Clinical Protocol
for the
BENEFIT-02 Study

BENEFIT-02

NCT03594266

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BENEFIT-02 Study

PROTOCOL SIGNATURE PAGE

The signature below constitutes the receipt and review of the BENEFIT-02 Study protocol and any attachments, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations, ICH and GCP guidelines.

PRINCIPAL INVESTIGATOR:

Signed: _____

Name (please print)

_____ _____

Signature Date

SUMMARY

Title	BENEFIT-02 Study
Design	Prospective, multi-center, randomized, parallel assignment, single-blind, interventional feasibility study
Purpose	To investigate the effects of two study spinal cord stimulation (SCS) therapies on subject reported pain and paresthesia perception
Subject Population	Subjects with chronic low back and/or leg pain who will undergo an SCS trial with a commercially available SCS system
Enrollment	The study will provisionally enroll up to 226 subjects, in order for 70 subjects to complete the study testing period
Clinical Sites	Up to 20 sites
Primary Endpoints	• Change since baseline in Numerical Rating Scale (NRS) for pain (overall) evaluated separately for each study SCS therapy • Inter-therapy comparison of change since baseline in Numerical Rating Scale (NRS) for pain (overall)
Secondary Endpoints	• Change since conclusion of commercial trial in Numerical Rating Scale (NRS) for pain (overall) evaluated separately for each study SCS therapy • Freedom from investigational device-related adverse events
Study Risk Determination	Nonsignificant risk device study
Sponsor	BIOTRONIK, Inc. Clinical Studies Department 6024 SW Jean Road Lake Oswego, Oregon 97035 Telephone: 1-800-547-0394 Email: benefit02@biotronik.com

1 INTRODUCTION

1.1 STUDY OVERVIEW

In the BENEFIT-02 study, a BIOTRONIK wearable stimulator will be utilized in order to investigate the effects of two study spinal cord stimulation (SCS) therapies on subject reported pain and paresthesia perception observed over 12 days of study stimulation testing following conclusion of a successful SCS commercial trial.

Subjects eligible for the study include those who plan to undergo trial testing of a commercially available SCS system including an SCS trial stimulator and percutaneously implanted SCS trial lead(s). Prior to enrollment procedures, subjects will be screened to ensure study eligibility and will sign an informed consent form. Consent must be obtained prior to the commercial SCS trial lead implant procedure where a sponsor provided ionic silver impregnated percutaneous site dressing will be applied in order to minimize the risk of infection during the extended SCS trial period.

At the standard of care in-office visit occurring at the end of the commercial trial period, provisionally enrolled subjects who are eligible and confirm they wish to undergo the study-specific extended testing period will be randomized, at which point they will be considered fully enrolled. These subjects will have the trial stimulator disconnected and the existing SCS trial lead(s) connected to the BIOTRONIK wearable stimulator that will be used to administer the randomly assigned study SCS therapy during the study testing period. At this randomization visit, stimulation testing will be performed in order to determine an initial set of programmed parameters that will be suitable for each subject.

Following randomization, subjects will initiate a two day washout period intended to mitigate carryover effects from the therapy administered during the commercial trial. Additionally, subject suitability for the study testing period will be verified based on demonstrated compliance with the schedule of required assessments. Study eligibility will also be confirmed based on the study inclusion criteria of a required increase in Numerical Rating Scale (NRS) for pain (overall) to a minimum of two NRS units less than baseline (i.e. NRS measurement from prior to the commercial trial collected at enrollment) following discontinuation of the trial SCS therapy during the washout period. The study definition of overall pain is pain for which the SCS therapy is indicated (limited to back and/or leg pain).

Subjects who do not experience the required increase in NRS for overall pain during the washout period, or are non-compliant with the study assessment schedule (e.g. do not complete the required phone call following the two day period), will not have the randomly assigned study SCS therapy initiated. These subjects will be exited from the study.

Following the conclusion of the washout period, subjects who are eligible to participate in the study testing period will have the randomly assigned study SCS therapy initiated. The study SCS therapy will be administered for 12 days, during which time phone calls scheduled with the subject, site personnel, and sponsor

personnel will occur up to once per day. During these phone calls, the study SCS therapy will be optimized via sponsor-directed subject reprogramming of the study stimulator and study data will be collected.

An initial study-specific in-office visit will occur six to eight days following randomization, and a final in-office visit will occur 14 days following randomization, at which time the subject's SCS trial lead(s) will be disconnected from the BIOTRONIK wearable study stimulator, and the subject's participation in the study will end.

