for participation in the study. If this happens your participation will end and you will not be enrolled in the study.

The total amount of time to complete the screening and baseline assessments will be approximately two to four hours and may require more than one visit to the study doctor. After the screening tests are completed, and if you qualify for the study you will be scheduled to have the Trial Stimulation Procedure described below.

Medications

The study doctor will carefully review your pain medications. You will need to take the same pain medications you currently take until the 3-month follow-up visit (this includes the same frequency and dosage) as failure to do so could make it difficult to tell if the study device is helping you. This is so the study can evaluate only the effect of the study device on your pain. The study doctor may prescribe pain medications while you recover from surgery, for new causes of pain or other safety reasons.

You may be receiving care from another doctor. If another doctor who is not part of this study wants to change your pain medications, you or the other doctor must talk to a study doctor before making any changes, unless there is a safety reason for the change. You are still able to receive any treatment necessary from any medical care provider in the event of an emergency, including changing or adjusting your medications. You are also able to have other medications prescribed or adjusted by another doctor. For study purposes, please notify your study doctor of any change to your medications or changes in your health during your participation.

Trial Stimulation Phase

The trial stimulation phase involves a surgical procedure to place temporary leads (wires) into your spine. The procedure will be done under anesthesia according to the investigator's standard practice. Typically, you are awake and given medicine to help you relax, but all study doctors have different techniques to help you. It is possible that you may feel some discomfort during the procedure, but every effort will be made to make you feel comfortable. On average, the procedure takes about 1 hour. The procedure may be recorded on video and/or photographs that do not show your face. Every effort will

be made to not reveal your identity in the video or photos. The recording or photographs may be provided to the sponsor of the study.

During the procedure, you will lie face down on the procedure table. The skin around the surgical area on your back will be cleansed with antibacterial solution to sterilize the area. A needle will be inserted into your spine and then the study doctor will insert 1 or 2 leads (wires) into your spine. The number of leads will be decided by the study doctor during the procedure and will depend on how many are needed to treat your pain. The procedure will occur under fluoroscopy (a moving x-ray machine) to allow the study doctor to guide the wires to the correct location in the spine to stimulate the target nerves.

At the end of the procedure, the needles will be removed. The leads will stick out of your back and be attached to a cable that is connected to a power source called a trial stimulator. The area where the needles were inserted and where the leads exit your body will be covered with a dressing. The trial stimulator will stay attached and remain outside your body.

Your stimulator will be programmed by a sponsor representative with the oversight of the study doctor to send electrical signals to help control your pain. You will be told when the stimulation is going to be turned on. This may feel like a tingling sensation. The study doctor will monitor your pain.

You will be randomized (assigned by chance, by a computer) to one of two stimulation modes. You have an equal chance of being in either group, like the flip of a coin (1:1). Both groups will receive the same device with active stimulation that continuously measures your body's response to the stimulation and the same remote control functions, but you will experience one of two different stimulation modes (automatic or manual) based on which group you are assigned to. In the automatic stimulation mode, the system changes settings automatically based on your body's response and your remote control, whereas in the manual stimulation mode, the system makes changes based on your remote control only. You, the study doctor and clinic staff will not know which group you are assigned until after the study is completed. You will need to wear the trial stimulator until the end of the trial stimulation phase, which typically lasts for about a week but may be up to 30 days. The study doctor will decide what programming is right for you based on how well the stimulator is controlling your pain. You will be given a remote control that will allow you to adjust the amount of stimulation that the stimulator delivers. The remote control will allow you to turn the stimulator on or off and adjust the amount of stimulation up or down like turning the volume up or down on a radio.

During the trial stimulation phase you will be asked to limit your activity level to low or moderate activity. You should talk to your study doctor if you are not sure about whether you can do certain activities.

During the trial stimulation phase you may return to the clinic as often as needed to get the stimulator reprogrammed. You may be asked to answer questions about your pain management, the sensations you feel from your stimulator (e.g., tingling, known as paresthesia), and medications.

At the end of this trial stimulation phase, the study doctor will remove the temporary leads. This process will take approximately 5 minutes and the visit will last about 30 minutes.

At the end of the trial stimulation phase, you and the study doctor will evaluate whether the trial stimulator worked to alleviate your pain and whether you want to continue to receive stimulation therapy. If your study doctor agrees that stimulation therapy may be appropriate for you and you want to continue in the study, you will move on to the implant phase of the study. If the study doctor does not believe stimulation therapy is right for you, or if you do not want to continue in the study, your participation will end after the trial stimulation phase.

Study Device Implantation – Implant Phase

If you proceed to the implant phase, the procedure will take place in an operating room. The procedure will be done under anesthesia according to the investigator's standard practice. Typically, you are awake but given medicine to help you relax, but all study doctors have different techniques to help you. It is possible that you may feel some discomfort during the procedure, but every effort will be made to make you feel comfortable. On average, the procedure takes about 2 hours.

During the procedure you will lie face down on the procedure table. The skin around the surgical area in the back or abdomen will be cleansed with antibacterial solution to sterilize the area. The study doctor will again place a needle and leads (wires) into your spine. The study doctor will also surgically implant a stimulator (battery back). The stimulator will usually be placed in either the upper buttocks or abdomen. Instead of connecting the leads to a box that is kept outside the body, the leads and stimulator will remain in your body under your skin. The procedure will occur under fluoroscopy (a moving x-ray machine) to allow the study doctor to guide the wires to the correct location in the spine to stimulate the target nerves.

The study doctor may decide to not implant a device. This may happen because the leads (wires) or stimulator could not be properly placed, or for other reasons. If this should happen, the study doctor will discuss the reason(s) and your other options for therapy. If you go into surgery but do not receive a device, you will be followed for a minimum of 30 days so we can check on your health and then you will be done being in the study.

The sponsor representatives will program the stimulator during the procedure with the oversight of the study doctor. You will be told when stimulation is going to be turned on. This may feel like a tingling sensation. The study doctor will monitor your pain.

After the implant procedure, you will again be given a remote control that will allow you to turn the study device on and off, and control the amount of stimulation you receive from the study device, similar to turning the volume up or down on your radio.

After the surgery you may need to stay in the surgical facility for observation by study doctors and nurses. You may be given antibiotics. Your study doctor may decide to have you stay a few nights, to continue to check on your health and study device settings.

About one week after your implant, you will go back to the study doctor to have your wound(s) checked. You may have additional visits to check the healing of your wound(s), if needed.

Before you are discharged you will be told how to operate the remote control. For about the first eight weeks after the surgery you will need to limit your activity level to low or moderate. You should limit the amount of lifting, bending, twisting and stretching you do. Also, you should not manipulate the implanted components as you may cause damage or movement of the device. You should talk to your study doctor if you are not sure about whether you can do certain activities.

