

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Dorsal root ganglion stimulator for pain relief

Device Trade Name: Axium Neurostimulator System

Device Procode: PMP

Applicant's Name and Address: Michele Chin-Purcell
Spinal Modulation
1135 O'Brien Dr.
Menlo Park, CA 94025

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P150004

Date of FDA Notice of Approval: February 11, 2016

II. INDICATIONS FOR USE

The Axium Neurostimulator System 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**.

* 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.

III. CONTRAINDICATIONS

Patients contraindicated for the Axium Neurostimulator System are those who:

- Are unable to operate the system
- Are poor surgical risks
- Patients who fail to receive effective pain relief during trial stimulation.

IV. WARNINGS AND PRECAUTIONS

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

V. DEVICE DESCRIPTION

The Axium Neurostimulator System is a totally implanted device that delivers electrical stimulation to the dorsal root ganglion for the treatment of chronic intractable pain of the trunk and/or limbs. The Axium Neurostimulator System is shown in Figure 1 below:

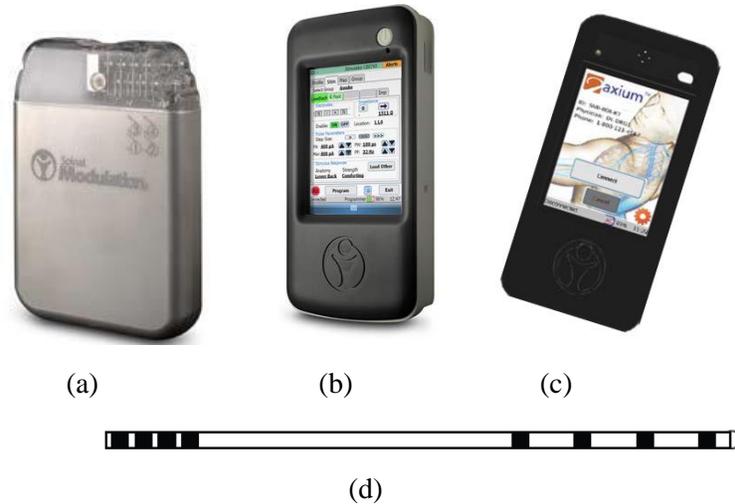


Figure 1: Axium Neurostimulator System (a) Implantable Neurostimulator (INS) (b) Clinical Programmer (c) Patient Programmer (d) Lead

1. Implanted Components

The implanted components of the Axium Neurostimulator System include the following:

- Implantable Neurostimulator (INS) (MN10200): The Axium INS is a non-rechargeable implanted device that can connect to up to 4-leads. It uses microelectronic circuitry, powered by a hermetically sealed battery (3.3 V Lithium Carbon Monofluoride), to generate a pulsed waveform to stimulate the dorsal root ganglion (DRG). The electronic circuitry and battery are housed in a hermetically sealed titanium case. The stimulation output parameters are listed in Table 1 below:

Table 1: Stimulation Output Parameters

Number of Channels	4 [†]
Waveform	Biphasic
Pulse Shape	Rectangular
Current or Voltage Regulated	Voltage
Maximum Current Amplitude	6000 μ A at 500 Ω 6000 μ A at 766 Ω [‡] 4600 μ A at 1000 Ω

Maximum Output Voltage	4.6 V
Pulse Width	40 - 1000 μ s
Frequency	4-80 Hz
Current Path Options	Bipolar or Multipolar

† Four lead connections with each lead having an independent control.

‡ Max amplitude is limited when 4.6 V is reached starting at 766 Ω

- **Percutaneous Leads:**

The leads are designed for percutaneous introduction into the epidural space near the DRG. Up to 4 leads can be placed using a special needle and a set of custom delivery tools provided in their respective kits. Each lead has four cylindrical electrodes spaced at equal intervals, which are intended to provide stimulation at the DRG. Lead models include the following: standard Trial Lead (MN10350-50, -90), SlimTip Trial Lead (MN10350-50A, -90A), standard Implant Lead (MN10450-50, -90), and implant SlimTip Lead (MN10450-50A, -90A). There is no difference in the design of the Trial and Implant leads. The lead specifications for the standard and SlimTip leads are the same except for the shape of the lead tip. Specifications are depicted in Table 2 below:

Table 2: Percutaneous Lead Specifications

Lead Length	50 cm or 90 cm
Lead Diameter	1 mm
Number of Electrodes	4
Electrode Material	80% Platinum/20% Iridium and 90% Platinum/10% Iridium
Electrode Spacing (edge-to-edge)	5 mm
Electrode Span	20 mm
Electrode Surface Area	4.05 mm ²
Impedance	< 20 Ω (50 cm) < 35 Ω (90 cm)
Ball Tip Diameter	1mm for Slim Tip 1.5mm for standard lead

- **Lead Extension (MN10550-50):** A 50 cm long lead extension is available for scenarios when additional length is needed to accommodate a patient's anatomy.
- **Soft Tissue Anchor:** To anchor the lead in the subcutaneous soft tissue or on the skin surface proximal to the distal contacts of the lead.

