Clinical Investigational Plan

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SJM-CIP-10113
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TARGET: A Post-Approval Study to Evaluate Targeted SCS (DRG) Stimulation for the Management of Moderate to Severe Chronic, Intractable, Pain of the Lower Limbs Due to CRPS Types I and II

Clinical Investigation Plan (CIP)

Sept 28th 2022

Sponsor

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Clinical Investigational Plan

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1.0 SYNOPSIS

Title:	TARGET (DRG) Post-Approval Study
Purpose:	The ACCURATE study evaluated spinal column stimulation of the dorsal root ganglion (DRG) with the Axium Neurostimulator System for the treatment of chronic, intractable lower extremity neuropathic pain associated with a diagnosis of complex regional pain syndrome (CRPS) and peripheral causalgia (PC). The ACCURATE study met its primary endpoint and the results of the study provide reasonable assurance of safety and effectiveness of the Axium Neurostimulator System. The Axium Neurostimulator System was approved for sale in the United States by FDA and is indicated for spinal column stimulation via epidural and intra-spinal lead access to the dorsal root ganglion as an aid in the management of moderate to severe chronic intractable* pain of the lower limbs in adult patients with Complex Regional Pain Syndrome (CRPS) types I and II.** The Proclaim Neurostimulation System was subsequently approved for the same indication and is replacing the Axium device in commercial distribution. This post-approval study is a condition of FDA approval. *Study subjects from the ACCURATE clinical study had failed to achieve adequate pain relief from at least 2 prior pharmacologic treatments from at least 2 different drug classes and continued their pharmacologic therapy during the clinical study. **Please note that in 1994, a consensus group of pain medicine experts gathered by the International Association for the Study of Pain (IASP) reviewed diagnostic criteria and agreed to rename reflex sympathetic dystrophy (RSD) and causalgia, as complex regional pain syndrome (CRPS) types I and II, respectively.
Primary Objective:	The primary objective of this study is to demonstrate that the proportion of serious adverse effects (SAEs) at 12 months for subjects who receive the permanent Implantable Pulse Generator (IPG) is lower than a pre-specified objective performance goal.
Secondary Objectives:	• To evaluate change in overall pain intensity • To evaluate change in physical function • To evaluate change in quality of life
Primary Endpoint:	The primary endpoint is the 12-month SAE rate for subjects receiving a permanent IPG.
Secondary Endpoints:	• Percent change from baseline to 12 months post-permanent implant for overall pain intensity measured using the Visual Analog Scale (VAS) • Change from baseline to 12 months post-permanent implant for physical function measured using the PROMIS-29 Profile

	• Change from baseline to 12 months post-permanent implant for quality of life measured using the PROMIS Global Health Scale
Descriptive Endpoints:	***Safety*** • Proportion of subjects with device, procedure or stimulation-related SAEs and non-SAEs among subjects who receive the permanent implant • Proportion of subjects who have AEs related to the trial implant procedure among subjects who fail the trial neurostimulator phase • Summary of procedure-related SAEs and non-SAEs by implanter experience ***Effectiveness*** • Change from baseline to 1, 3, and 6 months post-permanent implant for overall pain intensity measured using the Visual Analog Scale (VAS) • Change from baseline to 1, 3, and 6 months post-permanent implant for physical function measured using the PROMIS-29 Profile • Change from baseline to 1, 3, and 6 months post-permanent implant for quality of life measured using the PROMIS Global Health Scale • Change from baseline to 1, 3, 6 and 12 months post-permanent implant for neuropathic pain measured using the Neuropathic Pain Scale (NPS) • Change from baseline to 1, 3, 6 and 12 months post-permanent implant for sleep disturbance, anxiety, depression, fatigue, ability to participate in social roles and activities, pain interference and pain intensity measured using the PROMIS-29 Profile • Patient Global Impression of Change (PGIC) at 1, 3, 6 and 12 months post-permanent implant
Design:	This study is a prospective, single arm, observational post-approval study. Study follow-ups will occur at 1, 3, 6, and 12 months post-permanent implant.
Devices used:	DRG Neurostimulation System with Axium or Proclaim DRG Implantable Pulse Generator
Study Population	A maximum of 426 adult subjects with moderate to severe chronic, intractable pain of the lower limbs due to CRPS types I and II will undergo a trial of the neurostimulator system at up to 45 study sites in the United States.
Inclusion/Exclusion Criteria	Inclusion Criteria • Subject is male or female ≥ 22 and ≤ 75 years of age.

	• Subject has moderate to severe chronic intractable pain of the lower limbs resulting from Complex Regional Pain Syndrome (CRPS) types I or II. • Subject has a baseline VAS score of ≥ 60 mm for overall pain at the time of the baseline assessment. • Subject is willing and able to comply with the study requirements. • Subject is able to provide written informed consent. Exclusion Criteria • Subject has an active implantable medical device including but not limited to cardiac pacemakers and cardiac defibrillators. • Subject is currently involved in medically related litigation, including workers compensation. • Subject has a life expectancy of less than one year. • Subject is pregnant or of child bearing potential and not using adequate contraception as determined by the investigator. • Subject has, or plans to have, a spinal cord stimulation system or infusion pump system implanted. • Subject has, or plans to have, a peripheral nerve stimulation system (PNS) or peripheral nerve field stimulation system (PNfS) implanted. • Subject is considered to be a poor surgical or study candidate, which may include, but is not limited to the following: any medical, social, or psychological problem that could complicate the implant procedure and/or recovery from the implant procedure or could complicate the required procedures and evaluations of the study in the judgment of the investigator.
Data Collection	The following activities will occur during the study: Baseline Visit • Subject signs informed consent • Subject evaluated for eligibility • Brief treatment history • Pain mapping • Subject completes VAS, NPS, PROMIS-29 Profile, and PROMIS Global Health • Schedule system trial implant Trial System Implant (*approximately 30 days from Baseline visit)* • Trial system implantation • Program device • Provide subject with the trial neurostimulator • Record AEs (if necessary)

- Schedule End of System Trial visit

End of System Trial Visit *(length determined by the site's standard of care; typically 3-12 days after trial system implantation)*

- Document subject trial system evaluation results
- Collect programming parameters
- Remove trial leads
- Record AEs (if necessary)
- Schedule permanent system implant (if applicable)
- Schedule 1-Month safety follow-up call (if necessary)

Permanent System Implant (*approximately 30 days from End of System Trial visit)*

- Permanent system implantation
- Record AEs (if necessary)
- Schedule device activation visit

Device Activation *(timing determined by the site's standard of care; may occur at the time of permanent system implant)*

- Program device
- Provide subject with the patient programmer
- Record AEs (if necessary)
- Schedule 1-Month follow-up visit

1 Month [redacted]) Follow-up Visit

- Subject completes VAS, NPS, PGIC, PROMIS-29 Profile, and PROMIS Global Health
- Stimulation assessment
- Collect programming parameters
- Modify programming parameters (if necessary)
- Record AEs (if necessary)
- Schedule 3-Month follow-up visit

3 Month [redacted] Follow-up Visit

- Subject completes VAS, NPS, PGIC, PROMIS-29 Profile, and PROMIS Global Health
- Stimulation assessment
- Collect programming parameters
- Modify programming parameters (if necessary)
- Record AEs (if necessary)
- Schedule 6-Month follow-up visit

6 Month [redacted] Follow-up Visit

- Subject completes VAS, NPS, PGIC, PROMIS-29 Profile, and PROMIS Global Health
- Stimulation assessment
- Collect programming parameters

	• Modify programming parameters (if necessary) • Record AEs (if necessary) • Schedule 12-Month follow-up visit <u>12 Month [redacted]) Follow-up Visit</u> • Subject completes VAS, NPS, PGIC, PROMIS-29 Profile, and PROMIS Global Health • Stimulation assessment • Collect programming parameters • Record AEs (if necessary) • Modify programming parameters (if necessary) • Exit subject from study <u>Revisions, Replacements or Explants *(additional surgery)*</u> • Revision, replacement or explant procedure • Modify programming parameters *(if necessary)* • Record AEs • Schedule 1-Month safety follow-up call (if necessary) <u>Unscheduled Visits (*occurring after the permanent implant)*</u> • Modify programming parameters (if necessary) • Record AEs (if necessary)

1.1 STUDY CONTACTS

[redacted]

2.0 BACKGROUND AND JUSTIFICATION FOR CLINICAL STUDY

Chronic pain affects approximately 30% of the total United States population with an estimated 100 million adult pain patients in the United States alone.[1] Direct medical treatment costs, as well as lost productivity, costs the United States $560–635 billion each year and chronic pain rates are likely to continue to rise.[1] Chronic pain substantially diminishes a patient's quality of life and is often a debilitating condition. Current therapies for chronic pain include oral medications, physical and behavioral therapies, complementary and alternative medicine, injectable therapies, neuroablative techniques, transcutaneous electrical nerve stimulation, and ultimately surgical procedures such as spinal fusion and discectomy. Up to 15% of all chronic pain patients are unresponsive to standard medical therapy, exhausting all first- and second-line options and reaching the end of the treatment continuum.[1] Since its approval by the Food and Drug Administration (FDA) in 1989, neurostimulation techniques, including spinal cord stimulation (SCS), have traditionally been recommended as a last resort therapy for patients who have exhausted all other options.