You will be given an important card to carry with you. It will state you have a study device implanted in your body that is investigational. You must show this card and tell any doctors, health care facilities or hospitals that provide health care to you that you have this study device implanted. You may also show this before you go through any security scanners.

Study Follow-Up Phase

You will be required to return to the clinic for follow-up visits at 1 month, 3 months, 6 months, 9 months and 12 months after your surgery. Thereafter, you will be required to visit the clinic twice a year for up to 2 more years (a total of 3 years after implant). There is a required window of time for each of these visits to occur; every effort should be made to complete the visit within that window. Between your follow-up visits, clinic staff will contact you by phone to ask about your pain, pain medications, and how your study device is functioning.

You may come into the clinic at any time should your study device need reprogramming to better provide therapy. Your study doctor may want to see you more often if he/she thinks it is necessary. Your study doctor may require other tests that are not part of this study.

At all of the follow-up visits (1 month, 3 month, 6 month, 9 month, 12 month and twice yearly for up to 3 years), the following will occur:

- You will be asked questions about your health, the medications/therapies you are taking or any changes in medications/therapies since your last study visit.
- You will complete questionnaires that ask you about your pain, stimulation sensations, sleep, health, physical and emotional well-being, daily activities, and any limitations due to your pain.

- Your study device system will be tested and the setting of the study device will be changed if it is needed.

Optional: Stimulation Mode Crossover (after your 2-year visit)

- Upon completion of your 2-year study visit, you will be given the option to try programming in the other stimulation mode (this is known as a crossover). You and the investigator and site staff will remain blinded as to which stimulation mode you are assigned. There is no change to the duration of study participation, and the last study visit remains the 3-year visit after your implant. The crossover occurs between the 2-year and 2 ½ year visits only. If you decide not to participate in the crossover, you will stay in your current stimulation mode until the end of the study and there are no changes to your study visit schedule. By signing this updated consent document, you are not agreeing to participate in the crossover, but are confirming you have been given the details of the optional participation. Your decision to crossover will be documented on a separate form. Your participation in the crossover is entirely your choice.
- If you chose to try the other stimulation mode (crossover), you will need to come in for up to two additional scheduled visits after you are programmed in the new stimulation mode (1-month and 3-month post crossover), additional programming visits may also be needed. You will be required to be in the new stimulation mode for a minimum of 2 weeks before you have the option of returning to your original stimulation mode. If you continue to try the new stimulation mode at the 1-month post crossover visit, you will have one more additional scheduled visit before you resume the remaining visit schedule for the study (2.5 year, and final study visit at 3 years). Upon making your final decision on stimulation mode preference, you will be programmed in your preferred mode for the remainder of the study. The additional visits will take approximately 2 hours each. The same questionnaires and evaluations will be conducted at these additional visits (as compared to other follow-up visits) in addition to questions about your decision to crossover and questions about your crossover experience.
- If you decide to participate in the crossover, initially the device will be programmed in the other stimulation mode and then the device will be turned off. You will be instructed not to turn the device on until your pain returns, at which time you will be asked to complete a pain questionnaire. When you turn stimulation on, it will be operating in the crossover stimulation mode. This will be the only time you are requested to turn off stimulation.

It is possible the study could end before you have completed all follow-up appointments. It is very important that you keep your follow-up appointments so that your study doctor can keep track of how you are doing. Missed visits may have a harmful effect on the study results. If you think that you will be unable to return to the clinic for these visits, please tell us now.

HOW MANY PATIENTS WILL TAKE PART IN THIS STUDY?

Approximately 134 subjects are expected to participate in this study at up to 20 study sites in the United States.

HOW LONG WILL I BE IN THIS STUDY?

Your participation in this study and follow-up visits are expected to last up to 3 years after your surgery.

REPLACEMENT AND REMOVAL: STIMULATOR AND LEADS

Stimulator (Battery Pack)

The stimulator (battery pack) may need to be replaced or removed while you are in the clinical study. This could happen for the following reasons:

- Infection
- The battery pack fails to work
- The battery runs out of power

- When the battery is almost finished, you will need to have the battery surgically replaced, so you can continue your treatment. The battery should last about 10 years, but some subjects may require that the device be turned up higher. This may cause the battery life to be shorter.
- Implanting a new or different device system when it becomes available (although there is no guarantee this will happen).

Lead (Wire)

Your wire may need more surgery for the following reasons:

- Remove an infected wire
- Repair or fix the wire
- Put in a new wire or move the wire to get a better response
- Implanting a new or different device system when it becomes available (although there is no guarantee this will happen).

Some of the risks described in this form may be more likely to occur during a device removal or replacement, since the risk of re-operating is typically higher than the risk of the initial implant procedure. It may be too risky to surgically remove all or part of the device, and you may not be able to have the device removed after implant if you request that surgery. You should discuss these risks with the study doctor.

WHAT HAPPENS AT THE END OF THE STUDY?

If your participation ends early in the study for any reason or if the device is not approved by the US Food and Drug Administration (FDA) at the end of the study, the device can be left in place and turned off or it can be surgically removed (if your study doctor agrees it is not too risky to remove it). You should discuss these options with your doctor to determine which one is best for you. You can be told which group you were assigned to at the end of the study.

The sponsor has not agreed to pay for device removal, device replacement or other ongoing costs of medical care after your participation in the study ends. At that time, you or your insurer will be responsible for those costs.

WHAT ARE THE RISKS OR SIDE EFFECTS OF THIS STUDY?

All medical procedures involve some risk of injury. We do not expect that subjects in this study will be exposed to any significant risks other than those commonly associated with currently approved spinal cord stimulator systems.

This list is not meant to scare you, but to make you aware of the risks before you agree to take part in the study. This section describes the risks of the surgery and study device treatments, as well as risks of other procedures you will have only because you are in the study.

Below is a list of risks that would be associated with any surgical procedure:

- Abscess (collection of pus)
- Cellulitis (skin infection)
- Excessive fibrotic tissue (scarring)
- Wound dehiscence (splitting open)
- Infection of the wound, surgical area or body system
- Wound necrosis (dead tissue around the wound)
- Edema (swelling)
- Inflammation
- Thrombosis (blood clot)
- Embolism (blockage of a blood vessel due to a blood clot, gas bubble or other foreign matter)
- Thromboembolism (blockage of a blood vessel with a blood clot that has dislodged from where it was formed)
- Ischemia (insufficient blood flow to an organ)

- Hemorrhage (excessive bleeding)
- Thrombophlebitis (vein inflammation related to a blood clot)
- Reaction to anesthesia
- Hyper or hypotension (high or low blood pressure)
- Pulmonary (lung or breathing) complications
- Damage to organs, nerves and/or muscles
- Gastrointestinal (stomach, intestines) and/or genitourinary compromise (genital, urinary) issues
- Seizure (body's reaction to abnormal electrical activity in the brain)
- Convulsion (uncontrollable shaking of the body)
- Changes in mental health status
- Inability to resume activities of daily living
- Death

If you are taking any blood thinning medication, including aspirin, make sure to tell the study doctor as this may increase the risk of some of these procedure-related complications.