1.2 Background

Spinal Cord Stimulation (SCS) has been used for several decades, and is now considered a valid treatment option for patients with chronic, intractable pain [1]. Currently, about 34,000 patients worldwide receive a spinal cord stimulator annually for pain. Spinal cord stimulation (SCS) leads are placed in the epidural space to deliver electrical stimulation to the dorsal columns of the spinal cord. Successful pain relief generally requires activation of dorsal column fibers that innervate the patient's painful area. The patient subsequently feels moderate paresthesia located in the painful area and pain relief due to spinal and supra-spinal mechanisms. However, excessive stimulation can result in side effects such as uncomfortably strong paresthesia, paresthesia in unwanted areas, and muscle activation and/or cramping. Insufficient stimulation can result in reduced pain relief [2]. Historically, only 50% of patients respond to SCS therapy and many only achieve 50% pain relief with conventional SCS therapies.

Recent advances in SCS therapies may help to improve SCS outcomes. For example, continuous stimulation at a higher frequency (10 kHz) was shown to provide superior pain relief for low back and leg pain compared to traditional lower SCS stimulation frequencies [3]. Additionally, prior studies have indicated 1 kHz continuous stimulation [4], [5] or 500 Hz burst patterns [6] of stimulation may provide additional pain relieving benefit while reducing the stimulation energy required.

Despite these recent advances, the complete range of stimulation parameter options for SCS remains largely unexplored. In this regard, several study therapy options have been identified during product definition of a new SCS system. This study intends to investigate the effects of two study SCS therapies on pain relief and paresthesia perception.

1.3 Investigational Device Description

The BENEFIT-02 study stimulation system includes a wearable stimulator, clinician programmer, subject remote and lead adapters to allow connection of the wearable stimulator to commercially available SCS trial leads. The stimulation system is a current-based neuromodulation system designed and built by BIOTRONIK SE & Co. KG under validated revision and process control. It is designed to provide stimulation according to the requirements of the BENEFIT-02 study. Patient protection is ensured via current and charge limitation as described, mains-isolated battery power, as well as third party standards compliance testing

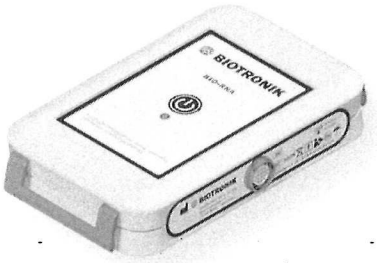
of leakage current and radiation limit conformance following ISO 60601-1 standard tests. Beyond design validation of performance, continued proper operation is confirmed via stimulation path tests prior to each clinical deployment.

System subcomponents:

- Wearable stimulator – worn by study subject; delivers stimulation energy
- Clinician programmer – used by clinician or designee to configure and adjust SCS stimulation therapies
- Subject remote – used by study subject to adjust therapy within clinician-defined limits
- Lead adapter – used to connect commercial SCS trial leads to the wearable stimulator. A unique lead adapter model is available for compatible commercially available SCS trial lead designs

Descriptions of the BENEFIT-02 study stimulation system components including representative images are provided in Table 1.

Table 1: BENEFIT-02 Study Stimulation System

Component	Representative Image	Description
Wearable Stimulator		Belt-worn portable stimulator, 16 channels, 20mA max. current source driven, battery powered
Clinician Programmer		Commercially available portable personal computer
Subject Remote		RF program and amplitude selection for wearable stimulator
Lead Adapter		Adapts to eight-electrode commercial SCS trial leads; silicone jacket

1.3.1 Wearable Stimulator

1.3.1.1 Stimulator Hardware

The study stimulation system will use a custom, belt-wearable stimulator to provide neuromodulation current to commercial percutaneous SCS trial leads implanted in the normal course of patient care by a physician. The stimulator current output will be coupled to the patients' percutaneous lead(s) via a lead adapter cable. The wearable stimulator is powered by 3.6 V AA batteries which will be replaced as needed during use.

The stimulator is capable of interfacing with up to sixteen electrodes, and provides current-controlled stimulation pulses, with stimulation parameters determined by the selection of one of four stimulation programs. Programmable stimulation amplitudes, pulse widths, and frequencies fall within the ranges of those used in commercially available stimulators, but may be configured in unique combinations not frequently utilized.

The stimulator is controllable from both the clinician programmer and subject remote. The clinician programmer is designed to permit modification of the stimulation configurations (programs) within fixed parameter ranges, while the subject remote permits subject selection between the physician configured programs, adjustment of stimulation amplitude, and the ability to turn stimulation on or off.