2. **External Components**

The external components of the Axium Neurostimulator System include the following:

- **Clinician Programmer (MN 10700):** Used by the clinician to wirelessly program output stimulation parameters for the INS and Trial Neurostimulator (TNS). It is portable, hand-held devices powered by internal rechargeable batteries and

contains an internal magnet to initiate communication with the INS and TNS devices.

- Patient Programmer (MN10600-02): A handheld battery operated unit able to communicate wirelessly with the INS or TNS. It allows the patient to adjust the stimulation strength within limits preset by the physician. It also allows the patient to select pre-programmed alternate groups of stimulation settings and turn stimulation off, if necessary.
- Trial Neurostimulator (TNS) (MN10100): Patients who are indicated for the Axium INS System will first undergo a temporary trial period using an external TNS connected to implanted leads. The TNS provides stimulation by emulating the INS during the intraoperative test and during the stimulation trial. The TNS stimulation parameters are the same as the INS.
- Connector Cable (MN11350): Connects the Leads or Lead Extension to the external TNS.

3. Accessories:

The following accessories are also available for use with the Axium Neurostimulator System:

- Small / Big Curve Delivery Sheath: To allow passage of the lead percutaneously into the epidural space.
- Axium Small / Big Curve Delivery Sheath: To allow passage of leads percutaneously into the epidural space. Axium sheaths are internally reinforced with thin stainless steel braiding.
- Complex Curve / Straight Stylet: To assist in steering and positioning the lead within the epidural space.
- 14G Delivery Needles: To access the epidural space, providing a conduit for lead, guidewire and delivery sheath placement. It is available as a straight needle or a curved needle.
- Guidewire: To verify that the needle is in the epidural space after using a loss of resistance technique. It also provides stability to the sheath before frontloading the SlimTip lead.
- Tunneling Tool: To provide a conduit for the Trial Lead, Implant Lead, or Lead Extension to the INS or away from the midline of the spine. It is packaged with 2 exchangeable tips: a blunt pencil tip and a sharp trocar tip.
- INS Sizer: Allows the physician to properly size the INS pocket.

- Port Plugs: To fill unused ports in the INS.
- Sterile Magnet Sleeve: The magnet is placed in the sterile sleeve to allow it to be used during the implantation of the INS.
- Auxiliary Magnet: Allows the user to turn the NS off or activate Radio-Frequency (RF) to allow the user to communicate with the NS.
- Hex Key: Allows the user to release a set screw in the INS header or Lead Extension header that has been unscrewed too far.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of chronic, intractable pain of the lower limbs in adult patients with Complex Regional Pain Syndrome (CRPS) types I and II.

1. Non-surgical treatment options:

- Oral medication
- Rehabilitative therapy
- Transcutaneous electrical nerve stimulation (TENS)
- Behavior modification
- Neurolysis (i.e., Therapeutic nerve block, Cryoanalgesia, RF Lesioning)

2. Surgical treatment options:

- Sympathectomy- severing the sympathetic nerve pathway
- Implantable intrathecal drug delivery systems
- Partially implanted spinal cord stimulation (SCS) Systems – RF implantable spinal cord stimulators (the power source in this system is external)
- Commercially available fully implanted SCS Systems

Each alternative has its own advantages and disadvantages. A patient should discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Axium Neurostimulator System for the treatment of chronic intractable pain has been approved for commercial distribution in Europe since 2011. In addition, the Axium Neurostimulator System for the treatment of chronic, intractable pain of the trunk and/or limbs has been approved for commercial distribution in Australia since 2013. In 2014, communications and manual updates were sent to the European and Australian regulators and physicians with regard to appropriate lead removal. The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device:

- 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.

Additional risks to the patients, as a result of the placement and stimulation of the lead in the area of the DRG, include pain due to setting the stimulation parameters too high.

