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Multicenter, Randomized, Double-Blind Study Protocol Using Human Spinal Cord Recording Comparing Safety, Efficacy, and Neurophysiological Responses Between Patients Being Treated With Evoked Compound Action Potential–Controlled Closed-Loop Spinal Cord Stimulation or Open-Loop Spinal Cord Stimulation (the Evoke Study)

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Background: The spinal cord (SC) response to stimulation has yet to be studied in a pivotal clinical study. We report the study design of an ongoing multicenter, randomized, double-blind, controlled, parallel-arm study of an evoked compound action potential (ECAP) controlled closed-loop spinal cord stimulation (SCS) system, which aims to gain U.S. Food and Drug Administration approval.

Methods: This study will enroll 134 SCS candidates with chronic trunk and limb pain from up to 20 United States sites. Subjects are randomized 1:1 to receive ECAP-controlled closed-loop or open-loop, conventional SCS. The primary objective is noninferiority of closed-loop stimulation determined by the proportion of subjects with $\geq 50\%$ reduction in overall trunk and limb pain and no increase in pain medications at the three-month visit. If noninferiority is met, superiority is tested. In addition, measures recommended by IMMPACT (e.g., pain intensity, functional disability, emotional functioning, quality of life, impression of change, and sleep), neurophysiological properties (e.g., SC activation, conduction velocity, chronaxie, and rheobase), and safety are analyzed.

Discussion: All approved SCS therapies, regardless of the presence or absence of stimulation induced paresthesias, produce fixed-output stimuli; that is, the energy delivered from the electrode array has a defined output irrespective of the neural response of SC fibers. An SCS system has been developed that directly measures the neurophysiologic activation of the SC to stimulation (i.e., ECAP amplitude) and uses this information in a feedback mechanism to produce closed-loop SCS to maintain optimal and stable activation of the SC. This study represents the first randomized, double-blind, pivotal study in the field of neuromodulation to measure SC activation in ECAP-controlled closed-loop versus open-loop stimulation and is expected to yield important information regarding differences in safety, efficacy, and neurophysiological properties. The potential clinical utility of these objective measurements of SC activation and other neurophysiological properties promises to improve outcomes of SCS for chronic pain patients.

Keywords: back pain, chronic pain, closed-loop, double-blind method, randomized controlled trial, spinal cord stimulation

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Conflict of Interest: Kasra Amirdelfan reports serving as a consultant for Biotronik; being a scientific advisory board member for Nalu and Nevro Corp.; and being an investigator for Saluda Medical Pty Ltd. Timothy R. Deer reports serving as a consultant for Abbott, Axonics Ltd., Flowonix Medical Inc., Mainstay, Nalu, Saluda Medical Pty. Ltd., Spinal Therapeutics, and Vertos Medical Inc.; being a scientific advisory board member for Abbott, Axonics Ltd., Bioness Inc., Flowonix Medical Inc., Jazz Pharmaceuticals PLC, Nalu, Nevro Corp., and Vertiflex; serving on the speakers' bureau for Jazz Pharmaceuticals PLC; and being a stock shareholder of Axonics Ltd., Bioness Inc., Cornerloc, Nalu, Saluda Medical Pty. Ltd., SpineThera, Vertiflex, and Vertos. Leonardo Kapural reports serving as a consultant for Abbott and Halyard Health. Angela Leitner reports being an employee of Saluda Medical Pty Ltd. Robert Levy reports being a minority stock shareholder of Bioness Inc., Nalu, Inc., Nevro Corp., and Vertos Medical Inc.; and serving as a consultant for Mainstay Medical, Nuvectra, Inc., Nalu, Inc., Saluda Medical Pty Ltd., and Abbott Inc. Nagy Mekhail reports being a consultant for Flowonix Medical Inc., Saluda Medical Pty Ltd., Abbott, Nuvectra, Stimwave Technology Ltd, and Vertos Medical; receiving research support from Mallinckrodt, Mesoblast, Halyard, Neuros Medical, and Boston Scientific; and being a medical monitor for the DRG stimulation "Accurate study," the Feed Back loop SCS "Evoke study," HF-10 for PDN, Motion Study for LSS, and HiFi Study for back and leg pain. Lawrence Poree reports serving as a consultant for Saluda Medical Pty Ltd., Medtronic, Nalu, Solis, and Gimer Ltd. Steven M. Rosen reports serving as a consultant for Saluda Medical Pty Ltd., and being a researcher for Flowonix Medical Inc., Nevro Corp, Medtronic, Biotronik, and Saluda Medical Pty Ltd. Nicole Soliday reports being an employee of Saluda Medical Pty Ltd.