Given that up to 15% of all chronic pain patients are unresponsive to standard medical therapy, spinal cord stimulation (SCS) is becoming an increasingly popular tool for the management of chronic, intractable pain, with an estimated 40,000 SCS systems implanted every year in the United States.[2] SCS has been used successfully to treat a variety of pain conditions including, diabetic neuropathy[3], failed back surgery syndrome[4-7], complex regional pain syndrome[8-10], phantom limb pain[11], ischemic limb pain[12], refractory unilateral limb pain syndrome[13], and postherpetic neuralgia and acute herpes zoster pain.[14] However, a recent systematic review showed that almost 50% of patients did not respond favorably to SCS when trial failures were included in the analysis.[15]

Stimulation of the dorsal root ganglion (DRG) may provide an additional option for chronic pain patients with several potential advantages over conventional SCS. One such potential advantage is providing targeted therapy for focal pain conditions. This ability to target may result from 1) the ability to control current delivered to the DRG with minimal shunting of energy in the cerebral spinal fluid (CSF), as is the case with the dorsal columns, 2) spinally segmented sensory input, and, 3) the ability to control the electrical field around the DRG through device programming.

The safety and efficacy of the use of DRG stimulation for the treatment of patients diagnosed with chronic intractable pain of the lower limbs is supported by data from a prospective, randomized, multicenter, controlled clinical trial. The ACCURATE Investigational Device Exemption (IDE) trial was approved by FDA to assess the safety and efficacy of DRG stimulation with the Axium Neurostimulator System for individuals with chronic lower limb pain associated with Complex Regional Pain Syndrome (CRPS I) or Peripheral Causalgia (CRPS II). In this study, 152 subjects (76 randomized to each the treatment and control group, where treatment was DRG stimulation and control was SCS) were enrolled across 22 investigational sites. The primary endpoint was the percentage of subjects who were considered treatment successes in the treatment group (DRG stimulation) compared to the control group (traditional SCS), where a treatment success was defined as a subject with at least a 50% lower limb(s) pain reduction on a visual analog scale (VAS) compared to baseline in the area of greatest baseline pain during both the trial stimulation phase and at the 3 month follow-up, and the absence of a stimulation-induced neurological deficit. The primary analysis was a test of non-

inferiority between the DRG stimulation group compared to the SCS group with a pre-specified 10% non-inferiority margin. The study met the primary endpoint with statistically significantly more treatment successes in the DRG stimulation group compared to the SCS group at 3 months post permanent implant (81.2% vs. 55.7%, respectively; p = 0.0004). This effect persisted at 12 months post implant (74.2% vs. 53.0%; p=0.0047). Secondary and tertiary outcomes including percent change in VAS scores, change in SF-36 scores, change in Profile of Mood States (POMS) scores, and change in Brief Pain Inventory (BPI) scores were also suggestive of improvements in the group who received DRG stimulation compared to the SCS group.

The most commonly reported definitely-related adverse events (AEs) in the group who received DRG stimulation with the Axium Neurostimulator System in the ACCURATE IDE study were pain at the implantable pulse generator (IPG) pocket (14.5% of subjects) and loss of stimulation due to lead migration (11.8% of subjects). There were a total of 21 serious adverse events (SAEs) in 19 subjects reported in this study. The difference in overall rate of SAEs between the Axium and Control groups was not found to be statistically significantly different (Axium 10.5%, Control 14.5%, p=0.6248). Additionally, the overall difference in the rate of SAEs during the system trial (Axium 1.3%, Control 3.9%, p=0.62) and after the permanent implant (Axium 9.2%, Control 10.5%, p=1.0) were not shown to be statistically significantly different. Only 1 serious adverse device effect (SADE; cardiac arrhythmia post-implant) was classified as possibly or definitely related to the device, procedure and/or stimulation in the group, which received the Axium Neurostimulator System. There were no reports of stimulation induced neurological deficits in either the control or Axium group at any point in the study.

[redacted]

3.0 RISKS AND BENEFITS OF THE CLINICAL STUDY

There are no additional risks of the clinical study beyond those associated with the implant and use of the FDA-approved trial and permanent neurostimulator systems. Please refer to Section 9.3 for the list of anticipated adverse events.

4.0 OBJECTIVES AND ENDPOINTS

4.1 Primary Objective

The primary objective of this study is to demonstrate that the proportion of serious adverse events (SAEs) at 12 months for subjects who receive the permanent DRG IPG is lower than a pre-specified performance goal.

4.2 Secondary Objectives

Secondary objectives of this study are as follows:

- To evaluate change in overall pain intensity
- To evaluate change in physical function
- To evaluate change in quality of life

4.3 Primary Endpoint

The primary endpoint is the 12-month SAE rate for subjects receiving the permanent DRG IPG.

[redacted].

4.4 Secondary Endpoints

Secondary endpoints include:

- Percent change from baseline to 12 months post-permanent implant for overall pain intensity measured using the Visual Analog Scale (VAS)
- Change from baseline to 12 months post-permanent implant for physical function measured using the PROMIS-29 Profile
- Change from baseline to 12 months post-permanent implant for quality of life measured using the PROMIS Global Health Scale

4.5 Descriptive Endpoints

Safety

- Proportion of subjects with device, procedure or stimulation-related SAEs and non-SAEs among subjects who receive the permanent implant
- Proportion of subjects who have AEs related to the trial implant procedure among subjects who fail the trial neurostimulator phase
- Summary of procedure-related SAEs and non-SAEs by implanter experience

Effectiveness

- Percent change from baseline to 1, 3, and 6 months post-permanent implant for overall pain intensity measured using the Visual Analog Scale (VAS)
- Change from baseline to 1, 3, and 6 months post-permanent implant for physical function measured using the PROMIS-29 Profile
- Change from baseline to 1, 3, and 6 months post-permanent implant for quality of life measured using the PROMIS Global Health Scale
- Change from baseline to 1, 3, 6 and 12 months post-permanent implant for neuropathic pain measured using the Neuropathic Pain Scale (NPS)
- Change from baseline to 1, 3, 6 and 12 months post-permanent implant for sleep disturbance anxiety, depression, fatigue, ability to participate in social roles and activities, pain interference and pain intensity measured using the PROMIS-29 Profile
- Patient Global Impression of Change (PGIC) at 1, 3, 6 and 12 months post-permanent implant

4.6 Additional Data

Additional data, including but not limited to, percentage of subjects achieving at least a 30% and 50% pain reduction, demographics, paresthesia coverage and intensity, subject satisfaction, programming parameters, implant procedure information, and system information may be compiled.

5.0 STUDY DESIGN

This study is a prospective, multicenter, single arm, observational post-approval study with follow-ups at 1, 3, 6 and 12 months post-permanent implant. The clinical study will be conducted

at up to 45 centers in the United States. A maximum of 426 subjects will be enrolled to achieve 319 subjects with a permanently implanted system, which will account for expected attrition, to yield 287 subjects for the primary analysis at 12 months post-implant (See Section 10.9 Sample Size for full details). After the last subject with a permanently implanted device reaches the 12-month study visit or crosses the 12-month study visit window, the endpoint analysis will be conducted and reported to the FDA.

After the subject signs the informed consent, s/he will be screened according to the inclusion/exclusion criteria and will undergo a baseline evaluation. Those subjects who meet the criteria for participation will undergo a trial of the DRG Neurostimulation System to assess response to DRG stimulation. Only subjects who report a 50% or greater reduction in overall pain intensity through direct patient-reported percentage of pain relief will receive the permanent implant. Device activation will occur according to the site's standard of care and may occur at the time of permanent system implant. Subjects will then return to the office for follow-up at 1, 3, 6 and 12 months post-permanent implant. Figure 2 below outlines subject flow through the study.

. This timeline may change the actual enrollment rate

[redacted]

.