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

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

1. Implantable Neurostimulator (INS)

Testing was conducted on the Model MN10200 INS, including: mechanical design verification (including testing on devices subjected to accelerated aging), electrical/firmware design verification testing, electromagnetic compatibility testing, and medical procedure compatibility testing. Key testing on the INS is summarized in Table 3 below. Testing demonstrated the INS operated according to specifications after exposure to the tested conditions (i.e., passed testing).

Table 3: Summary of key testing performed and passed on the Axium Neurostimulator System INS

Test	Test Purpose	Acceptance Criteria
Measurement of Output Pulses	Verify proper output (amplitude, pulse width, frequency, etc.) of the INS function are within specified tolerances. The characteristics of the output pulses shall be measured as described in International Standards Organization (ISO) 14708-3 clause 6.101.	Amplitude, Pulse width, Frequency, Etc. are within output specifications.
Dimensional Requirements	To demonstrate INS meet shape and profile requirements.	INS samples must meet size specifications for INS width, height, thickness, volume, mass, and radius.
DC Leakage Current	Verify the leakage current is in an acceptable range.	The maximum leakage current < 1 μ A
Atmospheric Pressure Exposure	To expose each INS to pressure extremes the device may encounter.	Testing per ISO 14708-1, 25. (Exposure to 70 kPa and 150 kPa (50 feet underwater)).
Storage Temperature	To expose each INS to pressure extremes the device may encounter during storage and distribution.	Testing per ISO 14708-1, 26.2. (Exposure to low (-10 \pm 3 $^{\circ}$ C) and high temperatures (55 \pm 2C)).
Operating Temperature	To demonstrate the INS remains mechanically intact and capable of normal operation during exposure to low and high temperatures.	Exposure to low (-5 $^{\circ}$ C) and high temperatures (45 $^{\circ}$ C).
Mechanical Forces - Vibration	The implantable parts of the neurostimulator shall be constructed to withstand the mechanical forces that can occur during normal conditions of use.	INS meets specifications after testing per ISO14708-3, 23.2.
Mechanical Forces - Connections	The connector joining the INS to the permanent implantable Leads or Lead Extensions shall be identified and its hold force declared in the instructions for use per ISO-14708-1 Section 23.6.	10 N max
Hermetic Leak Test	To demonstrate that the INS maintains hermeticity after exposure to environmental testing.	The INS enclosure shall be capable of passing an inert gas (20% HE, 80% Ar) leak test. The allowable helium leak rate shall be $\leq 2.5 \times 10^{-9}$ cc-atm/sec. Test per MIL-STD-202G, Method 112E, Condition C.
Header Adhesion Testing	To demonstrate the header meets fatigue requirements.	The header shall not be damaged by a force test of a minimum of 30 lbf applied both in tension and shear directions.

Test	Test Purpose	Acceptance Criteria
Lead Insertion	To demonstrate that the INS, port plug, and lead meet specified interface requirements for insertion force.	The Lead shall be able to be inserted easily into the header with a gloved hand without damage to the Lead. Lead insertion force must be < 1.1 lbf.
Particulate matter	Verify there is no unacceptable release of particulate matter when the device is used as intended.	ISO-14708-3, 14.2 (The excess average count of particles from the test specimen compared to a reference sample shall not exceed 100 counts/ml greater than 5.0 µm and shall not exceed 5 counts/ml greater than 25 µm.)
Temperature	Verify the protection of patients from damage caused from heat.	14708-3, 17 (No outer surface of the INS shall be greater than 2° C above the normal surrounding body temperature in normal operation or single-fault condition).
Battery	Electrical, Visual, Dimensional, Hermeticity, Short Circuit Testing, Environmental, and Forced Discharge Tests	Meets specifications.

2. Percutaneous Lead Testing

The percutaneous underwent numerous tests for dimensional verification, electrical safety, environmental, and mechanical conditions. Key testing on the leads is summarized in Table 4 below. Testing demonstrated the percutaneous leads operated according to specifications after exposure to the tested conditions (i.e., passed testing).