In addition, the following risks may occur only because the Evoke SCS system was implanted or activated. These are the same risks typically associated with all spinal cord stimulator systems.

- Pain or discomfort due to undesirable changes in stimulation sensation and/or location
- Pain or discomfort due to uncomfortable changes in stimulation (over and/or under stimulation)
- Persistent post-surgical pain at implant locations or over implant site
- Stimulator migration (moving), which may result in pain or difficulty in charging
- Seroma (collection of fluid) or hematoma (collection of blood)
- Epidural hemorrhage (excessive bleeding between the dura mater and the skull), spinal cord injury and possible paralysis
- Lead migration from the location chosen at initial implantation resulting in stimulation changes
- Breakage or failure of the lead or failure of other system components, which may result in loss of stimulation (that is, the device may stop working)
- Rejection of, or allergic reaction to, the implanted components
- Infection that may require hospitalization with intravenous antibiotic therapy
- Leakage of cerebrospinal fluid (CSF, the fluid that surrounds the brain and spinal cord)
- Inadequate pain relief following system implantation
- Erosion of the lead, lead extension or stimulator through the skin
- Weakness, clumsiness, numbness or pain below the level of lead implantation

Subjects may require surgery (including removing or replacing the leads or stimulator) as a result of any of the above.

Other Protocol Risks and Restrictions:

- Before the trial stimulation procedure, you may be asked to undergo a type of imaging called an MRI (Magnetic Resonance Imaging) which more clearly shows the tissue. An MRI machine looks like a tunnel that is open at both ends. You lie down on a movable table that slides into the opening of the tunnel. A technologist monitors you from another room. You can talk with him or her by microphone. The MRI machine creates a strong magnetic field around you, and radio waves are directed at your body. The procedure is painless. You don't feel the magnetic field or radio waves, and there are no moving parts around you. The MRI technician will ask you to remove any metal objects from your body and you will be asked about the presence of any metal devices inside your body. During the MRI scan, the internal part of the magnet produces tapping, thumping and other noises. Earplugs or music may be provided to help block the noise. If you are worried about feeling claustrophobic inside the MRI machine, talk to your study doctor beforehand. He or she may make arrangements for you to receive a sedative before the scan. An MRI typically lasts less than an hour. You must hold very still because movement can blur the resulting images. An MRI does not involve exposure to radiation however the exposure involved in the other forms of imaging does involve exposure to a very small amount of radiation. If you are unable to undergo an MRI, you will then be asked to have a CT scan, which is more like an x-ray and does involve some exposure to radiation.

- Once the study device is implanted, you will not be able to have a magnetic resonance imaging (MRI) scan (the device is considered MRI unsafe, as the safety of this system within an MRI environment has not been tested) or other tests requiring or producing strong energy in the area of the implanted device, such as shock wave lithotripsy (such as used to break apart kidney stones with sound waves), therapeutic ultrasound (such as used in physical therapy, ultrasound drug delivery, etc.), shortwave or microwave diathermy (used largely for physical therapy), or repetitive transcranial magnetic stimulation (used for various neurological conditions and major depression) since these tests may damage the device and may cause serious injury to you. If one of your doctors has talked with you about having any of these tests, please arrange for it prior to having the implant surgery. Following implant of the device, you will not be able to have these tests in the future unless the system (stimulator and leads) is removed. Should an MRI become necessary, you should discuss options with your doctor, such as a CT scan or removal of the leads and stimulator prior to the MRI.

- After implantation of the device, you will not be able to scuba dive. You must also turn off the device while driving or operating dangerous equipment. Failing to do so could cause serious injury to yourself or others.

- In this study, you are required to have x-rays and may need a CT scan. X-rays and CT scans expose you to small doses of radiation. To ensure that the implant is in the correct position, some x-ray imaging will be necessary during and after the trial stimulation procedure, during the full implant procedure, and may also be needed in the follow up period. At a minimum, this will involve a few minutes of the use of a moving x-ray (also called fluoroscopy) during and following the trial stimulation and implantation procedures. During follow-up, if your study doctor thinks there may be a study device problem, additional x-rays may be needed to find out about any study device problem you may have. If another procedure is needed to fix a study device issue, again, moving x-rays (fluoroscopy) will be done during and following the procedure. The risk of radiation exposure depends on the number of x-rays needed. We are all exposed to radiation every day of our lives; this radiation comes mainly from radon on the earth's surface and cosmic rays from space. Radiation dosages are measured in something called the millisievert (mSv). Each year, people in the US are exposed to about 6mSv of radiation. Your extra exposure due to this study is expected to be no more than 2mSv. At these dosages the risk to you is minimal.

- There are potential risks associated with the pre- and/or post-operative antibiotics you may be given. Potential risks that may result from antibiotic use are: rash, diarrhea, abdominal pain, nausea/vomiting, dizziness, headaches and hypersensitivity (allergic) reactions.

- Other risks you will be exposed to in this study are embarrassment from providing possibly sensitive information (such as that provided in the questionnaires).

It is possible in any medical research study that harmful things can happen that are not known at this time. Your condition may not get better or may become worse during this study. Since the Evoke system is an investigational device, there may be risks associated with this study that are presently unknown or unforeseeable, and you might develop new or worsening medical complications from participating in this study.

Are there risks related to pregnancy?

You may not participate in this study if you are pregnant, breastfeeding or plan to become pregnant during the study. A pregnancy test (if applicable) will be done before you enter the study. If you are a woman of childbearing age, you must use a reliable means of contraception before and during the study. Talk with the study doctor if you have any questions about pregnancy prevention options.

The effects of the study device on a breastfeeding or unborn baby are not known. If you become pregnant during this study you must tell the study doctor right away. If you have questions about this, please discuss it with the study doctor before agreeing to be a subject in the study.

WHAT HAPPENS IF THE STUDY DEVICE THERAPY NEEDS TO BE TURNED OFF?

In case of an emergency or an event that requires the device to be temporarily stopped, you can turn the study device off using your remote control or by using a strong magnet, which will be given to you. In addition, this can be done by any trained medical personnel or medical facility; it is not required to be done at the study facility.