[redacted]

5.1 Estimated time needed to enroll this subject population

[redacted]

5.2 Justification for Study Design

[redacted]

6.0 STUDY DEVICES

All study devices are in commercial distribution in the United States as aids in the management of CRPS I and II. St. Jude Medical (SJM) received FDA approval for the Axium Neurostimulator System under PMA P150004 on February 11, 2016 and approval for the Proclaim DRG IPG under PMA supplement P150004/S002 on November 28, 2016. The components of the DRG Neurostimulation Systems to be used in this study include the following devices:

Table 1: Description of Devices

Device Component	Model
50 cm SlimTip Trial Lead Kit	MN10350-50A
90 cm SlimTip Trial Lead Kit	MN10350-90A
50 cm SlimTip Implant Lead Kit	MN10450-50A
90 cm SlimTip Implant Lead Kit	MN10450-90A
Lead Accessories Kit	MN12050
22 cm Small Curve Delivery Sheath Kit	MN12150
22 cm Big Curve Delivery Sheath Kit	MN13650
Implantable Neurostimulator Kit (Axium Neurostimulator System)	MN10200
Proclaim DRG IPG	3664
Connector Cable	MN11350
30 cm Small Tunneling Tool Kit	MN11950
Clinician Programmer	MN10700
Patient Programmer	MN10600-02
St. Jude Medical Clinician Programmer App	3874
St. Jude Medical Patient Controller App	3875
Trial Neurostimulator	MN10100
DRG External Pulse Generator	7599 (Base) 7032 (Header)
Auxiliary Magnet Kit	MN23300
Programmer Charger Kit	MN23400
Programmer Carrying Case	MN13500
50 cm Lead Extension Kit	MN10550-50
Curved Needle	MN14000
Tunneling Tool	MN15000

6.1 SlimTip Lead Kits (MN10350-50A, MN10350-90A, MN10450-50A, MN10450-90A)

The leads are designed for percutaneous introduction into the body using a 14-gauge needle and a set of custom delivery tools provided in each kit. The lead is designed to provide stimulation to the intended DRG. It has four cylindrical electrodes spaced at 5 mm intervals on

the distal end. The proximal end fits into a four-conductor connector on the connector cable into a four-conductor connector on the extension lead, or into the header of the implantable neurostimulator. The straight stylet is pre-inserted into the lead and the lead is pre-loaded into the sheath during manufacturing.

The SlimTip trial lead kit and implant lead kit contains the lead and the individual delivery devices required to place the lead(s). The lead comes in two lengths 50cm and 90cm. The straight stylet is intended to assist in steering and positioning the lead within the epidural space and is inserted into the leads during manufacturing. A curved stylet is also included in the kit as an option. The delivery needle is intended to access the epidural space, providing a conduit for the lead, guidewire, and delivery sheaths. The suture anchors are intended to anchor the leads to the soft tissue or skin surface proximal to the distal contacts. The guidewire is optional and is intended to verify that the needle is in the epidural space after using a loss of resistance technique.

The delivery sheaths are intended to help deliver the lead percutaneously into the epidural space and are available in two lengths: (22cm and 30cm) as well as two curve shapes (small curve and big curve).

Lead model MN10450-50A is MR Conditional when used in conjunction with Proclaim DRG IPG.

6.2 Lead Accessories Kit (MN12050)

The lead accessories kit consists of additional tools to aid lead delivery. A 50cm lead extension is packaged with a torque wrench to enable the physician to extend the length of the lead or to provide a connection from the implant lead to the connector cable. The lead extension is intended for chronic implantation. A connector cable (MN11350) is provided in a separate package to connect the leads or lead extension to the trial neurostimulator.

6.3 Tunneling Tool Kit (MN11900)

A 30cm tunneling tool is available with associated accessories to provide a conduit for the lead or lead extension to pass under the skin away from the midline of the spine. The tunneling tool is packaged with two exchangeable tips: a blunt pencil tip and a sharp trocar tip. A straw slides over the tunneling tool and then the steel handle removed. The straw provides the conduit for tunneling. An implantable neurostimulator sizer is packaged with the tunneling tool to allow the physician to properly size the pocket for the stimulator.

6.4 Tunneling Tool (Model MN15000)

The tunneling tool is used to provide a conduit for the lead or lead extension to the IPG or away from the midline of the spine. It is packaged with two exchangeable tips (a blunt pencil tip and a sharp trocar tip), a straw, a hex key, and a torque wrench.

6.5 Trial Neurostimulator (MN10100)

The external trial neurostimulator provides energy and controls electrical signals delivered to the leads. It has a belt clip and must be worn over a piece of clothing by the subject.

6.6 DRG External Pulse Generator (EPG; 7599 & 7032)

The DRG EPG functions in the same way as the MN101000 but is compatible with the same programming platform as the Proclaim DRG.

6.7 Implantable Neurostimulator Kit (MN10200)

The implantable neurostimulator provides energy and controls electrical signals delivered to the leads. It is typically implanted by the physician in the abdomen or buttocks.

6.8 Proclaim DRG IPG, MR Conditional (Model 3664)

The Proclaim DRG IPG was developed based on the FDA approved Proclaim SCS and Axium DRG pulse generators. It is a 16-channel, 4-port, non-rechargeable, MR Conditional IPG. The internal electronics, battery and external casing (can) are identical to the Proclaim SCSIPG used for SCS indications (Model 3660 and 3665). The Proclaim DRG uses the Axium header design (adapted for the Proclaim IPG cannister) which accommodates up to four DRG leads. Additionally, the firmware capability for Proclaim DRG was developed to match the capabilities of the Axium pulse generator. A pocket sizer is an accessory packaged with the IPG and is used to assess the implant size for the IPG. The Proclaim DRG pocket sizer is made of the same material used in the FDA approved Proclaim SCS pocket sizer, but with a different design to reflect the Proclaim DRG IPG shape and form.

6.9 Patient Programmer (MN10600-02)

The patient programmer is set up under the instruction of the clinician or clinical staff to allow the subject to change the amplitude of the energy delivered by the implantable or trial neurostimulator system. The subject carries the programmer with them during daily use.

The patient programmer is powered by an internal rechargeable battery or it is plugged into a power outlet using the power supply cord provided. The patient programmer will be used by the subject to communicate with their implantable or trial neurostimulator system, to monitor the device, and to adjust the stimulation settings within their Investigator's prescribed limits. The subject is provided with a carrying case (MN13500) for carrying their patient programmer during their participation in this study.

The patient programmer has the following features:

- Turns OFF all stimulation
- Turns stimulation ON or OFF for each body region to be treated
- Adjusts stimulation amplitude for each lead in use
- Shows the subject's identification information
- Shows Investigator name and clinic name, along with contact information

The patient programmer contains an internal magnet to initiate communication with the implantable or trial neurostimulator system. The patient programmer is designed to be easy to use and establishes two-way communication with the implantable or trial neurostimulator system to control the stimulation delivered to the subject.

6.10 Clinician Programmer (MN10700)

The clinician programmer is used by trained staff under the guidance of the clinician to communicate wirelessly with the implantable and/or trial neurostimulator system.

The clinician programmer has the following features:

- Turns OFF all stimulation
- Turns stimulation ON for up to four leads and measures lead impedance
- Allows the user to assign body regions that each individual lead is intended to stimulate, modify electrode configurations and adjust stimulation settings for each lead
- Creates multiple groups of stimulation settings for the subject
- Enters subject and lead identification information, Investigator and clinic name and contact information, and Investigator's notes
- Performs real time test stimulation to assess the subject's response for each lead
- Enables subject-controlled therapy and configures subject-controlled therapy settings for each lead
- Acquires identification, diagnostic, and historic information about the neurostimulator device
- Programs configured therapy settings for continuous stimulation

The clinician programmer contains an internal magnet to initiate communication with the implantable or trial neurostimulator device.

6.11 Clinician Programmer App [redacted]

The stimulation parameter ranges allowed by Clinician Programmer App (Model 3874 Version 3.3) are the same as the approved Axium system. The IPG stimulation settings are established via the Clinician Programmer (CP) App, which is installed on an off-the-shelf Apple iPad Mini. Different stimulation programs may be stored and selected via the Patient Controller (PC) App, which is installed on an off-the-shelf Apple iPod Touch. The clinician programmer communicates with the pulse generator via Bluetooth.

6.12 Patient Controller App [redacted]

The stimulation parameter ranges allowed by the patient controller App (Model 3875 Version 3.3) are the same as the approved Axium system. The IPG stimulation settings are established via the Clinician Programmer (CP) App, which is installed on an off-the-shelf Apple iPad Mini. Different stimulation programs may be stored and selected via the Patient Controller (PC) App, which is installed on an off-the-shelf Apple iPod Touch. The patient controller communicates with the pulse generator via Bluetooth.

7.0 SUBJECT SELECTION

Subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible to participate in this study. All subjects in the clinical study (including system trial failures, those withdrawn from the clinical study and those lost to follow-up) will be accounted for and documented by assigning an identification code linked to their [redacted], alternative identification or

contact information. This log will be kept up to date throughout the clinical study by the principal investigator or his/her authorized designee.