1.3.1.2 Stimulator Software

The stimulator unit utilizes firmware. The firmware will be responsible for:

- Controlling ongoing stimulation
- Interfacing with the subject remote and clinician programmer
- Logging changes and impedance measurements
- Checking system integrity and responding to errors

1.3.2 Clinician Programmer

1.3.2.1 Clinician Programmer Hardware

Stimulation configurations will be set up by a clinician programmer which is an off the shelf control computer (laptop) running custom control software on a commercial operating system (Windows 10). Communication to the stimulator will make use of Bluetooth and the Operating system Bluetooth interface.

The clinician programmer will utilize custom software to allow rapid live program changes and program set-up for use with the subject remote.

1.3.2.2 Clinician Programmer Software

The control computer software will be responsible for:

- Providing a graphical user interface for stimulation control in the context of study execution
- Downloading and saving stimulator logs
- Logging program changes made by the clinician programmer
- Loading programs onto the stimulator for chronic use and subject remote control

1.3.3 Subject Remote

1.3.3.1 Subject Remote Hardware

The system includes a wireless subject remote which allows the subject to select between stimulation programs, change stimulation amplitude, and turn stimulation on and off on the wearable stimulator. The subject remote is a handheld device with buttons and an indicator-based user interface.

1.3.3.2 Subject Remote Software

The subject remote utilizes firmware. The firmware will be responsible for:

- Wireless session initiation with the wearable stimulator
- Accepting button-based user inputs and controlling indicator LEDs
- Transmitting program and amplitude changes to the stimulator
- Subject remote power management and automatic power off

1.3.4 Lead Adapter

Lead adapters support the connection between the wearable stimulator and the subject's percutaneous commercial SCS trial lead(s). The lead adapter will be long enough to reach from the belt mounted stimulator positioned on the subject's waist to the percutaneous lead exit site on the subject's lower back, where the adapter will be connected to the SCS trial lead(s). The portion of the adapter where the physical connection to the SCS trial lead(s) is made will be placed underneath the lead exit site outer cover bandage, and so the adapter is considered to be used in a clean environment and adjacent to a sterile environment (the primary lead exit site bandage). Therefore, the lead adapters will be sterilized and packaged appropriately.

Lead connection contacts are not standardized in the spinal cord stimulation industry, and each manufacturer currently utilizes different connection dimensions for their percutaneous SCS trial leads. Study lead adapter compatibility includes all major brands of currently available market released eight-electrode leads. If a 16-electrode SCS trial lead is used, a separate commercially available 2x8 lead adapter will be required.

1.4 Study Data Collection Watch

At the enrollment visit, subjects will be provided a CamNtech PRO-Diary study data collection watch (shown in Figure 1) that includes an accelerometer and programmable graphical user interface, and will receive initial training on its usage. The study data collection watch will be utilized throughout the study after the enrollment visit to collect activity metrics continuously and subject reported data from the following scheduled and subject triggered assessments:

1.4.1 Scheduled Assessments

- Acute Numerical Rating Scale (NRS) for pain (overall, back, leg) (twice daily at 12 hour intervals)
- Sleep quality (once daily in the morning only)

1.4.2 Subject Triggered Assessments

- Pain event
- Pain medication event
- Sleep quality

Figure 1: Data Collection Watch

1.4.3 Data Collection Watch Hardware

The CamNtech PRO-Diary is a compact activity monitor and electronic diary watch with the capability of storing user reported events and completed questionnaires. The watch consists of an OLED screen, touch sensitive slider, two buttons, and a rechargeable lithium ion battery. Activity metrics are measured via an integrated tri-axial accelerometer.

1.4.4 Data Collection Watch Software

Companion software will enable study assessments to be programmed for the CamNtech PRO-Diary watch. Additionally, the software interprets accelerometer data to quantify the intensity and duration of daily physical activity and also allows for downloading and viewing of the data captured from the CamNtech PRO-Diary watch for analysis via a USB and computer.

2 STUDY DESIGN

This prospective, multi-center, randomized, parallel assignment, single-blind, interventional feasibility study is designed to investigate the effects of two study spinal cord stimulation (SCS) therapies on subject reported pain and paresthesia perception.

Potential subjects will be identified by the investigator from their general patient population and must meet all of the study inclusion and none of the study exclusion criteria evaluated at the time of enrollment (Section 3.1.1 and Section 3.1.2). Once study eligibility is confirmed, written informed consent is obtained, after which enrollment visit data will be collected. Subjects will be considered fully enrolled after being randomly assigned to receive one of two study SCS therapies.