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

Test	Purpose	Acceptance Criteria
Dimensional	To ensure the leads meet dimensional requirements for Overall Lead Length, Lead Body Diameter, Distal Electrode Dimensions, Lead Tip Length, Connector Dimensions.	Meets dimensional specifications.
Stylet Interactions – Insertion/Removal	To demonstrate the force required to fully insert or remove each stylet into the lead.	The lead shall allow internal passage of a 0.254 mm (0.010”) diameter (maximum) removable stylet during insertion with sufficient clearance for 5 repeated insertion/removal cycles during the implantation process with exposure to blood or blood analog fluid. The proximal end of the lead shall allow easy insertion of the stylet into the stylet lumen in the lead.
Insertion Needle Insertion/Withdrawal	Demonstrate lead compatibility with Touhy Needle.	The distal ball of the lead (largest part of the lead) shall fit inside a 14 Ga thin wall delivery needle, as well as allowing the needle to be removed over the proximal end of the lead
Tensile Strength	Demonstrate the lead remains mechanically intact after a tensile load.	The lead’s distal end shall withstand a minimum tensile pull of 6.7 N (1.5 lbf) and the lead or lead extension’s proximal end shall withstand a minimum tensile pull of 5 N (1.1 lbf) without fracture of any conductor or cracking of either any functional electrical insulation or of the body of the lead.
Lead and Lead Extension Insertion Force	Demonstrate the lead shall be able to be inserted easily into the header with a gloved hand without damage to the lead.	Lead insertion force must be < 1.1 lbf.

Test	Purpose	Acceptance Criteria
Lead Body and Anchor Flexural Fatigue	Demonstrate that the leads do not fatigue after flexural stressors.	Verify no breakages, wears, tears or cracks are observed in any of the Implantable Leads or Proximal Soft Tissue Anchors (PSTA) after 3.5 million cycles of flexural fatigue. The maximum resistance of each post-fatigued Lead should remain < 20 Ω (50 cm lead) and <35 Ω (90 cm lead).
Proximal Connector End Flex Fatigue	Demonstrate that the lead proximal connector does not fatigue after flexural stressors.	No breakages, severe wear or tears in any of Lead proximal connectors (flexural region) after 110,000 cycles of flexural fatigue. The maximum resistance of each post-fatigued Lead should be < 20 Ω (50 cm lead) and <35 Ω (90 cm lead).
Lead & Lead Extension Insertion into INS	Demonstrate the Leads & Lead Extension can be inserted and removed from the IPG during expected use without damaging the INS or the Lead.	The Leads & Lead Extension shall be insert-able and removable from the INS 5 times, without damaging the INS or the Lead.
Maximum Resistance of Lead and Extension	Demonstrate the lead resistance is according to specification	The resistance of the Lead Extension shall be less than 60 ohms (when used with the lead) and the resistance of the Lead shall be less than 20 Ω . (50 cm lead) and <35 Ω (90 cm lead)

3. Programmers

The software associated with the Clinical Programmer and Patient Programmer were documented and tested in accordance with the FDA guidance document entitled, “Guidance for the Content of Pre-market Submission for Software Contained in Medical Devices” (May 11, 2005) and all requirements were met. Electrical and mechanical verification and environmental testing were also performed per the following standards and all testing met specifications:

- ISO 14708-1: Implants for Surgery – Active implantable medical device, Part 1: General requirements for safety, marking and information to be provided by the manufacturer
- ISO 14708-3: Implants for Surgery – Active implantable medical devices, Part 3: Implantable neurostimulators
- IEC 60601-1: Medical electrical equipment Part 1 General requirements for basic safety and essential performance
- IEC 60601-1-11: Medical electrical equipment – part 1-11: General requirements for basic safety and essential performance – Collateral Standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment
- IEC 60601-1-6: Medical electrical equipment Part 1-6: General requirements for safety - Collateral Standard: Usability
- IEC 60601-1-2: Medical electrical equipment, Part 1-2: General requirements for basic Safety and essential performance Collateral standard: Electromagnetic compatibility – Requirements and tests.

4. Trial Neurostimulator (TNS)

Testing was conducted on the TNS, including: mechanical design verification, electrical/firmware design verification testing, electromagnetic compatibility testing, and firmware testing. The standards listed below were used in the testing. Testing demonstrated the TNS operated according to specifications after exposure to laboratory conditions (i.e., passed testing).

- IEC 60601-1: Medical electrical equipment, Part 1: General requirements for basic safety and essential performance.
- IEC 60601-1-11: Medical electrical equipment Part 1 General requirements for basic safety and essential performance Collateral Standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment.
- ISO 14708-3: Implants for Surgery – Active implantable medical devices, Part 3 Implantable neurostimulators.
- IEC 60601-1: Medical electrical equipment Part 1 General requirements for basic safety and essential performance.
- IEC 60601-1-2: Medical electrical equipment, Part 1-2: General requirements for basic Safety and essential performance Collateral standard: Electromagnetic compatibility – Requirements and tests.