INTRODUCTION

Chronic pain is one of the most common reasons for medical care resulting in one of the most significant medical health problems in the developed world (1–3). Spinal cord stimulation (SCS), also referred to as dorsal column (DC) stimulation, is an established therapy that has been used to provide relief from chronic pain for over 50 years (4). In recent years, SCS innovation has focused on developing new programming parameters (e.g., high frequency and burst), but the clinical effectiveness of SCS has remained highly variable, with minimal improvement because of the inception of the technology (5) and high rates of long-term treatment failures (6–8). While high frequency stimulation showed a marked improvement in efficacy in two studies (9,10), these results have not been replicated in recent investigator-initiated studies that reported responder rates more in line with conventional SCS (11,12). The most-recent innovation in SCS therapy to treat chronic trunk and limb pain (i.e., burst stimulation) failed to achieve even an average of 50% of patients experiencing 50% reduction in pain intensity (13). Although 50% pain relief is well-recognized as a substantial change (14), there is significant opportunity to improve the amount of pain relief and offer more patients the opportunity to realize meaningful, long-term reductions in pain and corresponding improvements in quality of life.

A better understanding of the mechanisms of action (MOA) may lead to improved SCS efficacy and long-term pain relief through more appropriate patient selection and optimization of stimulation parameters (15). However, the MOA of SCS for chronic pain has proven to be complex, with incomplete knowledge of the neural circuits and systems underlying chronic pain. The working hypothesis that inspired the development of SCS is the gate control theory (16). The gate control theory, however, fails to explain a number of clinical observations of SCS including its lack of efficacy for acute nociceptive pain and its efficacy post-stimulus cessation. More complex mechanisms have been described, which include multiple inhibitory neurotransmitters (e.g., GABAergic inhibitory interneuron) and complex local and supraspinal neuro-circuits (5). Nevertheless, these additional mechanisms are modulated by the activity of the low threshold DC sensory fibers as has been described extensively in the literature summarized in Zhang et al. (2014) (5,15,17–19). DC A β -fibers, the target of SCS, are low threshold sensory fibers, which ascend toward the brain in the

DCs, and send arborizations into the spinal dorsal horn close to the level at which they enter the SC. It is the activation of these fibers that drives the segmental and supra-spinal pain modulatory effects of SCS (Fig. 1).

SCS works by applying an electrical stimulus to the DCs in the SC, which contain a large number of axons from low threshold sensory fibers that transmit sensory information. Axons transmit information via action potentials, which can be detected as a brief rise in the membrane potential of the cell. This rise in potential is the result of ionic flow and naturally propagates along the axon from its origin to its destination. Action potentials are naturally generated in neurons in response to neurotransmitter release from other axons or specialized receptor cells (e.g., stretch receptors on the skin). Action potentials can also be generated artificially via electrical impulses, as in SCS. Applying an above threshold electrical stimulus to the SC causes a number of fibers to generate action potentials. These potentials summed together form the electrically evoked compound action potential (ECAP). ECAPs comprise the contribution of all responding fibers (e.g., A-fibers). The parameters of the ECAP represent the real-time response of the activated fiber population to stimulation and can be used to determine the properties of the fibers being stimulated, for example, their conduction velocity. Clinicians currently do not have a tool for determining the effectiveness of stimulation to produce action potentials that are required for pain inhibition because all systems are open-loop without an ECAP measurement capability. Researchers have been recording these potentials as a way of understanding the properties of neurons for many years (20), but because of the large artifact that is produced to generate the potentials, it has been difficult to record ECAP signals in close proximity to the stimulation electrodes (21) until now.

All approved SCS therapies (e.g., low frequency, high frequency, high density, and burst), regardless of whether stimulation induces paresthesia, are open-loop in that they produce fixed-output stimuli; the energy delivered from the electrode array has a defined output irrespective of the neural activation of the SC fibers (e.g., fixed frequency, fixed pulse width, fixed amplitude, and fixed pulse train) as seen in Fig. 2. These SCS systems do not take into account the broad range of electrical field strengths reaching the spinal cord due to changes in distance between the electrode and the spinal cord resulting from normal physiological activity (e.g., breathing and heartbeat) and movement (22–24). With decreased distance between the spinal cord and the