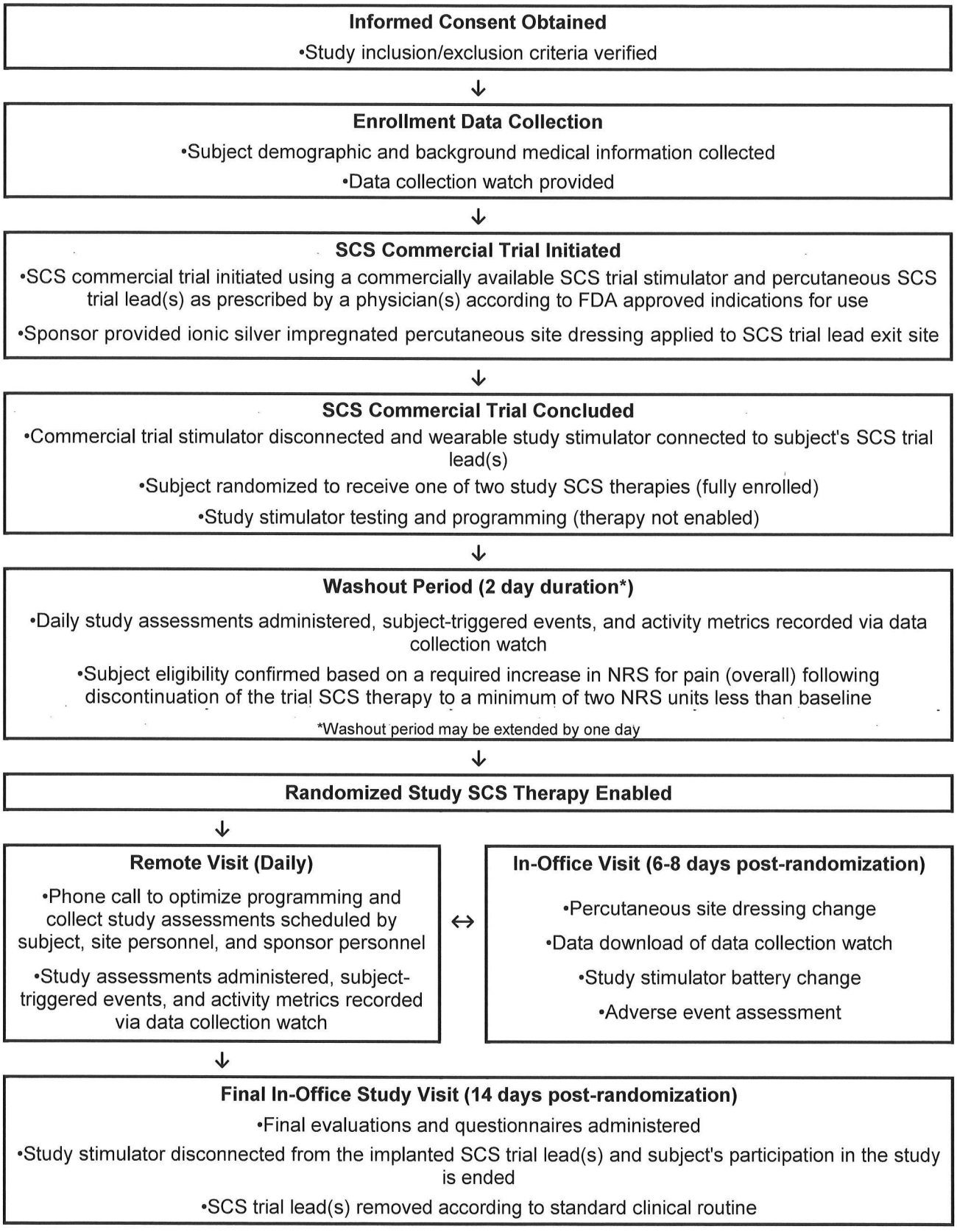
In order to meet the objectives of this investigation, a target of 70 subjects should complete the randomized study stimulation period (~35 subjects for each study SCS therapy). Therefore, to account for subject attrition, up to 110 subjects will be randomized at up to 20 study sites. The study population will consist of patients with chronic low back and/or leg pain who have been identified as candidates for trial testing of a commercially available SCS system including percutaneous SCS trial lead(s), but have not yet undergone trial lead implant. The commercial trial test period will be conducted independently from the study according to standard of care. The commercial trial period is referred to as the "trial" and the BENEFIT-02 interventional study stimulation period is referred to as the "study" throughout this protocol.