ARE THERE ANY BENEFITS TO TAKING PART IN THIS STUDY?

Your chronic pain may improve while you are in this study; however, this cannot be promised. You might not receive any benefit from being in this study. The results of this study may help people with chronic pain in the future.

WILL I BE PAID TO BE IN THIS STUDY?

Option 1: You will not be paid for being this study.

OR

Option 2: You will not be paid to be in this study. You will be reimbursed by the site for reasonable and modest expenses for transportation (e.g., parking, tolls, mileage) up to $75 per implant phase visit, which includes the completed 1 month, 3 month, 6 month, 9 month, 12 month, 18 month, 24 month, crossover visits at 1-month and 3-month post-crossover (if you choose to participate), 30-month and 36 month visits.

WHAT ARE THE COSTS TO ME?

- The main goal of a research study is to learn things to help patients in the future.
- The main goal of standard medical care is to help each patient.
- Parts of this study may involve standard medical care. Standard care is the treatment you would receive for a condition or illness even if you were not participating in the study.
- Other parts of this study may involve experimental (investigational) procedures that are being tested for a certain condition or illness. Experimental (investigational) procedures would not normally be performed as part of standard medical care.

- You will not be charged for tests or procedures that are only required for this study. Saluda Medical will reimburse the medical center and/or doctors for their fair costs for the tests and procedures required only for the study. This includes the baseline imaging (if required, such as MRI or CT scan), physical and psychological exam, trial stimulation and permanent implant procedure, and study required activities at follow-up visits described above in this consent form. Saluda Medical will also provide the study device free of charge.

- You or your insurance company will be billed for tests or procedures that are considered standard of care and would have been part of your medical treatment if you did not participate in this study. The standard of care treatment costs include any care provided in connection with the study that is not described in the preceding paragraph, including, but not limited to drugs, routine laboratory tests, routine medical care, and physican charges. Your physician may also recommend or perform additional tests or procedures that are not part of the study and are considered standard of care. Your health insurance company may not pay for these standard of care charges because you are in a research study. If your insurance company does not pay for costs associated with this research study that are considered standard care for your medical treatment, then you will be billed for these costs. You are responsible for paying for any insurance co-pays and any deductibles due under your insurance policy, and any charges your insurance company does not pay. You will need to contact your insurance company to find out what will be covered. Ask the research team if you need help.

- If the study device needs to be removed or replaced while you are in the study you will not be billed for the removal or replacement costs. The sponsor has not agreed to pay for voluntary removal or replacement after your participation in the study ends for any reason.

- Saluda Medical has not agreed to pay you or anyone else for any other medical costs related to your pain condition or participation in the study. This includes, but is not limited to any prescriptions you may take, medical equipment, etc. After your final follow-up visit (up to 3 years), any care you receive would not be part of the study and Saluda Medical has not agreed to pay for costs of that standard medical care.

Please ask your study doctor if you are unsure about whether a specific test or procedure is required for the study, and what costs will or will not be paid by Saluda Medical. You or your insurer will be responsible for those costs not paid for by Saluda Medical.

WHAT IF I AM INJURED OR BECOME ILL DURING THE STUDY?

If you get hurt or sick during the study, please contact the study doctor. He/she will treat you or arrange for your treatment. The study sponsor, Saluda Medical, has agreed to reimburse the research center for its reasonable and necessary costs for the short-term treatment of your injury if it is caused only by the Evoke system (device) or by properly performed research procedures or testing required only for the study. These tests and procedures include the screening/baseline tests, implant procedure and the tests listed in the follow-up phase in this form.

The Sponsor has not agreed to pay for injury or illness that occurs as a result of negligence, malpractice or other wrongful acts on the part of the study doctor or the study staff. The sponsor has not agreed to make any payments directly to you. The sponsor has not agreed to pay for injuries or illnesses that are the result of a pre-existing condition or the normal progression of your disease, because you have not followed the directions of the study doctor, standard of care medical procedures or medications performed or delivered during the study, or any other reason.

The Sponsor has not agreed to pay for any other costs, including pain, worry, lost income, or non-medical care costs that occur from taking part in the study. For example, Saluda Medical cannot promise that the device will make your pain better, and Saluda Medical has not agreed to pay for medical costs related to the fact that your pain gets worse, including hospitalization, prescriptions, etc.

You are not giving up any of your legal rights by signing this consent form.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

You do not have to participate in this research study to be treated for your pain. Hard to control pain of the truck and/or limbs is typically managed with a variety of treatments, with less invasive treatments prescribed first. Some non-surgical treatments include oral medications, massage therapy, physical/occupational/exercise therapy, psychological therapy (such as behavior modification or hypnosis), acupuncture, nerve root blocks, transcutaneous electrical stimulation (TENS), epidural injections, transforaminal injections and radiofrequency-based techniques. Surgical treatment options include sympathectomy, implantable intrathecal drug delivery system, and commercially-available spinal cord stimulation devices (fully or partially implanted). Each treatment option has its own advantages and disadvantages. You should fully discuss these alternatives with your study doctor in order to pick the best treatment option for you.

WHAT IS THE ROLE OF THE SPONSOR'S REPRESENTATIVE?

As part of this study, a representative of Saluda Medical may:

- Provide technical expertise on the study device system you will receive;
- Be present at the procedures and at the follow up visits;
- Program your study device;
- Have direct contact with you; and
- Be aware of how your study device system is programmed and your test results.

The study doctor or their designee will always be present or nearby.

You should not ask Saluda Medical representatives questions about the study as they are not allowed to discuss the study with you. In particular, they are not allowed to make any promises or give information to a study subject that is different from any of the information in this form. If you think you have heard something that is different from the information in this form, please tell the study team as the information may be incorrect. If you have questions, please ask the study doctor or a member of the study team.

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

As part of this study, your study doctor and surgical facility will keep records of your participation in the study. This section of the consent form describes how your personal information may be used and disclosed as part of the study. Under federal law, your personal information cannot be used or shared for the study by the Researchers unless you sign this form. You do not have to sign this form. If you do not sign it, you will not be able to be in the study, but it will have no other effect on the medical care you receive.

What information about me can be used or shared in the study?

The personal information that may be used or shared is:

- All information collected during the study, including your birth date, treatment dates, device identifiers and other details about you.
- Information in your medical records that is relevant to the study, including past medical records and the results obtained during the study.
- Videotapes, films or photographs of the implant of the device and trial stimulation phase. Every effort will be made to not reveal your identity in the video or photos.
- Records relating to your medical charges (your medical bills) regarding your treatment that are relevant to the study
- If the sponsor pays for treatment of a research related injury or complication, you may be required to provide additional personal identification information (such as your social security number or health insurance claim number) and some of your personal health information to the Sponsor for the purposes of reporting such compensation to the Centers for Medicare & Medicaid Services.