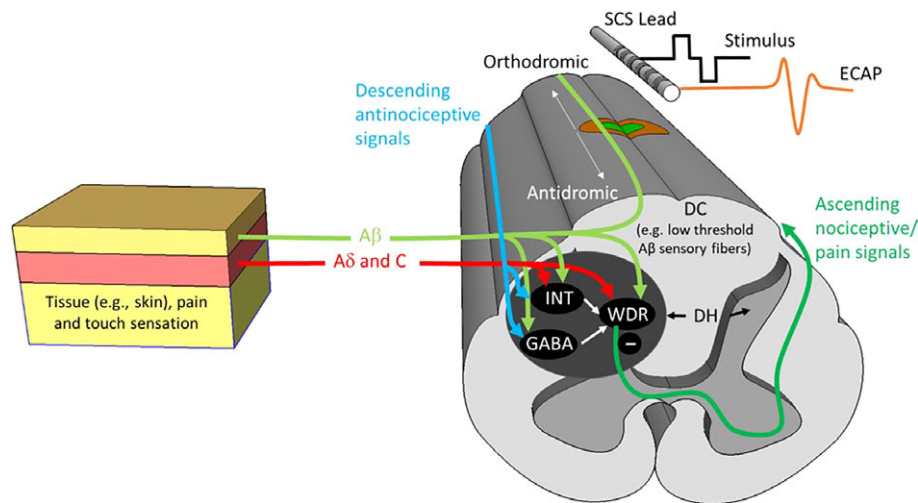


Figure 1. Schematic representation of the mechanisms of action of spinal cord stimulation (SCS). SCS activates dorsal column (DC) fibers, which excite various inhibitory interneurons within an interneuron pool (INT) in the dorsal horn (DH) and thus inhibit pain transmission via wide dynamic range (WDR) projection neurons. An example from that pool is the GABAergic inhibitory interneuron, which can be activated locally by DC fibers or via descending signals that are also triggered by SCS activation of DC fibers. The evoked compound action potential (ECAP) is the activation of the spinal cord (SC) fibers. Figure adapted from Linderöth B, Meyerson BA. *Anesthesiology* 2010;113:1265–1267. (Spinal Cord Stimulation: Exploration of the Physiological Basis of a Widely Used Therapy, Bengt Linderöth, M.D., Ph.D.; Björn A. Meyerson, M.D., Ph.D.) [Color figure can be viewed at wileyonlinelibrary.com]

electrode, there is an increase in the strength of the electric field at the spinal cord and the volume of tissue stimulated. This may be perceived as uncomfortably strong stimulation, stimulation in unwanted areas, muscle activation, and/or cramping (24–26). Paresthesia-based systems have the advantage that the uncomfortable stimuli are felt by the patients and can be managed via programming. In paresthesia-free programming, stimulation of nerve root fibers that reduce pain-relief may occur without uncomfortable side effects and therefore go unacknowledged by patient and clinician. Side effects resulting from this overstimulation, however, may be responsible for the loss of efficacy of SCS over time. Conversely, increased separation between the leads and the spinal cord results in decreased electrical field strength at the spinal cord and may be perceived as insufficient stimulation with reduced therapeutic effect (22–24). Stimulation intensity

changes that occur with movement may be nontherapeutic (i.e., outside the therapeutic usage range or window) and result in patients manually adjusting stimulation current to minimize overstimulation and under-stimulation at the expense of optimized pain relief (24–26).

In contrast to these open-loop SCS systems that do not use feedback from the spinal cord to adjust stimulation, a new neuromodulation system has been developed that offers closed-loop stimulation via a feedback mechanism that uses ECAP measurements to adjust the stimulation output level after every stimulation pulse to maintain the ECAP near the ECAP amplitude target. Thus, ECAP-controlled SCS modulates the energy delivered in real time to maintain consistent SC activation, whereas modeling shows that changes in posture can result in activation ranging from periods of zero activation to more than five times the

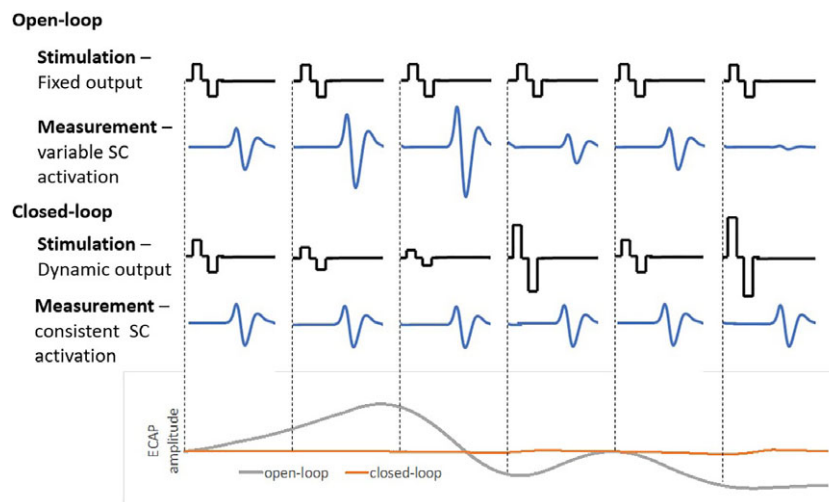


Figure 2. SCS stimulation modes. Open-loop stimulation delivers fixed output stimulation regardless of the neural response (i.e., SC activation), which does not control for variable SC activation due to proximity changes between the electrode and the spinal cord caused by normal physiology (e.g., heartbeat and breathing) and movement. ECAP-controlled closed-loop stimulation delivers dynamic stimulation currents based on SC activation as measured by ECAPs. [Color figure can be viewed at wileyonlinelibrary.com]

desired level with open-loop SCS systems. ECAP-controlled closed-loop SCS reduces the variation with posture by more than ten times and eliminates the periods of no activation entirely (27).