7.1 Inclusion Criteria

To participate in this clinical study, the subject must meet all of the following inclusion criteria:

- Subject is male or female ≥ 22 and ≤ 75 years of age.
- Subject has moderate to severe chronic intractable pain of the lower limbs resulting from Complex Regional Pain Syndrome (CRPS) types I or II.
- Subject has a baseline VAS score of ≥ 60 mm for overall pain at the time of the baseline assessment.
- Subject is willing and able to comply with the study requirements.
- Subject is able to provide written informed consent.

7.2 Exclusion Criteria

Subjects are not eligible for this clinical study if they meet any of the following exclusion criteria:

- Subject has an active implantable medical device including but not limited to cardiac pacemakers and cardiac defibrillators.
- Subject is currently involved in medically-related litigation, including workers compensation.
- Subject has a life expectancy of less than one year.
- Subject is pregnant or of child bearing potential and not using adequate contraception as determined by the investigator.
- Subject has, or plans to have, a spinal cord stimulation system or infusion pump system implanted.
- Subject has, or plans to have, a peripheral nerve stimulation system (PNS) or peripheral nerve field stimulation system (PNfS) implanted.
- Subject is considered a poor surgical or study candidate, which may include, but is not limited to the following: any medical, social, or psychological problem that could complicate the implant procedure and/or recovery from the implant procedure or could complicate the required procedures and evaluations of the study in the judgment of the investigator.

8.0 METHODS AND PROCEDURES

8.1 Study Procedures

The clinical study will be conducted in accordance with the CIP. All parties participating in the conduct of the clinical study will be qualified by education, training, or experience to perform their tasks. The clinical study will not commence until St. Jude Medical receives written approval from the IRB and relevant regulatory authorities and all required documents have been collected from the site.

All required study procedures at each specified interval are outlined in the sections below. A table outlining the timing of all study activities by each visit is located at the end of this section.

8.2 Informed Consent

[redacted]

8.3 Blinding

There is no blinding for the subject or the Investigator.

8.4 Subject Screening and Point of Enrollment

All subjects presenting at the investigational site will be screened by a member of the investigational team previously trained on the CIP and delegated to do so. After completion of the baseline visit, eligible subjects will be scheduled for the trial system implant. [redacted]

8.5 Baseline Visit

Baseline measurements for the subject's pain symptoms and location will be taken along with a brief treatment history and completion of subject self-reported questionnaires.

The following information will be collected at the baseline visit:

- Demographics
- Diagnosis
- Pain and treatment history
- VAS score
- NPS
- PROMIS-29 Profile domain scores
- PROMIS Global Health Scale score
- Protocol Deviations (if applicable)

8.6 Trial System Implant (approximately 30 days from Baseline Visit)

Subjects will use the trial system in accordance with the standard practice of the clinical site (typically 3-12 days). Trial system activation will occur in post-operative recovery after the implantation. At each visit, SJM field representatives may assist with programming of the subject's device under the supervision of the investigative team.

The following information will be collected at the trial system implant visit:[redacted]

8.7 End of System Trial Visit (length determined by the site's standard of care; typically 3-12 days after trial system implantation)

At the end of the system trial phase, subjects will complete their trial system evaluation prior to removal of the system components. Only subjects who report a 50% or greater reduction in overall pain intensity through direct patient-reported percentage of pain relief will be eligible to receive the permanent implant.. The subject will then be withdrawn from the study.

The following information will be collected at the end of the system trial visit:

- Programming parameters
- Length of trial (days)
- Pain relief (direct patient report of percentage of pain relief)
- Decision on whether to proceed to permanent implant
- Reason subject will not proceed to the permanent implant (if applicable)

- AEs (if applicable)
- Protocol Deviations (if applicable)

8.8 Permanent System Implant (approximately 30 days from End of System Trial visit)

The permanent implant should occur approximately 30 days from the End of System Trial visit. The following information will be collected at the permanent system implant visit:

- Procedure information
- Device information
- AEs (if applicable)
- Protocol Deviations (if applicable)

8.9 Device Activation (timing determined by the site's standard of care; may occur at the time of permanent system implant)

Permanent system device activation will occur according to the site's standard of care and may occur at the time of the permanent system implant. At each visit, SJM field reps may assist with programming of the subject's device under the supervision of the investigative team.

The following information will be collected at the activation visit:

- AEs (if applicable)
- Protocol Deviations (if applicable)

8.10 Scheduled Follow-ups

Subjects will report to the office at [redacted] months after the activation visit. The following information will be collected at these visits:

- VAS score
- NPS
- PROMIS-29 Profile domain scores
- PROMIS Global Health Scale score
- PGIC score
- Change in occupational status
- Change in activity level
- Satisfaction with device/therapy
- Willingness to undergo the procedure again
- Willingness to recommend the procedure to someone
- Sensations generated by stimulation
- Programming parameters
- AEs (if applicable)
- Protocol Deviations (if applicable)

All information, including subject questionnaires, should be collected prior to reprogramming, if reprogramming is needed. Missed visits and visits that occur outside of the specified time windows will be documented as protocol deviations.

If a study participant is unable or unwilling to attend an in-person visit, the visit may be conducted remotely using telemedicine as provided by the study center. Questionnaires may be

administered during the remote visit. The numeric rating scale (NRS) may be used to collect a subject's pain score in place of the visual analog scale. Both are valid measures of pain intensity and studies support a strong relationship between both [23, 24]. The Coordinator or designee must document the subject's responses on the worksheet, note that the responses were collected via phone, save that document as source data, and enter the information in the EDC system. Alternately, questionnaires may be mailed to the participant in a return postage provided envelope. If this method is chosen, the Coordinator or designee should schedule a call with the subject to clearly explain the questionnaires and answer any questions the subject may have.

8.11 Revisions, Replacements, or Explants (Additional Surgery)

The subject and the implanting physician will collectively make the decision about any possible revision of the device based upon what is medically safe, what is desired by the subject, and what is in the subject's best medical interests. Any system revision, replacement or explant will be recorded on the appropriate eCRFs. If the device is explanted for any reason and re-implantation is not an option, the subject will be followed for 1 month post-explant and then withdrawn from the study. Subjects who undergo a revision or replacement procedure will resume their previous follow-up schedule.

8.12 Unscheduled Visits

An unscheduled visit is defined as any visit that occurs outside of a specified study visit. Only unscheduled visits occurring after the permanent implant will be recorded. Examples of unscheduled visits may include subjects returning to the office for an AE or programming change.

Table 1: List of all study specific activities/procedures

[redacted] if applicable

8.13 Validated Questionnaires

All validated questionnaires should be completed prior to reprogramming as applicable. The Study Coordinator or designee will give the subject the questionnaires to complete on his or her own. It is important that the subject understands the meaning of all the words in the questionnaires. The subject should be instructed to ask any questions about the questionnaires if further explanation is needed. Once the subject has completed the questionnaire, the Study Coordinator or designee will review the questionnaire for completeness to verify that all questions have been answered and only one response is chosen for each item.

Visual Analog Scale (VAS) for Pain
The VAS is a common, self-administered measure in which subjects rate their pain intensity by marking a vertical line through a 100 mm horizontal line anchored by word descriptors on each end (no pain to worst imaginable pain). The distance between the beginning of the horizontal line and the vertical line is measured to produce a score between 0 and 100 mm (or 0 to 10 cm). A higher score indicates higher pain intensity and a 30% reduction in VAS score from baseline to follow-up is considered clinically relevant.[16] VAS scores for overall pain intensity will be collected.