When you see the phrase “personal information” in this form, it means all of this information.

Who can disclose my personal health information and who might receive it?

As part of the study, your personal information may be kept by the (facility name), (practice group name) (investigator name), and the people who work for them. The people who work with them include the Institutional Review Board, which is a group of people who watch over the study for the hospital or practice. It also includes other employees and contractors who need to see your personal information to help with the study or make sure it is being run right. Any of these people or groups of people may disclose your information. These people and groups are called the “Researchers” in this form.

People working with any of the following groups might receive your information:

- Saluda Medical, the Sponsor of the study, including its employees, contractors and representatives;
- The Institutional Review Board;
- Other institutions and laboratories that are participating in the study and their Institutional Review Boards;
- Government organizations such as the Food and Drug Administration (FDA), Office of Human Research Protections and similar agencies in other countries and other persons (such as the Data Safety Monitoring Committee) have the right to see your information required to watch over the safety, effectiveness, and conduct of research.

How can my personal health information be used?

Information about you can be used and disclosed (shared) by the Researchers and Sponsor for any of the following reasons:

- To monitor and/or audit the study and to confirm the research results;
- To prepare publications or presentations (but no publication about the study will reveal your identity without a different specific, written permission from you);
- For regulatory purposes, such as meeting the reporting requirements of government agencies and getting the approval of government agencies to sell products made by the Sponsor;
- To create a data set from which all personal information that could be used to identify subjects has been removed;
- To support the marketing, distribution, sale and use of the research device;
- To conduct new medical research and other activities related to research and development of new medical products or therapies;
- For reimbursement advocacy purposes, that is to decide how the procedure that is the subject of the study will be paid for by Medicare, Medicaid, or insurance companies in the future;
- As required by applicable laws.

Can I take back (revoke) my signature on this form?

Yes. You can change your mind about allowing your personal information to be used or shared at any time by sending a written notice to your study doctor. If you change your mind, you will be taken out of the study and no personal information about you will be gathered for the study after that date, but any information previously recorded about you cannot be removed from the records and will continue to be used as part of the research.

Is my personal information always protected?

After the Researchers have shared your personal information with third parties, including the Sponsor, federal laws may not protect it from being further shared.

Can I see my personal information?

You will not have access to personal information related to this research study until the study is done. This information is available to your doctor in the case of an emergency. At the end of the study, you will again have access to personal information that is normally within your medical records. However, some research records will not be part of your medical record and you may not be allowed to see those research records. There may be other limitations on access to medical information unrelated to this study.

Does this form have an expiration (end) date?

The Researchers may use and share your information until the study and any necessary follow-up activities for the study have been finished. There is no end date for when the Sponsor can use your personal information.

WHAT ARE MY RIGHTS AS A RESEARCH SUBJECT?

Your participation in this study is entirely your choice. You may decide not to participate or you may leave the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled. If you withdraw from the study, you are asked to notify the study doctor so that your future care can be discussed and your participation can be stopped in a safe and orderly manner.

You will be told about any new findings about the device or this study, or if any changes are made to the study plan that may make you change your mind about staying in the study.

Your participation in this study may be stopped at any time by the study doctor or the sponsor without your consent for any reason, such as:

- if it is in your best interest,
- if you need additional treatments,
- if you do not follow the study instructions,
- your medical condition changes,
- the study doctor feels it is in your best interest to stop the study,
- if you do not consent to continue in the study after being told of changes in the research that may affect you,
- decisions made in the commercial interests of the sponsor, or
- for administrative reasons.

SOURCE OF FUNDING FOR THE STUDY

This clinical research study is paid for by the sponsor, Saluda Medical, who makes the device being tested. The study site is being paid by the Sponsor for their time, staff and facilities required to conduct the study. Research monies may help support the research and educational programs of the clinical site, including salaries of the study doctors and study nurses who conduct the study. [as applicable, add a statement of the Investigators' financial compensation]

QUESTIONS

Contact [name] at [number(s)] for any of the following reasons:

- if you have any questions about your participation in this study,
- if you feel you have had a research-related injury or a reaction to the study device, or
- if you have questions, concerns or complaints about the research.

If you have questions about your rights as a research subject or if you have questions, concerns or complaints about the research, you may also contact:

[IRB Name]
[Address]
[Telephone]
[E-mail]

An IRB is a group of people who independently review research.

An IRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact the IRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

RESEARCH SUBJECT'S BILL OF RIGHTS

The rights below are the rights of every person who is asked to be in a research study. As an experimental subject I have the following rights:

1) To be told what the study is trying to find out,

2) To be told what will happen to me and whether any of the procedures, drugs, or devices is different from what would be used in standard practice,

3) To be told about the frequent and/or important risks, side effects, or discomforts of the things that will happen to me for research purposes,

4) To be told if I can expect any benefit from participating, and, if so, what the benefit might be,

5) To be told of the other choices I have and how they may be better or worse than being in the study,

6) To be allowed to ask any questions concerning the study both before agreeing to be involved and during the course of the study,

7) To be told what sort of medical treatment is available if any complications arise,

8) To refuse to participate at all or to change my mind about participation after the study is started. This decision will not affect my right to receive the care I would receive if I were not in the study,

9) To receive a copy of the signed and dated consent form,

10) To be free of pressure when considering whether I wish to agree to be in the study.

CONSENT

My signature on this consent form and authorization to use and disclose health information means that I have read and understand the information in this form about the research study. My signature also means that my study doctor or their designee has talked with me about the study and I have had a chance to ask questions. I know that taking part in this research study is my choice and that I can quit at any time. If I decide not to take part in the study, it will not affect my medical care outside of the study in any way. By signing this consent form I do not give up any of my legal rights.

Signature of Subject	Date
Printed Name of Subject	
Signature of Consenting Investigator or Designee	Date
Printed Name of Consenting Investigator or Designee	

Statistical Analysis Plan

Evoke Study: A prospective, multicenter, randomized double-blind study examining the safety and efficacy of using the Evoke™ Spinal Cord Stimulator (SCS) System with feedback to treat patients with chronic pain of the trunk and/or limbs.