Experience with animals and human subjects to date has established the feasibility of using ECAP measurements for continual evaluation of SC activation and as a feedback mechanism for closed-loop SCS (28–30). We report here the study methods for an ongoing pivotal study being conducted under an investigational device exemption to gain U.S. Food and Drug Administration (FDA) approval for a neuromodulation system with these capabilities (ClinicalTrials.gov ID: NCT02924129). The study was designed to not only obtain the core patient-reported outcomes per recommendations from IMMPACT (31,32), but also to collect objective measures of neural properties to gain insight into the MOA of SCS and the underlying pathophysiology of chronic pain (33).

MATERIALS AND METHODS

Objectives

The purpose of this study is to evaluate the safety and efficacy of closed-loop SCS to treat patients with chronic pain of the trunk and limbs. The primary efficacy objective is to demonstrate noninferiority of ECAP-controlled closed-loop SCS compared to open-loop SCS by comparing the proportion of subjects with $\geq 50\%$ reduction in average overall trunk and limb pain and no increase in pain medications at the three-month visit. If noninferiority is met, superiority is tested. The safety of closed-loop SCS is determined by comparing the incidence and severity of all adverse events recorded in both treatment groups.

Secondary objectives include evaluation of the following patient-reported outcomes: overall trunk and limb pain, leg pain, back pain, functional disability, emotional functioning, sleep, quality of life, impression of change, satisfaction, and stimulation characteristics. Programming parameters, objective measures based on ECAPs, and the neural response profiles are collected and stored on the device for evaluation of the characteristics of the SC activation and comparison to the ECAP target and therapeutic window, both in clinic and during activities of daily living.

Trial Design

The Evoke study is a multicenter, prospective, randomized, double-blind, parallel-group clinical trial. One-hundred and thirty-four (134) subjects at up to 20 United States sites will be enrolled. Subjects who provide informed consent and meet eligibility criteria are enrolled and randomized at the time of the trial procedure. Subjects are randomized 1:1 to Evoke ECAP-controlled closed-loop SCS (investigational arm) or Evoke open-loop SCS (control arm). As this is a double-blind study, the treatment allocation is concealed from the study subjects, investigators, and their staff. Subjects first undergo a trial period with the external trial stimulator to determine eligibility for the permanent implant. Subjects who have at least a 50% reduction compared to baseline in overall trunk and limb pain as measured by a visual analog scale (VAS) are approved to receive a permanent implant. Follow-up is at 1-, 3-, 6-, 9-, and 12-months after the permanent implant and biannually thereafter for up to 3 years. The study design is summarized in Fig. 3.

Ethics

This study is being conducted in accordance with FDA regulatory requirements, good clinical practice, approving Institutional

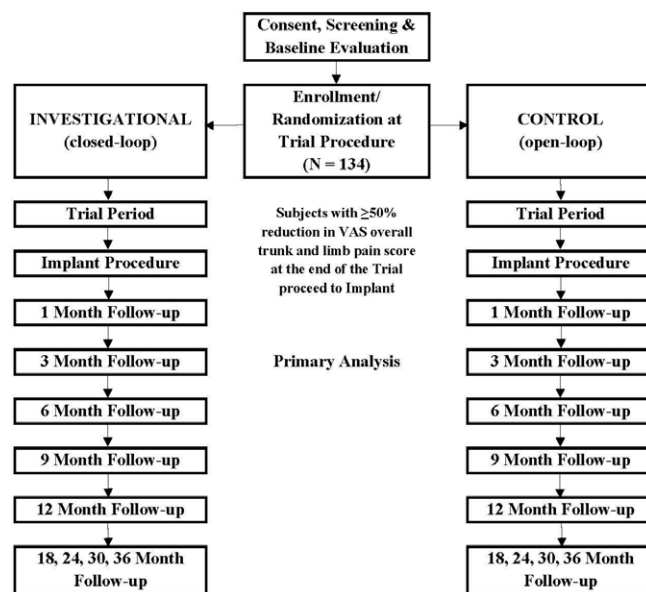


Figure 3. Evoke study design.

Review Boards (IRBs), and the ethical principles that have their origin in the Declaration of Helsinki.

Patient Selection

The study population comprises subjects suffering from chronic trunk and limb pain. A subject must meet all the inclusion criteria and none of the exclusion criteria to be eligible for the study (Table 1). Additionally, an independent medical monitor confirms all inclusion/exclusion criteria are being consistently interpreted for each patient prior to study entry.