Numeric Rating Scale for Pain (telemedicine visits)
The pain NRS consists of 1 question that will be asked by interviewing the subjects. Patients will be asked to rate, from 0 (no pain) to 10 (worst imaginable pain), their average pain over the past 24 hours specific to the area(s) of chronic pain being treated. A higher score indicates greater pain intensity

Neuropathic Pain Scale (NPS)[17]
The NPS is a self-administered validated questionnaire designed to assess pain qualities and symptoms associated with neuropathic pain. The questionnaire is comprised of 10 scales which assess two global pain domains (pain intensity and unpleasantness), six specific pain qualities (sharp, dull, sensitive, hot, cold, and itchy pain), and two spatial qualities (deep and surface pain). Respondents rate the intensity or severity of each descriptor item on a scale from 0 to 10, where 0 represents no intensity/severity and 10 represents the most intensity/severity. The questionnaire takes 5 minutes to complete and yields scores for each pain quality/symptom as well as an overall mean score for all 10 scales. The NPS can be used to differentiate neuropathic pain from non-neuropathic pain. Mean scores of 5.5 or greater reflect presence of neuropathic pain whereas those below 5.5 reflect non-neuropathic pain.[18]

PROMIS-29 Profile v2.0 [19-20]

The PROMIS-29 Profile is an instrument made up of seven individual short forms (physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, pain interference) that are scored individually. The instrument also includes a single

pain intensity item which is reported as its raw score (e.g., 0 to 10). Each item has five response options ranging in value from 1 to 5, except for the Pain Intensity item which has eleven response options ranging in value from 0 to 10. A raw score is created from each short form that makes up the Profile. Raw scores are calculated by summing the values of the response to each question within each domain. For example, for the 29-item Profile, the lowest possible raw score within anxiety is 4 (a score of 1 on all four items); the highest possible raw score is 20. Raw scores are converted into t-scores, where higher scores represent more of the concept being measured (i.e. physical function). For the depression, anxiety, physical function, pain interference, fatigue profile domains, a t-score of 50 is the average for the US general population with a standard deviation of 10. For the Ability to Participate in Social Roles and Activities and Sleep Disturbance profile domains, a score of 50 represents the average of a calibration sample, which generally contained more individuals with chronic illness. Thus, a score of 50 likely represents somewhat sicker people than the general population.

PROMIS Global Health Version 1.1

The PROMIS Global Health short form is a validated, 10-item instrument designed to assess multiple health domains.[19] The questionnaire yields a total score and sub-scale scores for Global Physical and Mental Health. Each question has potential five response options ranging in value from one to five to give a total score ranging from 10 to 50. All questions must be answered to arrive at a total score as one or more missing responses will render scores unusable. Scores are converted into t-scores where the average for the general US population is 50 and the SD is 10. Higher scores indicate better global health.

Patient Global Impression of Change (PGIC)[21]

The PGIC is the most commonly used patient-reported, anchor based method of assessing clinically important change.[22] The PGIC consists of one question to assess change in activity limitations, symptoms, emotions, and overall quality of life related to their condition rated on a seven-point Likert scale. PGIC values of 6 or more are reported to correlate best with actual change.[22]

8.14 Study Conclusion

When the subject's participation in the clinical study has been completed, the subject will return to medical care as per their physician's recommendation. The study will be concluded when all sites are closed and the final report generated by St. Jude Medical has been provided to sites or St. Jude Medical has provided formal documentation of study closure.

9.0 ADVERSE EVENTS

9.1 Definitions

9.1.1 Medical Device

Any instrument, apparatus, machine, appliance, implant, software, material or other similar or related article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of:

- Diagnosis, prevention, monitoring, treatments or alleviation of disease,
- Diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury,
- Investigation, replacement, modification, or support of the anatomy or of a physiological process,
- Supporting or sustaining life,

- Control of conception,
- Disinfection of medical devices and
- Which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means.

9.1.2 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the medical device under study. This definition includes events related to the medical device and to the procedures involved.

9.1.3 Serious Adverse Event (SAE)

A planned hospitalization for a pre-existing condition, or a procedure required by the CIP, are not considered SAEs.

9.1.4 Adverse Device Effect (ADE)

An AE related to the use of a medical device used in this study.

This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the medical device.

This definition includes any event resulting from the use error or from intentional misuse of the medical device.

9.1.5 Serious Adverse Device Effect (SADE).

9.2 Assessing, Recording and Reporting AEs

Safety surveillance within this study and the safety reporting both performed by the investigator, starts as soon as the subject is consented for the study. The safety surveillance and the safety reporting will continue until the last investigational visit has been performed, the subject/investigator concludes his participation into the study or the subject/investigator withdraws the subject from the study, except as otherwise specified in the CIP.

Records related to the subject's subsequent medical course must be maintained and submitted (as applicable) to the Sponsor until the event has subsided or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained. All AEs will be monitored until they are adequately resolved. The status of the subject's condition should be documented at each visit.

AE data will be collected throughout the clinical study and will be reported to the Sponsor on a dedicated case report form through the EDC system. Reportable events to sponsor are considered:

1. ***All SAEs (whether or not the event is device and/or procedure related)***
2. ***All procedure, device and/or stimulation-related AEs (whether or not the event is considered serious)***

Device, procedure, and stimulation-related AEs are defined as follows:

- Device-related: A malfunction or migration of any device component including leads, extensions, IPGs and accessories.
- Procedure-related: Biological reaction (hematoma, infection, pain, etc.) as a result of the surgical procedure to implant the device.
- Stimulation-related: Event known to be caused by stimulation from the device. Normally stimulation-related events resolve when the device is turned off or reprogrammed.

The investigator should report all SAEs to the Sponsor as soon as possible but no later than outlined below.

Clinical Site	Reporting timelines
All Sites	SAEs must be reported no later than 3 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

The date the site staff became aware the event met the criteria of an SAE must be recorded in the source document.

The Investigator will further report the SAE to the local IRB/EC according to the institution's IRB/EC reporting requirements.

Adverse events that are not serious will be reported to the Sponsor, as soon as possible after the occurrence of the event.

Please reference Section 3 of this document for risk information and Section 9.3 for a complete list of adverse effects related to DRG Neurostimulation Systems.

For unexpected failure modes or unexpected for all AEs, the site should follow their standard reporting practices for medical device reporting (MDR). As defined in 21 CFR 803, a MDR reportable event (or reportable event) is an event that device user facilities become aware of that reasonably suggests that a device has or may have caused or contributed to a death or serious injury. A device user facility must report deaths and serious injuries that a device has or may have caused or contributed to, establish and maintain AE files, and submit summary annual reports to FDA.

The Investigator will assign degree of relatedness to the device for all SAEs and device, procedure and stimulation-related AEs based on NIH definitions as follows:

***Possibly* Device/Procedure-Related:** (must meet at least **2** criteria)

- Has a reasonable temporal relationship to intervention,
- Could not readily have been produced by the subject's clinical state,
- Could not readily have been due to environment or other interventions,
- Follows a known pattern of response to intervention.

Related to Device/Procedure: (must meet at least **3** criteria)

- Has reasonable temporal relationship to intervention,

- Could not readily have been produced by the subject's clinical state or have been due to environmental or other interventions
- Follows a known pattern of response to intervention,
- Disappears or decreases with reduction in dose or cessation of intervention.

Additionally, AEs can be classified as *unrelated* if the causal relationship cannot be attributed to the device and/or procedure related.

Additional information may be requested, when required, by the Sponsor in order to support the reporting of AEs to regulatory authorities.

9.3 Anticipated AEs

Possible risks to the subjects include both device- and procedural-based risks. Below is a list of the potential adverse effects associated with the implant and use of the Axium Neurostimulator System.

Risks associated with any surgical procedure: abscess; cellulitis; excessive fibrotic tissue; wound dehiscence; wound, local or systemic infection; wound necrosis; edema; inflammation; foreign body reaction; hematoma; seroma; thrombosis; ischemia; embolism; thromboembolism; hemorrhage; thrombophlebitis; adverse reactions to anesthesia; hypertension; pulmonary complications; organ, nerve or muscular damage; gastrointestinal or genitourinary compromise; seizure, convulsion, or changes to mental status; complications of pregnancy including miscarriage and fetal birth defects; inability to resume activities of daily living; and death.

Risks associated with system placement procedures: pain at the implant site, swelling; infection, cerebrospinal fluid (CSF) leakage, CSF fistula, epidural hemorrhage, bacterial meningitis, seroma, weakness, hematoma, tissue damage, nerve damage, sensory loss, spinal cord compression; and paralysis. Patient use of anticoagulation therapies may increase the risk of procedure-related complications, such as hematomas, which could produce paralysis.

Risks associated with the use of the system: lead migration; INS migration; allergic response or tissue reaction to the implanted system material; hematoma or seroma at the implant site; skin erosion at the implant site; persistent pain at the INS and/or lead site, extension, or lead site; radicular chest wall stimulation; disturbed urination; dysesthesia; decubitus; headache; allodynia; hyperesthesia; premature battery depletion; loss of pain relief over time; escalating pain; clumsiness; numbness; temporary muscle activation; and uncomfortable stimulation or ineffective pain control caused by random failure of the system components or battery, changes in electrode position, loose electrical connections, lead or extension insulation breaches or fractures, lead retention, and inability to achieve the desired pain relief results.

An additional risk to the subject is pain due to setting the stimulation parameters too high as a result of the placement and stimulation of the lead in the area of the DRG.