Study ID: SCLSH1503
Revision: 5.00
Date: 01 February 2018

IDE Number: G150266

Sponsor:
Saluda Medical Americas, Inc.
Contact: Dan Brounstein
Email: dan.brounstein@saludamedical.com

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1 Study Design

1.1 Introduction

This study is a prospective, multicenter, randomized, double-blind clinical trial designed to assess the safety and efficacy of the Saluda Medical Evoke Spinal Cord Stimulator (SCS) System with feedback control for the treatment of subjects suffering from chronic, intractable pain of the trunk and/or limbs. This study will compare the Saluda Medical Evoke SCS System with feedback to Control spinal cord stimulation (Saluda Medical Evoke SCS System without feedback).

The primary objective is to demonstrate non-inferiority of the Investigational mode of stimulation to Control stimulation in the primary composite endpoint for the treatment of subjects suffering from chronic, intractable pain of the trunk and/or limbs. The primary analysis and submission of the Premarket Approval (PMA) supplement will occur after the last subject reaches their 3-month follow-up.

1.2 Timing of Analyses

The primary composite endpoint will be tested after the final subject completes their 3-month follow-up. If the primary endpoint is successfully met, the PMA report will be submitted in support of product approval and include analyses of the primary composite endpoint and testing of the hierarchical secondary endpoints defined at 3 months. Additionally, all data collected up to the point of data lock will be submitted for approval.

An additional analysis will be completed assessing all defined endpoints when the final subject completes their 12-month follow-up. Additional annual reporting will be completed as required.

1.3 Randomization

Subjects who provide informed consent and meet the study eligibility criteria will be randomly assigned in a 1:1 fashion to receive either Investigational or Control stimulation at the time of the trial procedure. The randomization will be generated utilizing permuted blocks of size 4 and 6, stratified by study site, to ensure within-site balance.

Specifically, for each study site the randomization will be developed by first creating 3 blocks of size 6 and 2 blocks of size 4 and then placing those 5 blocks in random order. Each site is limited to the 26 randomization assignments that are provided under this method. PROC PLAN will be utilized in SAS® to generate the randomization assignments.

1.4 Study Endpoints

1.4.1 Primary Composite Endpoint

The primary endpoint is a composite endpoint, where a subject is deemed a success if:

- They experience a 50% reduction in overall trunk and limb pain as determined by the Visual Analog Scale (VAS) at the 3-month visit, AND
- They have no increase in baseline pain medications within 4 weeks of the 3-month visit

The efficacy component of the primary endpoint will be determined using the in-clinic, subject-completed VAS for overall trunk and limb pain (average pain in the last 24 hours). The VAS assessment of pain is a validated measure, and a 50% reduction from baseline is clinically accepted as a subject success (1,2).

Subjects who increase their baseline pain medications under the following conditions will be 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 is 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 has not stopped within 4 weeks of primary endpoint visit.
    - Exceptions: Tylenol/rescue medication will be allowed up to two weeks prior to the primary endpoint visit.

1.4.2 Secondary Endpoints for Hierarchical Testing

A number of secondary endpoints are pre-defined for hierarchical testing so that all endpoints achieving statistical significance under the closed statistical testing procedure will be reported in the clinical study report. The secondary endpoints for hierarchical testing will be determined using the in-clinic subject-completed VAS. The following secondary endpoints will be tested in order if the primary endpoint is met:

- Percentage change in VAS leg pain at 3 months
- Percentage change in VAS back pain at 3 months
- Incidence of ≥80% reduction in VAS overall trunk and limb pain at 3 months
- Incidence of ≥50% reduction in VAS back pain at 3 months

In addition, when the 12-month follow-up data are complete, an additional analysis will be performed to include:

- The Primary composite endpoint and;
- The Secondary Endpoints for hierarchical testing in the same specified order

1.4.3 Additional Secondary Endpoints

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

- Comprehensive summary of all Adverse Events (AEs)
- Change, percent change, incidence of ≥50% and ≥80% reduction, and cumulative proportion of responders analysis in VAS pain scores
- EQ-5D-5L
- ODI
- Pain diary

- Pain map
- Stimulation characteristics
- Posture change assessment
- PGIC
- Patient satisfaction
- PSQI
- POMS
- SF-12
- Programming and neurophysiologic properties

1.5 Sample Size

This study will randomize up to 134 subjects at up to 20 study sites. In order to help ensure the generalizability of the study results, no study site will randomize more than 26 subjects (~20% of the total randomized).

1.5.1 Calculation

For purposes of sample size calculation, the Sponsor assumes that the true success rate associated with the Investigational stimulation for the primary composite endpoint is at least 57%, and that the success rate associated with Control stimulation may be as large as 45%.

Non-inferiority Calculation

In order to have 80% power to determine that Investigational stimulation is non-inferior to Control stimulation at a one-sided significance level of 0.05 and a non-inferiority margin (δ) of 10%, a minimum of 60 subjects per group (120 total) are required with known or presumed primary endpoint status (refer to section 2.1.4 for details on how presumed non-responders are classified). This calculation was performed in PASS 2013 and is based upon an unpooled z-test without continuity correction for a non-inferiority test of two proportions.

Adjustment for Subject Loss

In order to conservatively account for potential post-randomization subject loss of up to 10%, a total of 134 subjects will be randomized in order to obtain at least 120 subjects with known or presumed primary endpoint status. See section 2.1.5 for a complete description of how missing data will be handled.

1.5.2 Justification for Sample Size Input Parameters

Success Rates in VAS

Table 1 below shows the results obtained from prior RCTs including conventional open-loop stimulation. The selected studies were included in a systematic review by Grider et. al. (2016) (3), and represent the

three RCTs available that both met the author's criteria for inclusion in the systematic review and contained efficacy data in the publication.

The Control stimulation system in this trial is designed to provide substantially equivalent stimulation to that provided in the studies below, and therefore similar success rates in VAS reduction are expected. Based upon review of these prior studies, it appears reasonable to assume that the overall pain VAS success rate in the control group should be 50% or lower; particularly under an ITT randomized design where stimulation trial and medications failures are counted as presumed study failures.

Table 1: VAS Success Rate in Prior Conventional Open-loop Stimulation Studies

Study	**Study Design** **Study Population** **Device** **Follow-up** **Pain region**	**Incidence of ≥50% VAS responders**
North et al., 2005 (4)	RCT N = 19 permanent implant subjects available for follow-up in conventional open-loop SCS arm Medtronic X-trel or Itrel Follow-up = mean 2.9±1.1 years Pain region not specified (subjects had radicular pain with or without low back pain)	47%
Kapural et al., 2015 (5)	RCT N = 81 permanent implanted subjects in conventional open-loop SCS arm Boston Scientific Precision Plus Follow-up data referenced = 3 month Pain region in primary endpoint: Back; Pain region in secondary endpoint: Leg	43.8% back 55.5% leg
Kumar et al., 2007 (6)	RCT N = 50 implanted in conventional open-loop SCS arm (includes trial failures) Medtronic Synergy Follow-up data referenced = 6 months Pain region in primary endpoint: Leg	48%

Saluda anticipates that the true success rate in the Feedback is at least 12% higher than with conventional open-loop stimulation. Preliminary data from Saluda Medical's single-arm study of feedback-controlled stimulation being conducted in Australia shows 71% responders in overall pain in the permanent implant subset, and 61% responders when trial failures are considered. Therefore, it is anticipated that the true difference between treatment groups will be in the range of 10-15%, or greater. Saluda has selected 12% as the anticipated difference for purposes of study design.