Interventions

The SCS trial procedure is conducted using standard techniques with leads placed percutaneously and connected to the external trial stimulator. The trial period typically lasts up to 1 week; however, the protocol permits up to 30 days. Surgical implant of the permanent system occurs if the subject achieves at least 50% pain relief at the trial and chooses to move forward with the implant.

The neuromodulation system (Evoke System, Saluda Medical, Sydney, Australia) offers both closed-loop and open-loop stimulation modes and is capable of measuring the SC activation produced by stimulation regardless of the stimulation mode by recording the neural response (i.e., ECAPs) after each stimulation pulse on the same leads used for stimulation. When enabled, the system produces closed-loop stimulation via a feedback mechanism that measures ECAPs and adjusts the stimulation current after every stimulus to maintain the clinician-prescribed target ECAP amplitude, and in doing so, works to maintain reliable SC activation (Fig. 4). Because the system offers both closed-loop and open-loop stimulation modes, and it is the only system that can measure neurophysiological responses, it served as the investigational and control device. This also allowed for a double-blind study to be conducted.

Programming in both treatment groups utilizes conventional programming parameters (frequency, pulse width, and amplitude), in addition to ECAP measurements, to optimize outcomes.

Table 1. Evoke Study Inclusion and Exclusion Criteria.

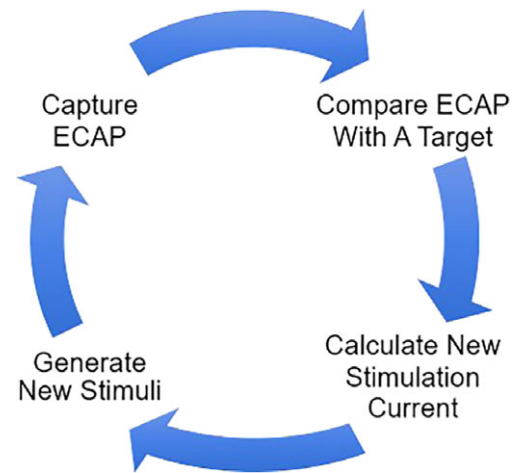
Inclusion criteria

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. Visual analog scale (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 a spinal cord stimulation (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

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, or sacral nerve stimulator.
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 postmenopausal).
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 or transcranial magnetic stimulation.
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.

FDA, US Food and Drug Administration; ODI, Oswestry Disability Index.

**Figure 4.** Evoke system ECAP-controlled feedback mechanism. [Color figure can be viewed at wileyonlinelibrary.com]

The difference is that the investigational arm (closed-loop) has the feedback mechanism enabled. Subjects are asked not to change their study indication pain medications from baseline through the three-month follow-up visit to assess the true treatment effect of the stimulation.

Assessments and Objective Measurements

Outcome measures selected for this trial are based on a review of previous SCS randomized controlled trials (RCTs) and consideration of the IMMPACT recommendations (31,32). Objective data on programming parameters, neural activation measurements, and neurophysiological properties are also collected and studied along with the patient-reported clinical outcome measures to yield a more complete understanding of the mechanisms and pain-alleviating effects of SCS than was previously possible. Standard programming parameter data such as stimulation amplitude (mA), frequency (Hz), pulse width (μ s), number of programs, and utilization are collected. In addition, objective neural response measurements obtained from the device are collected continuously as a measure of SC activation, stored as histogram data, and used to determine the percent stimuli activating the SC fibers within the therapeutic window. The range of SC fiber activation for therapeutic stimulation, that is, within the therapeutic window (25,28,34,35), is determined by collecting the subject's SC activation (i.e., ECAP amplitude) at patient reported perception threshold to discomfort threshold (i.e., maximum). In the clinic setting, SC activation and associated subject-reported stimulation intensity based on a published rating scale (36) are collected together to correlate subject sensation of stimulation with level of SC activation while performing postures that mimic activities of daily living. In addition to SC activation data, other objective neurophysiological properties are collected including: ECAP waveform features (e.g., ECAP amplitude, width, slope, and shape), conduction velocity (i.e., the speed at which an ECAP propagates along the spinal cord), rheobase (i.e., the minimum stimulus current needed for neural activation at an infinitely long pulse width), chronaxie (i.e., the minimum pulse width needed for neural activation at twice the rheobase), and late latency responses (i.e., dorsal root activation). Assessments are performed per the schedule outlined in Table 2.

Table 2. Study Visits and Associated Assessments.