Below is a list of the potential adverse effects associated with the implant and use of the DRG Neurostimulation System with Proclaim DRG IPG:

- Unpleasant sensations or motor disturbances, including involuntary movement, caused by stimulation at high outputs (if either occurs, turn off IPG immediately)

- Undesirable changes in stimulation, which may be related to cellular changes in tissue around the electrodes, changes in electrode position
- Changes in stimulation or reduced pain relief due to loose electrical connections
- Changes in stimulation or reduced pain relief due to lead failure.
- Stimulation in unwanted places (such as stimulation of the chest wall)
- Lead migration, causing changes in stimulation or reduced pain relief
- Epidural hemorrhage
- Hematoma
- Infection
- Spinal cord compression
- Paralysis from placement of a lead in the epidural space
- Cerebrospinal fluid (CSF) leakage
- Tissue damage or nerve damage
- Paralysis, weakness, clumsiness, numbness, sensory loss below the level of the implant
- Pain below the level of the implant
- Pain or bleeding where the needle was inserted
- Persistent pain at the electrode or IPG site
- Escalating pain
- Seroma (mass or swelling) at the implant site
- Headache
- Allergic or rejection response to device or implant materials
- Implant migration
- Skin erosion around the implant
- Battery failure, leakage, or both
- Hardware malfunction that requires replacing the neurostimulator
- Pain from a noninjurious stimulus to the skin or an exaggerated sense of pain
- Formation of reactive tissue in the epidural space around the lead, which can cause delayed spinal cord compression and paralysis and requires surgical intervention (time to onset can range from weeks to many years after implant).

Additional risks to the patients, as a result of the placement and stimulation of the lead in the area of the dorsal root ganglion (DRG), include pain from setting the stimulation parameters too high. This may occur once the lead is in place and is connected to the neurostimulator and activated.

Below is a list of the potential adverse effects associated with the implant and use of MR Conditional Neurostimulation devices that may occur in the MRI environment:

- Lead electrode heating resulting in tissue damage or serious patient injury
- IPG heating resulting in tissue damage in the implant pocket or patient discomfort or both

- Induced currents on leads resulting in overstimulation or shocking sensations
- Damage to the IPG or leads causing the system to fail to deliver stimulation or causing the system to deliver overstimulation
- Damage to the functionality or mechanical integrity of the IPG resulting in the inability to communicate with the IPG
- Movement or vibration of the IPG or leads

9.4 Subject Death

All patient deaths that occur during this investigation must be reported to St. Jude Medical as soon as possible (per Section 9.2). It is the investigator's responsibility to notify the IRB per the IRB policy. Should death occur, the investigator is required to record death information in the hospital records, and document the information on the case report form through the EDC system.

Subject Death may be an outcome of an SAE.

- Death is therefore related to an SAE: all efforts to obtain the SAE details should be made and the AE form must be completed or updated accordingly.
- The subject's death is an Early Conclusion of the subject's participation in the study. Therefore, the investigator is requested to complete the Withdrawal form.

9.5 Complaint Reporting

A complaint is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Complaints may be submitted from the time of consent through the end of the study.

If a complaint involves an adverse device effect category or death as described in the protocol (Section 9.1-9.3), then the investigator shall notify the Sponsor by completing the adverse event or death case report form as applicable and must provide the Sponsor with all necessary documentation needed.

If the complaint does not involve a reportable adverse event per protocol, the investigator should notify the SJM Product Surveillance Department through one of the methods listed below as soon as possible after becoming aware of a complaint. The following is the contact information for reporting complaints: via email at CCoordinators@abbott.com or by phone at 972-309-8000.

10.0 DATA ANALYSIS

The primary objective of this study is to demonstrate that the proportion of serious adverse effects (SAEs) at 12 months for subjects who receive a permanently implanted DRG stimulation system is lower than a pre-specified performance goal. The primary endpoint is the 12-month SAE rate from permanent implant until 12-month follow-up. [redacted]

[redacted]

10.1 Primary Endpoint

The hypothesis is stated as follows:

H_0: p ≥ 15.5%

H_1: p < 15.5%

where p is the 12-month SAE rate for subjects who receive the permanent Axium or Proclaim DRG IPG (proportion of subjects who experience at least one SAE from permanent implant through 12-month follow-up). The hypothesis will be tested at the 5% significance level. The analysis population will include subjects who received the permanent Axium or Proclaim DRG IPG, who either have an SAE after permanent implant or complete the 12-month follow-up visit.

The primary endpoint analysis will be conducted using Kaplan-Meier method on subjects who received the permanent Axium or Proclaim DRG IPG (primary analysis population). The serious adverse events (SAE) include adverse events which CEC adjudicates as serious events. The 12-month SAE rate will be estimated using Kaplan-Meier method with a 95% upper confidence bound (UCB) estimated using log-log transformation. If the 95% UCB is less than the 15.5%, the null hypothesis will be rejected.

[redacted].

10.2 Secondary Endpoints

10.2.1 Reduction in pain intensity (VAS)

The endpoint will test whether subjects achieve a clinically relevant change (mean percentage reduction of at least 30%) in VAS score at 12 months from baseline. Percentage change in VAS score is calculated within each subject as:

% Change in VAS score = (VAS at baseline – VAS at 12-month)/VAS at baseline*100%

The following hypothesis will be tested:

H_0: Mean % Change in VAS score ≤ 30%

H_1: Mean % Change in VAS score > 30%

The hypothesis will be tested at the 5% significance level. The analysis will be carried out by calculating the 95% lower confidence bound (LCB) on the mean % Change in VAS from baseline to 12-month visit based on a t-distribution. If the 95% LCB is greater than 30.0%, the null hypothesis is rejected. The analysis population for this secondary endpoint will include subjects who complete both baseline and 12-month VAS scales, irrespective of IPG types.

10.2.2 Change in Physical Function (PROMIS Physical Function score)

The endpoint will test whether there is a change in mean PROMIS-29 Physical Function domain scores at 12 months from baseline. Change in PROMIS-29 Physical Function domain score is calculated as:

Change in PROMIS-29 Physical Function domain score = (PROMIS-29 Physical Function domain score at 12-Month – PROMIS-29 Physical Function domain score at

Baseline)

The following hypothesis will be tested:

H_0: Change in PROMIS-29 Physical Function domain score ≤ 0

H_1: Change in PROMIS-29 Physical Function domain score > 0

The hypothesis will be tested at the 5% significance level. The analysis will be carried out by calculating the 95% LCB on the mean change in PROMIS-29 Physical Function domain score from baseline to 12-month visit based on a t-distribution. If the 95% LCB is greater than 0, the null hypothesis is rejected. The analysis population for this secondary endpoint will include subjects who complete both the baseline and 12-month PROMIS-29 Profile, irrespective of IPG types.

10.2.3 Change in Global Health (PROMIS Global Health score)

The endpoint will test whether there is a change in mean PROMIS Global Health Score from baseline to 12 months. Change in PROMIS Global Health Sore is calculated as:

Change in PROMIS Global Health Score = (PROMIS Global Health Score at 12-Month – PROMIS Global Health Score at Baseline)

The following hypothesis will be tested:

H_0: Change in PROMIS Global Health Score ≤ 0

H_1: Change in PROMIS Global Health Score > 0

The hypothesis will be tested at the 5% significance level. The analysis will be carried out by calculating the 95% LCB on the mean change in PROMIS Global Health Score from baseline to 12-month visit based on a t-distribution. If the 95% LCB is greater than 0, the null hypothesis is rejected. The analysis population for this secondary endpoint will include subjects who complete both baseline and 12-month PROMIS Global Health questionnaire, irrespective of IPG types.

10.3 Descriptive Endpoints

The following descriptive endpoints will be reported:

- Proportion of subjects with device, procedure or stimulation-related SAEs and non-SAEs among subjects who receive the permanent implant
- Proportion of subjects who have AEs related to the trial implant procedure among subjects who fail the trial neurostimulator phase
- Summary of procedure-related SAEs and non-SAEs by implanter experience
- Change from baseline to 1, 3, and 6 months post-permanent implant for overall pain intensity measured using the Visual Analog Scale (VAS)
- Change from baseline to 1, 3, and 6 months post-permanent implant for physical function measured using the PROMIS-29 Profile
- Change from baseline to 1, 3, and 6 months post-permanent implant for quality of life measured using the PROMIS Global Health Scale
- Change from baseline to 1, 3, 6 and 12 months post-permanent implant for neuropathic pain measured using the Neuropathic Pain Scale (NPS)

- Change from baseline to 1, 3, 6 and 12 months post-permanent implant for sleep disturbance, anxiety, depression, fatigue, ability to participate in social roles and activities, pain interference and pain intensity measured using the PROMIS-29 Profile
- Patient Global Impression of Change (PGIC) at 1, 3, 6 and 12 months post-permanent implant

The analysis population for these descriptive endpoints will include subjects with available data.