2 Planned Statistical Analyses

2.1.1 General Statistical Procedures

The following general statistical methods will be employed to assess the study data:

- Standard summary statistics will be used to summarize key study variables. Categorical variables will be summarized via incidence and percent. Continuous variables will be summarized via mean, median, standard deviation, and range. 95% confidence intervals will also be included with summary statistics as appropriate.

- Standard two-group tests for significance will be employed, including two sample t-tests, Chi-square tests, and the normal approximation to the binomial two-sample z-test.

- In the event planned parametric methods are found to be inappropriate based upon observed distributions of individual variables, appropriate non-parametric methods will be employed.

- Unless stated otherwise, statistical significance is defined as achieving a p-value less than 0.05. One-sided tests will be performed for assessments of non-inferiority and two-sided tests will be performed for assessments of superiority.

- For analysis of the primary composite and hierarchical secondary endpoints, all data obtained within 30 days of the target visit date will be included. This analysis window definition applies to all analysis sets. Data that falls outside this window will be assumed missing.

  NOTE: If a subject requires a device (e.g. lead or pulse generator) revision/replacement prior to the 3-month follow-up, a minimum of 1 month (30 days) follow-up or the subject's remaining follow-up, whichever is greater, is required in order to assess the primary composite and hierarchical secondary endpoints. The updated '3-month follow-up' date will be calculated based upon this rule and study/analysis windows will be applied to this updated date, allowing for a comparable visit window.

- Additional exploratory analyses for primary and secondary endpoints may be performed on data collected from case report forms and the device and include correlation analysis, ordinary least squares regression, logistic regression analyses, repeated measures analyses, and generalized estimating equation (GEE) analyses as appropriate.

Any departures from this statistical analysis plan will be reported in the final clinical study report.

2.1.2 Assessment of Baseline Characteristics

Baseline characteristics of interest, including baseline pain measures and relevant medical conditions will be summarized by treatment group and compared statistically to ensure balance between treatment groups. Comparisons between groups will be performed utilizing two sample t-tests for continuous variables and chi-square methods for categorical variables.

Any differences identified in baseline characteristics and measures will be investigated and elucidated in the clinical study reports. Supplementary regression analyses of the primary composite endpoint and the hierarchical secondary endpoints may be provided utilizing any baseline variables found to be unbalanced between treatment groups.

2.1.3 Assessment of Poolability

All study data will be pooled across all study sites to facilitate the testing of the primary composite and the hierarchical secondary endpoints. In the event major deviations within (a) study site(s) are identified during the course of the study, supplementary analyses will be provided showing the impact of both including and removing the offending study site(s) on the final study results.

Summary statistics of the primary composite endpoint and each hierarchical secondary endpoint will be presented by study site in order to assess visual differences in outcomes between study sites. In the event marked visual differences are observed, they will be investigated and elucidated in the clinical study reports.

2.1.4 Handling of Missing Data in Primary and Hierarchical Analyses

All randomized subjects will be eligible for inclusion in the ITT analyses of the primary and hierarchical secondary endpoints. The analysis set will be comprised of all subjects with complete data and those with missing data classified as presumed non-responders.

The incidence of and reasons for missing primary endpoint data will be summarized and compared between the two study groups. Distinct Endpoints will be handled as follows:

Primary Composite Endpoint

In order to appropriately lower the success rates of both treatment groups when missing data is known to be associated the device or stimulation, the following events eliciting missing data at three months will cause the subject to be classified as a presumed non-responder and will be analyzed as a failure for the primary endpoint:

- Failure of the trial stimulation phase (<50% improvement in 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.

All other missing data will be classified as missing and no data imputations will be performed on these data for the primary endpoint analysis. The rate of missing is expected to be low and balanced between treatment groups. Events that will be categorized as missing include:

- Subject voluntary withdrawal for any reason other than a device or stimulation-related AE.
- Investigator withdrawal for any reason other than a device or stimulation-related AE.
- Subject fails to return for follow-up visits and 3 attempts to contact the subject are not successful.
- Subject returns for follow-up outside of the 30-day analysis window associated with the given visit.

Missing Data Sensitivity Analyses; Primary Endpoint

A number of sensitivity analyses will be performed on the ITT analysis population to help understand the potential impact of missing data that will include, at a minimum:

- Best case scenario (all Investigational missing data assumed a success and all Control missing data assumed a failure).
- Worst case scenario (all Control missing data assumed a success and all Investigational missing data assumed a failure).

- Tipping point analysis (determine the point between best and worst case where the significance threshold is achieved).

In the event the above sensitivity analyses do not adequately assess the robustness of the study conclusions, a multiple imputation model based on the following covariates will be constructed: treatment group, age, sex, race/ethnicity, and pain scores including baseline pain, end of trial pain, and 1-month pain (VAS overall, VAS back, and VAS leg for each). Inclusion of post-baseline variables is valid and allows for the incorporation of more information into the imputation process.

Any missing covariates will be first imputed via full conditional specification imputation, via a logistic regression for categorical variables or linear regression for continuous variables, to produce a data set with a monotone missing pattern. If there are fitting issues with the covariate imputation process, individual covariates may be omitted to still allow for imputation of the endpoint for the full randomized cohort. Alternatively, if there are fitting issues due to the separation or quasi-separation of data points, an augmented likelihood approach will be used.

Following construction of a monotone missing data set, imputation for the outcome based on covariates will be performed via a logistic regression model to handle the binary nature of the endpoint. Imputation will be performed for 100 data sets and inferences combined from these imputed data sets to produce a single estimate of treatment effect, along with the associated p-value for the hypothesis test.

Hierarchical Secondary Endpoints

Missing data will be addressed as follows in the hypothesis testing for the hierarchical secondary endpoints:

- For incidence measures (e.g., incidence of ≥50% reduction in VAS scores), missing data will be managed in the same manner described above for the primary composite endpoint.

- For continuous measures (i.e. changes from baseline in VAS scores):
    - Subjects with missing data categorized as presumed non-responders will utilize a last-value carried forward imputation methodology.