Assessment	Screening/ baseline	Trial procedure	Trial end	Implant procedure	1 month	3 months	6 months	9 months	12 months	18, 24, 30, and 36 months
Informed consent, inclusion/exclusion, baseline evaluation	X									
Pain medication/therapies	X	X	X	X	X	X	X	X	X	X
Procedure/X-rays		X	X	X						
Programming/ neurophysiological measurements		X		X	X	X	X	X	X	X
Pain assessment (VAS and 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-5 L	X				X	X	X		X	X
ODI	X				X	X	X		X	X
Pain diary	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					X	X	X	X	X	X
PGIC and patient satisfaction					X	X	X		X	X
Blinding assessments						X			X	
Adverse event	X	X	X	X	X	X	X	X	X	X

EQ-5D-5 L, European Quality of Life-Five Dimensional-Five Level (licensed from EuroQol); FU, follow-up; ODI, Oswestry Disability Index (licensed from Mapi Research Trust); PGIC, patient global impression of change; POMS, profile of mood state (licensed from Multi-Health Systems, Inc.); PSQI, Pittsburgh Sleep Quality Index (licensed from the University of Pittsburgh); SF-12, Short-Form Health Survey (licensed from OptumInsight Life Sciences, Inc.).

OUTCOMES

Primary Outcome

The primary endpoint is a composite endpoint, where a subject is deemed as a success, if they experience 50% or more reduction in average overall trunk and limb pain as determined by VAS at the three-month visit and have no increase in baseline pain medications within 4 weeks of the three-month visit.

Secondary Outcomes

Secondary outcomes compare treatment group responders and high responders ($\geq 50\%$ and $\geq 80\%$) and percent change from baseline to three-month follow-up in overall trunk and limb pain, back pain, and leg pain as measured on VAS. Additional secondary outcomes include comparison of the following outcomes between groups: pain diary, functional disability measured by the Oswestry Disability Index, emotional functioning measured by the profile of mood states, sleep measured by the Pittsburgh Sleep Quality Index, quality of life measured by the Short-Form Health Survey (SF-12, version 2) and the European Quality of Life Five-Dimensional Five-Level (EQ-5D-5 L), Patient Global Impression of Change (PGIC), patient satisfaction, stimulation characteristics, posture change assessment of SC activation and corresponding subject-reported stimulation intensity, programming parameters, and the neural response profiles characterizing SC activation. The neurophysiological properties of the fibers being stimulated (i.e., ECAP features, conduction velocity, chronaxie/rheobase, and late responses) are also examined. Additionally, the safety profile is compared between groups.

Procedures to Minimize Bias

The Evoke study protocol has been developed to preserve objectivity and minimize intentional or unintentional bias. A randomized design is utilized to increase the likelihood of having comparable treatment groups with respect to baseline characteristics and to remove investigator bias in the allocation of the treatment assignment. The randomization is generated using permuted blocks and stratified by study site to ensure within-site balance.

The study is double-blind, in that the treatment allocation is concealed from the study subjects, the investigators, and their staff to reduce the potential of data being systematically distorted by knowledge of the treatment received. A blinding assessment is performed to assess maintenance of blinding.

Lead placement by the investigator is equivalent in both study arms and performed per a standard surgical protocol. The Field Clinical Engineer (FCE) does not receive the randomization allocation until after leads are placed and the trial procedure is complete.

The FCEs follow a standard clinical programming protocol to program all subjects, which are equivalent in both study arms (i.e., ECAPs are acquired and optimized to confirm activation of pain inhibition process) with the exception of enabling the feedback mechanism. All subjects, regardless of treatment allocation, are programmed and optimized using ECAP measurements and subject feedback. As recommended by the FDA, investigator oversight of FCEs is documented to confirm comprehensive programming and optimization for all study subjects (37). FCEs do not have direct contact with study subjects outside the clinic; subjects may contact the site at any time to coordinate a phone call or clinic visit as needed.

Data Quality and Management

Data quality and management are ensured through study and device training, data management, and monitoring. Investigators and their staff are trained on the device, study protocol, and procedures. The study data are collected in an FDA 21 CFR Part 11 compliant electronic data capture system. Additionally, the study is monitored to ensure protection of human subjects, accuracy of the data, and the conduct of the study, which complies with the protocol and ethical and regulatory requirements.

Statistical Methods and Data Analysis

Sample Size

Based on the preliminary results of the prospective observational study of the device in Australia (Avalon study; ACTRN12615000713594) (28) and the literature (38) on SCS, the sample size calculation assumes that the true success rate of the primary composite endpoint is at least 12% higher for closed-loop compared to open-loop SCS.

To have at least 80% power to determine closed-loop is noninferior to open-loop SCS at a one-sided significance level of 0.05 and a noninferiority margin (δ) of 10%, a minimum of 60 subjects per group (120 total) is required with known or presumed primary endpoint status. The sample size was calculated in PASS 2013 and is based on an unpooled z-test without continuity correction for a noninferiority test of two proportions. In order to account for potential subject loss postrandomization of up to 10%, 134 subjects need to be randomized in order to obtain at least 120 subjects with known or presumed primary endpoint status.

Analysis Populations

The primary analysis population is the intent-to-treat (ITT) group, which includes all randomized subjects who either have known endpoint status at three months or are presumed nonresponders.

Presumed nonresponders are subjects with $\leq 50\%$ pain reduction in overall trunk and limb pain or who exit due to a device- or stimulation-related adverse event; these subjects are analyzed as failures.