To participate in this study, subjects must be willing to undergo an extended 14 day testing period following the conclusion of their commercial trial, where their existing SCS trial lead(s) will be connected to a BIOTRONIK study stimulator and one of two randomly assigned study SCS therapies will be administered for an additional 12 days after a two day washout period. After completion of the 12 day study testing period, the subject's participation in the study ends, the study stimulator will be disconnected, and the commercial SCS trial lead(s) will be removed according to the standard clinical routine.

This feasibility study includes the assessment of two primary endpoints and two secondary endpoints that are designed to provide preliminary information regarding the effectiveness and safety of the two study SCS therapies under investigation in the study.

Figure 2 provides an overview of the clinical study design.

Figure 2: Study Design Flowchart



2.1 STUDY ENDPOINTS

This clinical study includes the assessment of two primary endpoints and two secondary endpoints that are designed to provide preliminary information regarding the effectiveness and safety of the two study SCS therapies under investigation. Since the effect size of each study SCS therapy on the primary outcome measure (Numerical Rating Scale (NRS) for pain (overall) [7]) is unknown, there are no formal tests of hypotheses or other pre-specified statistical tests associated with the study primary endpoints.

2.1.1 Primary Endpoint 1

The purpose of primary endpoint 1 is to evaluate the change since baseline in Numerical Rating Scale (NRS) for pain (overall) for each study SCS therapy.

The evaluation of primary endpoint 1 will be based on the NRS for pain (overall) obtained at the final study testing visit (NRS_{Final}) compared with the baseline measurement obtained prior to initiation of the commercial trial period ($NRS_{Baseline}$), for subjects randomized to each study SCS therapy.

Primary endpoint 1 analyses will include all subjects with measurements for both NRS_{Final} and $NRS_{Baseline}$.

2.1.2 Primary Endpoint 2

The purpose of primary endpoint 2 is to provide an inter-therapy comparison of change since baseline in Numerical Rating Scale (NRS) for pain (overall).

The evaluation of primary endpoint 2 will be based on a comparison of the results of primary endpoint 1 between the two study SCS therapies. Primary endpoint 2 analyses will include all subjects included in primary endpoint 1 analyses.

2.1.3 Secondary Endpoint 1

The purpose of secondary endpoint 1 is to evaluate the change in Numerical Rating Scale (NRS) for pain (overall) since conclusion of the commercial trial for each study SCS therapy.

The evaluation of secondary endpoint 1 will be based on the NRS for pain (overall) obtained at the final study testing visit (NRS_{Final}) compared with the measurement obtained following conclusion of the commercial trial but prior to initiation of the randomized study SCS therapy ($NRS_{Commercial\ Trial}$), for subjects randomized to each study SCS therapy.

Secondary endpoint 1 analyses will include all subjects with measurements for both NRS_{Final} and $NRS_{Commercial\ Trial}$.

2.1.4 Secondary Endpoint 2

The purpose of secondary endpoint 2 is to collect preliminary safety information regarding the investigational device and study SCS therapies (stimulation parameters are within the ranges of existing commercial therapies).

The evaluation of secondary endpoint 2 will be based on the number of subjects free from investigational device-related adverse events (as defined in Section 11.3):

$$\text{Adverse event-free rate (AEFR)} = \frac{\text{(Number of subjects without an investigational device-related AE)}}{\text{(Total number of subjects)}}$$

Evaluable subjects for secondary endpoint 2 will include all subjects who undergo randomization and have the investigational stimulation system connected to their SCS trial lead(s).

2.1.5 Additional Data of Interest

In addition to the data collected in support of the study primary and secondary endpoints, other data of interest will also be collected, including:

- Subject demographic and background medical information
- Medical information from the commercial trial period (e.g. information related to the perioperative protocol, SCS trial system information, and stimulation parameters from the most effective/preferred programming)
- Other data of interest collected during the study via assessments such as:
  - Numerical Rating Scale (NRS) for pain (back)
  - Numerical Rating Scale (NRS) for pain (leg)
  - Oswestry Disability Index [8]
  - Brief Pain Inventory (Short Form) [9]
  - Patient Global Impression of Change (PGIC) [10]
  - Paresthesia and pain maps
  - Paresthesia coverage (i.e. paresthesia/pain overlap)
- Data collected via the study data collection watch:
  - Acute NRS for pain (overall, back, leg)
  - Pain event log
  - Pain Medication event log
  - Sleep quality
  - Activity metrics
- Data collected via subject diary (e.g. subject reported pain, medication usage, etc.)
- Subject reported satisfaction with the study SCS therapy
- Site reported adverse events excluded from secondary endpoint 2 analysis