10.4 Additional Data

The following additional data, including but not limited to: percentage of subjects achieving at least a 30% and 50% pain reduction, demographics, paresthesia coverage and intensity, subject satisfaction, programming parameters, implant procedure information, and system information will be summarized and reported.

10.5 Sample Size

[redacted]

10.6 Subgroup Analysis

Primary and secondary endpoints will be analyzed by comparing subjects who had previously failed SCS for lack of pain relief (i.e. did not receive ≥ 50% pain relief) to those who had not previously failed SCS (i.e. naïve subjects or those who failed SCS due to reasons other than pain relief).

Primary, secondary and descriptive endpoints will be analyzed for two distinct cohorts based upon the type of IPG received at permanent implant (Axium or Proclaim).

10.7 Interim Analysis

There are no planned interim analyses intended to test hypotheses or modify the study. However, the safety endpoints will be descriptively summarized annually in the progress report until the study is closed. The following safety endpoints will be summarized for each interim analysis:

- 12-month SAE rate for permanent implants.
- Proportion of subjects with device, procedure or stimulation-related SAEs and non-SAEs among subjects who receive the permanent implant
- Proportion of subjects who have AEs related to the trial implant procedure among subjects who fail the trial neurostimulator phase
- Summary of procedure-related SAEs and non-SAEs by implanter experience

10.8 The Treatment of Missing, Unused, or Spurious Data, Including Drop-Outs and Withdrawals

Analyses of each endpoint will be performed in subjects who provide complete data for each endpoint. Subject accountability for enrolled subjects will be performed prior to analyses of the primary and secondary endpoints. There are no plans to perform imputations for missing data,

[redacted]

subject dropouts or withdrawals. If spurious data are discovered, these data will be excluded from analyses. Reasons for exclusion of any data from analyses will be summarized.

10.9 The Exclusion of Particular Information for the Testing of the Hypothesis

There is no intent to exclude particular information for the testing of hypotheses.

11.0 SUBJECT RECRUITMENT

Sites will be provided with IRB-approved laminated cards that list the study inclusion criteria for easy identification of eligible subjects. All sites are expected to develop and implement their own site-specific subject recruitment plan. Study recruitment materials, such as IRB-approved posters and brochures, will be provided to the site upon request.

[redacted]

12.0 SUBJECT RELOCATION

If a subject moves from the geographic catchment area of their investigator, then St. Jude Medical (SJM) will first attempt to place the subject with another investigator in the study. If it is not possible to place the subject with another investigator, the subject will be considered lost to follow up per the lost to follow up definition in Section 13 below.

13.0 SUBJECT WITHDRAWAL OR DISCONTINUATION

Subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled and withdrawal from the study will not jeopardize their future medical care or relationship with the investigator. Subjects will be asked to specify the reason for the termination, but have the right not to answer.

The subject's future care will not be influenced by a decision, voluntary or otherwise, to withdraw from the study. All reasonable efforts should be made to retain the subject in the clinical study until completion of the study.

Reasons for subject's withdrawal include, but are not limited to:

- Subject refuses to continue participating in the study
- Subject is deceased (cause must be documented)
- Subject's non-compliance
- Subject is 'lost to follow up': Subject does not adhere to the scheduled follow up visits but has not explicitly requested to be withdrawn from the clinical study. Site personnel should at all times make all reasonable efforts to locate and communicate with the subject in order to achieve subject compliance to the scheduled follow up visits:

    1. A subject will be considered 'Lost to Follow Up' after a minimum of 2 phone calls of a physician or delegate at the investigational site to the subject or contact. These 2 phone calls need to be documented in the subject's medical records.

2. If these attempts are unsuccessful, a letter should be sent to the subject's last known address or the subject's general practitioner (GP) and a copy of this letter should be maintained in the subject's medical records.

Note: If a subject misses one or more of the scheduled follow up visits (inclusive of the assigned visit windows) without being lost to follow-up this will be considered as a missed visit. The subject may, therefore, still return for subsequent visits and will not be withdrawn from the study.

If there is a potential withdrawal in the study, please contact a member of the study team to see if there is anything that can be done to keep the subject in the study.

An analysis will be performed to compare demographics and key clinical characteristics for the subjects who have withdrawn and those who continue to be enrolled in the study. This analysis will be reported in the annual progress reports.

14.0 COMPLIANCE TO CIP

14.1 Adherence to the CIP

A deviation is defined as an event where the clinical investigator, site personnel, sponsor or sponsor representative did not conduct the clinical study according to the Clinical Investigational Plan, IRB requirements or the Investigator Agreement. The investigator is not allowed to deviate from the CIP, except as specified under emergency circumstances.

In some cases, failure to comply with the CIP may be considered failure to protect the rights, safety and well-being of subjects, since the non-compliance exposes subjects to unreasonable risks. For example, failure to adhere to the inclusion/exclusion criteria: these criteria are specifically defined by the Sponsor to exclude subjects for whom the device is not beneficial and the use involves unreasonable risks. This may be considered failure to protect the rights, safety and well-being of the consented subject. Similarly, failure to perform safety assessments intended to detect AEs may be considered failure to protect the rights, safety and well-being of the consented subject. Investigators should seek minimization of such risks by adhering to the CIP.

Simultaneously, in the event that adhering to the CIP might expose the subject to unreasonable risks, the investigator is also required to protect the rights, safety and well-being of the subject by intentionally deviating from the requirements of the CIP, so that subjects are not exposed to unreasonable risks.

It is the responsibility of the investigator to provide adequate medical care to a subject consented for participation in a study.

Regulations require that the Investigator maintain accurate, complete, and current records, including documents showing the date of and reason for every deviation from the Clinical Investigational Plan.

Regulations require Investigators obtain approval from St. Jude Medical and the IRB [as required] before initiating changes in or deviations from the protocol, except when necessary to protect the life or physical well-being of a subject in an emergency. Under emergency

circumstances, deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the IRB. Such deviations shall be documented and reported to the sponsor and the IRB as soon as possible, but no later than 5 working days.

Prior approval must be requested when the Investigator anticipates, contemplates, or makes a conscious decision to depart from the CIP, except when unforeseen circumstances are beyond the investigator's control (e.g. a subject who fails to attend a scheduled follow-up visit, a subject is too ill to perform a CIP-required test, etc.). All deviations, including those beyond the investigator's control, must be reported to the St. Jude Medical as soon as possible and to appropriate regulatory authorities in specified timelines (if appropriate). The Investigator is required to adhere to local regulatory requirements for reporting deviations to IRB.

Investigator will notify St. Jude Medical and the reviewing IRB within 5 working days of:

- Any deviation to protect the life or physical well-being of a subject in an emergency
- Any failure to obtain informed consent

14.2 Repeated and Serious Non-Compliance

In the event of repeated non-compliance or a one-time serious non-compliance, as determined by the Sponsor, a Clinical Research Associate or clinical representative will attempt to secure compliance by one or more of the following actions:

- Visiting the investigator
- Contacting the investigator by telephone
- Contacting the investigator in writing
- Retraining of the investigator

If an investigator is found to be repeatedly non-compliant with the signed agreement, the CIP or any other conditions of the clinical study, the Sponsor will either secure compliance or, at its sole discretion, terminate the investigator's participation in the clinical study.

15.0 AMENDMENTS TO CLINICAL INVESTIGATIONAL PLAN

Study related documents such as, the CIP, Informed Consent form and other subject information, or other clinical study documents will be amended as needed. Proposed amendments to the CIP will be agreed upon between the Sponsor and the coordinating investigator (if applicable). The amendment will identify the changes made and the reason for the changes. The amendments to the CIP and the subject's Informed Consent will be notified to, or approved by, the IRB and regulatory authorities, if required.

Any amendment affecting the subject requires that the subject be informed of the changes and a new consent be signed and dated by the investigator at the subject's next follow up.

16.0 INVESTIGATION SUSPENSION OR TERMINATION

The Sponsor reserves the right to stop the study at any stage, with appropriate written notice to the investigator. Possible reasons for early termination of the study by the sponsor, either at local, national or international level, may include, but are not limited to:

- The device / therapy fails to perform as intended

- Occurrence of SAE which cannot be prevented in future cases
- Sponsor's decision
- Request from Regulatory bodies
- Request of IRB
- Concern for subject safety and welfare
- Failure to secure subject Informed Consent prior to any investigational activity
- Repeated non-compliance with this CIP or the Clinical Trial Agreement
- Inability to successfully implement this CIP
- Falsification of data, or any other breach of ethics or scientific principles
- Loss of or unaccounted use of investigational device inventory

The study will be terminated according to applicable regulations. The investigator may also discontinue participation in the clinical study with appropriate written notice to the Sponsor. Should either of these events occur, the investigator will return all documents to the sponsor; provide a written statement as to why the premature termination has taken place and notify the IRB. Follow-up for all consented subjects will be as per CIP requirements. An Investigator, IRB or regulatory authority may suspend or prematurely terminate participation in a clinical study at the investigational sites for which they are responsible.