All other missing data are classified as missing, and sensitivity analyses are performed to qualify the potential impact on the trial outcome (e.g., best- and worst-case scenario, tipping point analysis, and multiple imputation).

Two additional analysis populations of interest have been defined a priori and are utilized to assess study outcomes. First, the permanent implant subset (PIS) includes all ITT subjects who received a permanent implant. Second, the per protocol (PP) analysis population includes all PIS subjects who have evaluable primary endpoint data and no major deviations.

Primary Analysis

The primary composite endpoint is analyzed via the normal approximation to the binomial distribution, utilizing an unpooled estimate of the standard error, and no correction for continuity. Noninferiority of closed-loop relative to open-loop SCS is assessed against the clinical significance margin (δ) of 10% at a one-sided significance level (α) of 0.05. If noninferiority is met, then superiority is tested at a two-sided significance level of 0.05.

Additional Analyses

If noninferiority is met in the testing of the primary composite endpoint, the hierarchical secondary endpoints are tested. In order to preserve the experiment-wise error rate of 0.05, a closed testing procedure is used. If the first endpoint passes, the second is tested, and so forth. If an endpoint fails, none of the endpoints

following in the list is formally tested. All initial tests are for noninferiority. If all secondary endpoints pass at the three-month analysis, hierarchical testing continues when the 12-month data are analyzed, beginning with the primary endpoint and continuing in the same order specified until a hypothesis test fails. All secondary endpoints that pass their noninferiority test are tested for superiority at a two-sided level of significance of 0.05. For incidence measures (i.e., responder rates), missing data are managed in the same manner described above for the primary composite endpoint. For continuous measures (i.e., percent change from baseline), subjects with missing data categorized as presumed nonresponders utilize a last-value carried forward imputation methodology. Subjects who fail the medication component of the primary endpoint have a change from baseline value of "0" imputed for the hierarchical secondary endpoint calculation.

The additional secondary endpoints are assessed using standard summary statistics, and findings of significance may be presented and include *p*-values and/or confidence intervals as appropriate. Standard methods are utilized to compare statistics between study groups at time points of interest (e.g., two-sample *t*-test, Chi-square tests, and normal approximation to the binomial two-sample *z*-test).

The blinded independent adjudication committee determinations are reported for all adverse events that occur during the study. The safety profile of both treatment groups is characterized using appropriate descriptive statistics.

All statistical analyses are conducted with a validated statistical analysis software (e.g., SAS).

DISCUSSION

The Evoke System is the first and only neuromodulation system to measure the response of the SC to stimulation, and additionally, to use this information in a feedback mechanism that modulates the stimulation amplitude delivered to the SC in real time to produce ECAP-controlled closed-loop SCS. This is important because when using open-loop stimulation the electrical field strength reaching the spinal cord varies with changes in distance between the electrode and spinal cord. These changes occur with normal physiological activity (e.g., breathing and heartbeat) and movement and may result in over/under activation of the SC, outside the therapeutic window for an individual patient. The Evoke study, which is currently ongoing, is the first large multicenter, prospective, randomized, double-blind study comparing ECAP-controlled closed-loop to open-loop SCS and measuring human spinal cord electrophysiology during SCS in both treatment groups. The design of the study is intended to provide evidence to support FDA approval of this system for treatment of chronic pain of the trunk and/or limbs by establishing noninferiority of closed-loop stimulation to open-loop stimulation. This study will provide comparative efficacy and safety data for closed-loop stimulation in patients with chronic trunk and limb pain. Additionally, the objective data on SC activation and other neurophysiological properties may provide insight into the MOA of SCS and the underlying pathophysiology of chronic pain.

Every attempt is taken to minimize any potential bias that may result from using the same device for both the investigational and control treatment groups, including following the same procedures for device implantation and programming (with the exception of enabling or disabling the feedback mechanism), allocating randomization assignments after implantation of the trial

leads, and prohibiting direct contact between FCEs and study participants outside the clinic. Use of the same device for both treatment arms provides distinct advantages over the use of another commercially available device for the control arm of the study. It enables a rigorous double-blind study design, which reduces the potential of data being systematically distorted by knowledge of the treatment received and perceptions of which treatment may be better. Also, because this is the only neuromodulation system capable of measuring and recording SC activation and other neurophysiological properties, using it as the active control allows for the collection and comparison of this objective data between treatment groups.

The potential clinical utility of these objective measurements of SC activation and other neurophysiological properties is promising. These data may lead to improvements in diagnosis, assessment, and treatment of chronic pain and provide the foundation for an individualized mechanism-based treatment approach for more effective neuromodulation therapies in alignment with IMMPACT recommendations (33). Additionally, closed-loop stimulation may prove to provide stimulation within the therapeutic window based on SC activation and lead to better long-term outcomes.