    - Subjects with missing data who are not classified as presumed non-responders will not have endpoint data imputed.

    - Subjects that fail the medication component of the primary endpoint will have a change from baseline value of “0” imputed for the hierarchical secondary endpoint calculation.

Sensitivity analyses of the hierarchical secondary endpoints may be conducted in the event the above analyses provide borderline results. Analysis methods employed will be similar to those planned above for the testing of the primary composite endpoint.

2.1.5 Analysis Populations

The primary analysis population is the Intent to Treat subgroup (ITT) in which all randomized subjects will be eligible for analysis. Subjects will be analyzed according to their randomization assignment and must either have known endpoint status or be classified as presumed non-responders as discussed below in section 2.1.5 in order to be included in the analysis. In order for the study to be deemed a success, the primary composite endpoint must pass in the evaluation of non-inferiority in the ITT analysis population. In addition, the secondary test of superiority on the primary composite endpoint must also pass in the ITT

analysis population in order for superiority to be sought as a labeling claim. All testing of the hierarchical secondary endpoints in support of labeling claims will also be performed on the ITT analysis population.

Two additional analysis populations of interest are defined *a priori* and will be utilized to assess study outcomes. First, the Permanent Implant Subset (PIS) will include all subjects who received a permanent implant. Second, the Per Protocol (PP) analysis population will include all subjects who received a permanent implant, and who also have evaluable primary endpoint data and no major deviations.

It is not a requirement for study success that either the PIS or PP analysis elicit a successful test of the primary composite endpoint. However, any differences in inferences drawn between the three analysis populations will be investigated and elucidated in the clinical study reports.

2.2 Analysis of Study Endpoints

2.2.1 Primary Composite Endpoint

The primary composite endpoint will be analyzed via the normal approximation to the binomial distribution, utilizing an unpooled estimate of the standard error and no correction for continuity. Non-inferiority of Investigational relative to Control will be assessed against the clinical significance margin (δ) of 10% as detailed in the following hypothesis statement:

H_0: $\pi_F \leq \pi_C - \delta$
H_1: $\pi_F > \pi_C - \delta$
Where: π_F= success rate with Investigational; π_C = success rate with Control

In the event non-inferiority is met at the 1-sided significance level of 0.05, superiority will be tested at the 2-sided significance level of 0.05. The superiority hypothesis is denoted as follows:

H_0: $\pi_F = \pi_C$
H_1: $\pi_F \neq \pi_C$; superiority accepted where $\pi_F > \pi_C$

2.2.1.1 Primary Composite Endpoint; Supplementary Analyses

In order to provide supplementary evidence for the primary endpoint findings, the hypothesis test will be repeated based upon the subject's diary data. The same hypothesis structure presented above will be tested where a responder is defined as a subject in whom the average of the pain diary's daily 'average level pain' scores at 3 months is at least 50% lower than at baseline. If non-inferiority is met, superiority will be tested.

In the event non-inferiority is not met for the diary data, it will not affect the findings on the primary endpoint or testing of the hierarchical secondary endpoints as defined below.

2.2.2 Hierarchical Secondary Endpoints

Closed Testing Procedure

If non-inferiority is met in the testing of the primary composite endpoint, the hierarchical secondary endpoints will be tested in the order presented below in Table 2.

In order to preserve the experiment-wise error rate of 0.05, a closed testing procedure will be employed. If the first endpoint passes, the second will be tested, and so forth. If an endpoint fails, none of the endpoints following in the list will be formally tested.

All initial tests will be for non-inferiority. Testing will continue until a hypothesis test fails. If all four secondary endpoints pass at the 3-Month analysis, hierarchical testing will continue when the 12-Month data is analyzed, beginning with the primary endpoint defined above in Section 1.4.1 and continuing through Table 2 in the same order specified until a hypothesis test fails.

All hierarchical secondary endpoints that pass their non-inferiority test will be tested for superiority at a two-sided level of significance of 0.05. Failing to pass a superiority test will not affect the testing or interpretation of the other hierarchical endpoints.

Table 2: Closed Testing Parameters for Hierarchical Secondary Endpoints

Endpoint	Test Type	Test Parameters
Percentage change in VAS leg pain at 3 months	Non-inferiority	One-sided α=0.05 δ=10%
Percentage change in VAS back pain at 3 months	Non-inferiority	One-sided α=0.05 δ=10%
Incidence of ≥80% reduction in VAS overall trunk and limb pain at 3 months	Non-Inferiority	One-sided α=0.05 δ=10%
Incidence of ≥50% reduction in VAS back pain at 3 months	Non-inferiority	One-sided α=0.05 δ=10%

Hypotheses

The non-inferiority test for the incidence measures can be stated as follows:

H_0: $\pi_F \leq \pi_C - \delta$
H_1: $\pi_F > \pi_C - \delta$
Where: π_F= success rate with Investigational; π_C = success rate with Control

Superiority tests for incidence measures will be tested at the 2-sided significance level of 0.05. The general form of the superiority hypothesis is denoted as follows:

H_0: $\pi_F = \pi_C$
H_1: $\pi_F \neq \pi_C$; superiority accepted where $\pi_F > \pi_C$

The remaining hierarchical secondary endpoints all involve statistical inferences on population mean responses and can be stated with the following general hypothesis statement:

H_0: $\mu_F \leq \mu_C - \delta$
H_1: $\mu_F > \mu_C - \delta$
Where: μ_F= success rate with Investigational; μ_C = success rate with Control

Secondary superiority tests for continuous measures will be tested at the 2-sided significance level of 0.05. The general form of the superiority hypothesis is denoted as follows:

H_0: $\mu_F = \mu_C$
H_1: $\mu_F \neq \mu_C$; superiority accepted where $\mu_F > \mu_C$

Analyses

The incidence measures will be analyzed via the normal approximation to the binomial distribution, utilizing an unpooled estimate of standard error and no correction for continuity.

The continuous hierarchical secondary endpoints will be assessed via two-sample t-tests.

2.2.3 Other Secondary Effectiveness Endpoints

The remaining secondary endpoints as well as observed relationships between endpoints will be assessed per the methods described above in Section 2.1.1. Findings of significance may be presented and include p-values and/or confidence intervals as appropriate. Standard methods will be utilized to compare statistics between study groups at time points of interest (e.g. two-sample t-test, normal approximation to the binomial).

2.2.4 Adverse Events

AEs will be summarized by treatment group. The incidence of all distinct AEs will be presented along with 95% confidence intervals for the ITT analysis population. AEs will also be summarized by seriousness, severity, and relatedness to the procedure, device, and/or stimulation. AEs will be reported based on the adjudication committee determination.

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