If suspicion of an unacceptable risk to subjects arises during the clinical study or when so instructed by the IRB or regulatory authority, St. Jude Medical may suspend the clinical study as appropriate while the risk is assessed. St. Jude Medical will terminate the clinical study if an unacceptable risk is confirmed.

St. Jude Medical will consider terminating or suspending the participation of a particular investigational site or investigator in the clinical study if monitoring or auditing identifies serious or repeated deviations on the part of an investigator.

If suspension or premature termination occurs, the terminating party will justify its decision in writing and promptly inform the other parties with whom they are in direct communication. The Principal Investigator and St. Jude Medical will keep each other informed of any communication received from IRB or regulatory authority.

If for any reason St. Jude Medical suspends or prematurely terminates the study at an individual investigational site, St. Jude Medical will inform the responsible regulatory authority, as appropriate, and ensure that the IRBs are notified, either by the Investigator or by St. Jude Medical. If the suspension or premature termination was in the interest of safety, St. Jude Medical will inform all other Principal Investigators.

If suspension or premature termination of enrollment occurs, St. Jude Medical will remain responsible for providing resources to fulfill the obligations from the CIP and existing agreements for following up the subjects consented for participation in the clinical study, and the Investigator or authorized designee will promptly inform the consented subjects at his/her investigational site, if appropriate.

17.0 RESUMING THE STUDY AFTER TEMPORARY SUSPENSION

When St. Jude Medical concludes an analysis of the reasons for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, St. Jude Medical will inform the Investigators, IRB, or regulatory authority, where appropriate, of the rationale, providing them with the relevant data supporting this decision. Concurrence will be obtained before the clinical study resumes from the IRB or regulatory authority where appropriate. If subjects have been informed of the suspension, the Principal Investigator or authorized designee will inform them of the reasons for resumption.

18.0 ADMINISTRATIVE REQUIREMENTS AND QUALITY ASSURANCE

18.1 Study Investigators

The study will be conducted by qualified investigators who have been evaluated and have completed the required training related to implant and use of DRG Neurostimulation Systems.

18.2 Institutional Review Board (IRB)

Before study enrollment can begin, the Investigator must provide the Sponsor with a copy of the approval notice for the protocol and informed consent forms, signed by the committee Chairperson or designee. 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.

18.3 Informed Consent

Written Informed Consent will be obtained from all subjects before any study-related procedures are performed. All potential subjects must be properly informed as to the purpose of the study and the potential risks and benefits known or that can be reasonably predicted or expected. The Investigator will retain the original copy of the Informed Consent Form signed by the subject and a duplicate will be provided to the subject. Only the consent form approved by the IRB should be used.

19.0 DATA MANAGEMENT

The Sponsor will be responsible for the data handling. The sponsor and/or its affiliates will be responsible for compiling and submitting all required reports to governmental agencies.

St. Jude Medical respects and protects personally identifiable information collected or maintained for this clinical trial. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data. Confidentiality of data will be observed by all parties involved at all times throughout the clinical trial. All data will be secured against unauthorized access.

Data will be captured in a validated electronic database management system hosted by St. Jude Medical. Only authorized site personnel will be permitted to enter data into the electronic data capture (EDC) system deployed by St. Jude Medical. An electronic audit trail will be used to track any subsequent changes of the entered data.

19.1 Data Management Plan (DMP)

A detailed Data Management Plan will be established to ensure consistency of the data. This document will include procedures used for data review, database cleaning, and issuing and resolving data queries. If appropriate, the DMP may be updated throughout the study duration. All revisions will be tracked and document controlled.
Data will be captured in a validated electronic database management system hosted by St. Jude Medical. Only authorized site personnel will be permitted to enter data into the electronic data capture (EDC) system deployed by St. Jude Medical. An electronic audit trail will be used to track any subsequent changes of the entered data.

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20.0 MONITORING

It is the responsibility of St. Jude Medical as the sponsor of the study to ensure the study is conducted, recorded, and reported according to the approved protocol, subsequent amendment(s), applicable regulations, and guidance documents. Monitoring will be conducted according to the St. Jude Medical Clinical Monitoring standard operating procedure.

Prior to beginning the study, St. Jude Medical will contact the investigator or designee to discuss the study and data requirements. A St. Jude Medical monitor will periodically review the subject records and associated source documents. The investigator shall make subject and study records available to the clinical monitor for monitoring.

Centralized monitoring will occur through routine internal data review. This monitoring is designed to identify missing and inconsistent data, data outliers, and potential protocol deviations that may be indicative of site non-compliance. On-site monitoring may occur at the discretion of the Sponsor.

21.0 REGULATORY INSPECTIONS

The investigator and/or delegate should contact St. Jude Medical immediately upon notification of a governmental agency inspection at the site. A clinical monitor or designee will assist the investigator and/or delegate in preparing for the audit.

An investigator, or any person acting on behalf of such a person with respect to the study, will permit authorized governmental agency employees, at reasonable times and in reasonable manner, to inspect and copy all records relating to the study.

An investigator will permit authorized governmental agency employees to inspect and copy records that identify subjects, upon notice that governmental agency has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator, to the Sponsor or IRB have not been submitted or are incomplete, inaccurate, false or misleading.

22.0 DOCUMENT RETENTION

St. Jude Medical and the Principal Investigators will maintain the clinical study documents as required by St. Jude Medical, Inc. and applicable regulatory requirements. They will take measures to prevent accidental or premature destruction of these documents. The Principal

Investigator or St. Jude Medical may transfer custody of records to another person/party and document the transfer at the investigational site or at St. Jude Medical's facility.

These documents must be retained by the investigational site for a period of 2 years after clinical study conclusion and made available for monitoring or auditing by St. Jude Medical's representative or representatives of the FDA and other applicable regulatory agencies. The Investigator must ensure the availability of source documents from which the information was derived.

23.0 DEVIATIONS FROM THE INVESTIGATION PLAN

All deviations from the Investigational plan will be recorded on a worksheet and in the EDC system. In accordance with 21 CFR 812.150(a)(4), 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.

24.0 CLINICAL EVENTS COMMITTEE (CEC)

A Clinical Events Committee (CEC) will be responsible for providing an independent review and adjudication of all subject deaths and adverse events. The CEC will review adverse events and determine device and/or procedure relatedness and whether serious or not (ADEs, SADEs, and SAEs). The CEC will base their final adjudication on the information provided on the case report forms, medical records, and their clinical knowledge and experience. The committee will consist of a minimum of three (3) members, comprised of pain specialists with experience in medical device implants/studies. The CEC will meet on an as-needed basis, at a minimum twice a year, to assess individual events in the study. [redacted]

25.0 PUBLICATION POLICY

The results of the clinical study will be submitted for publication, regardless of the outcome. A 'Publication Agreement' will be signed between the Principal Investigator and the Sponsor either as a separate Publication Agreement or within the Clinical Trial Agreement. The International Committee of Medical Journal Editors (ICMJE) guidelines on publication will be followed (www.icmje.org). This study will be posted on ClinicalTrials.gov and results will be posted on ClinicalTrials.gov as required.

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APPENDIX A: ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
CEC	Clinical Events Committee
CIP	Clinical Investigational Plan
CRPS	Complex Regional Pain Syndrome
DMP	Data Management Plan
DRG	Dorsal Root Ganglion Stimulation
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ICMJE	International Committee of Medical Journal Editors
IPG	Implantable Pulse Generator
IRB	Institutional Review Board
ISO	International Organization for Standardization
MP	Monitoring Plan
NA	Not Applicable
PG	Pulse Generator
RDC	Remote Data Capture
SAE	Serious Adverse Event
SJM	St. Jude Medical
TENS	Transcutaneous Electrical Nerve Stimulation

APPENDIX B: CIP REVISION HISTORY

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APPENDIX C: DECLARATION OF HELSINKI

The most current version of the document will be followed.

APPENDIX D: LIST OF CLINICAL INVESTIGATION SITES AND IRB
A list of Clinical Investigational sites and IRB will be kept under a separate cover and is available upon request.

APPENDIX E: SAMPLE INFORMED CONSENT
Sample Informed Consent form will be kept under a separate cover and is available upon request.

APPENDIX F: CASE REPORT FORMS
Final Case Report Forms will be kept under a separate cover and are available upon request.

APPENDIX G: INSTRUCTIONS FOR USE

IFUs will be kept under a separate cover and are available upon request.