CONCLUSION

This randomized, controlled trial represents the first RCT human study to collect objective data on SC activation and other neurophysiological properties along with clinical outcome data for both closed-loop and open-loop SCS. The benefits of using the same device for both treatment groups outweigh the potential limitations. Collection of electrophysiological data in both treatment groups allows for comparisons of spinal cord activity and function between groups. The double-blind study design reduces bias permitting statistically significant observations of differences in ECAPs that may be correlated with observed differences in efficacy. This may not only provide data for FDA approval but also provide data to support the mechanism of action of SCS for chronic pain in humans.

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All authors made substantial contributions to the research design, or the acquisition, analysis or interpretation of data, and to drafting the paper or reviewing it critically. All authors have approved the submitted version.

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COMMENTS

The Irreproducibility Crisis of Modern Science, especially in biomedical and behavioral fields, was summarized in a 2018 report from the National Association of Scholars and expressed in a lighter vein by a Boston Globe headline, “Studies show many studies are false” (1,2). The epistemological dissection of broadly held, yet unlikely beliefs in current medical science owes its current popularity to the work of Ioannidis and colleagues (3). Some of us have been rolling our eyes over the neurostimulation pain literature for even longer.

For nearly two decades we and other reviewers have offered plausible explanations for the near uniformly positive results of published neurostimulation case series, clinical trials, reviews and meta-analyses. Critical analyses have found irreparable structural biases in the data sets and analytical methods that constitute the historical and contemporary neurostimulation pain literature (4–16). Thereafter, investigators and sponsors co-opted the language of evidence-based medicine to undertake neurostimulation pain studies that evaded genuine bias-control measures such as early randomization, effective blinding (deliberate deception), long endpoints (years instead of weeks or months), strict intention-to treat analyses (before implant), monometric analgesic efficacy endpoints, and other means of bias-control (17–22). Thus, a focus on the formalities of trial design and analysis – namely, what should versus what should not count as evidence – has failed to address why physicians, device manufacturers and even patients consistently ignore the contradictions between claims of analgesic efficacy versus their own (and their patients’) real world experiences (23,24).

One answer may lie in reactions to the word “bias”. Assertions of biased methods provoke reflexive denial owing to the connotations of bigotry and injustice attached to the word itself. Bearing that semantic baggage in mind, we’ll risk a further assertion: that advocates for neurostimulation pain therapies (those who believe in the existence of stimulation-produced analgesia) manifest cognitive biases that foreclose serious discussions (4,5). The cognitive bias catalogue includes such phenomena as anchoring (focalism), false equivalence (of non-equivalent conditions), illusory statistical power (large aggregate N numbers), illusions of experience (long time intervals),

illusions of truth (repetitive publications), the illusion of explanatory depth (underestimation of one’s own knowledge lacunae), the seductive allure of neuroscience explanations (especially when accompanied by neuroimaging), pro-innovation bias (conflation of new with better), misattribution (post hoc ergo propter hoc), illusory superiority (Dunning-Kruger or Lake Wobegon effects), and ultimately – the fallacy of misplaced rationality.

Despite the Evoke Study sponsor’s efforts, the protocol described here has fallen prey to structural and cognitive biases (1–16,25–34) – chief among which is the fallacy of misplaced rationality. For decades, advocates for analgesic neurostimulation have swerved from one set of hypothetical, discredited, or implausible mechanisms of action to another. Purported mechanisms – and the clinical methods to select patients based on them – have included: a series pain classification schemes (acute/chronic; somatic/visceral; nociceptive/neuropathic, etc.); psychometric or personality tests; drug infusions (morphine/barbiturate); somatosensory evoked-potentials; functional neuroimaging; brief- or long-duration trial implants; and simple, complex, perceptible, or imperceptible stimulus parameter programming, among others (35–42).

None have led to consistently replicable analgesia in a majority of patients, nor consistent with advocates’ claims of 80-, 70-, or even 50 percent efficacy. Naturally, this reviewer is skeptical of a claim that pulse-by-pulse adjustment of stimulation parameters using short-feedback-loop detection of spinal neuronal potentials will achieve anything better or even different than what’s been tried before. This is where the fallacy of misplaced rationality comes in – the most common example of which is posing the question “How many angels can dance on the head of a pin?” Since there are no such things as angels, the question is, by definition, fallacious. To-date, no effectively blinded or legitimately controlled clinical or laboratory study has detected consistent and clinically meaningful analgesic effects from any form (or any anatomic site) of neurostimulation to treat chronic non-cancer pain. Moreover, no study or case series has documented (by blood or urine tests, or even pill counts) a long-term decrease in narcotic analgesic drug intake by chronic non-cancer pain patients implanted with a neurostimulation device. We’ll hazard a further prediction that no matter what this study shows, the practice patterns of committed clinicians won’t change, either.

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