5. Electromagnetic Compatibility (EMC) and Wireless Technology

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

- IEC 60601-1-2: 2007, “Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral standard: Electromagnetic compatibility - Requirements and tests” (appropriate essential performance criteria were used)
- ISO 14708-3:2008(E): Implants for surgery – Active implantable medical devices – Part 3: Implantable neurostimulators”, Part 27
- FCC Part 95 Federal Communications Commission PART 95 MedRadio

Testing to address compatibility with Radio-frequency Identification (RFID) and Electronic Article Surveillance systems was also provided.

6. System Testing

Testing to verify that system-level design requirements were met for interactions between Axium Neurostimulator System components was performed. All test articles met defined acceptance criteria for the system

integration tests conducted. System validation testing demonstrated that the system operated as expected and has been validated for safe and effective use.

B. Biocompatibility

Biocompatibility testing was performed on the finished, sterilized devices for all patient-contacting components of the Axium Neurostimulator System in accordance with ISO 10993-1 Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process. All biocompatibility studies were conducted in compliance with Good Laboratory Practices (GLP), 21 CFR Part 58. The implanted components of the Axium Neurostimulator System are considered permanent (> 30 days) implants in contact with tissue/bone. The Axium Neurostimulator System also contains external communicating components with limited (\leq 24 hours) tissue/bone contact and skin-contacting component with prolonged (> 24 hours – 30 days) contact. The biocompatibility test data are summarized in Table 5 below. All pre-specified test acceptance criteria were met and all tests passed.

Table 5: Biocompatibility Test Data on the Implantable, External Communicating, and Skin-Contacting Components of the Axium® Neurostimulator System *

Biological Effect (Applicable Standard)	Test Method	Acceptance Criteria	Results
Implanted^a, External Communicating^b, and Skin-contacting^c Components:			
Cytotoxicity (ISO 10993-5)	ISO MEM Elution Assay	Reactivity grade is not greater than mild reactivity (Grade 2).	PASS
Sensitization (ISO 10993-10)	ISO Guinea Pig Maximization Sensitization Test	Grades of <1 in the test group provided grades of < 1 are observed on the control animals. (If grades of \geq 1 are noted on the control animals, then the reactions of the test animals which exceed most severe control reaction are presumed to be due to sensitization).	PASS
Intracutaneous Reactivity (ISO 10993-10)	ISO Intracutaneous Reactivity Test	The difference between the test article and the control mean score is \leq 1.0.	PASS
Implanted^a and External Communicating^b Components			
Systemic Toxicity (ISO 10993-11)	ISO Acute Systemic Toxicity Test	None of the test animals show a significantly greater biological reaction than the animals treated with vehicle control.	PASS
	Materials Mediated Rabbit Pyrogen Test*	No rabbit shows an individual rise in temperature of 0.5°C or more above the baseline temperature.	PASS
Implanted^a Components			
Genotoxicity (ISO 10993-3)	Bacterial Reverse Mutation Assay (Ames Test)	There is less than 2-fold increase in the number of revertants when compared to the solvent controls in strains TA98, TA100, and WP2uvrA and less than 3-fold increase in the number of revertants when compared to the solvent control in strains TA1535 and TA1537.	PASS
	In Vitro Mouse Lymphoma	There is less than 2-fold increase in mutant	PASS

Biological Effect (Applicable Standard)	Test Method	Acceptance Criteria	Results
	Assay	frequency over the negative control.	
	In Vivo Mouse Peripheral Blood Micronucleus Assay	There is no statistically significant increase in the frequency of micronucleated reticulocytes (% MN-RET) in the test group as compared to the concurrent negative control.	PASS
Implantation (ISO 10993-6), Subchronic and Chronic Toxicity (ISO 10993-11)	ISO Subcutaneous Implantation Study in Rabbits – 2 weeks and 6 Weeks	The test results are considered acceptable based on an overall interpretation of the degree of biocompatibility exhibited by the test article based on the macroscopic and microscopic analysis of the implantation sites comparing test to control article (USP high density polyethylene reference standard), as well as clinical observations.	PASS
	Systemic Toxicity Study in Rats following Subcutaneous Implantation – 13 weeks and 26 weeks	The test results are considered acceptable based on an overall interpretation of the degree of biocompatibility exhibited by the test article based on the clinical observations, body weights, necropsy results, organ weights and organ/body weight percentages, microscopic evaluation of organs, hematology and clinical chemistry values, and gross and microscopic evaluation of the implantation sites comparing the test article to the control article (USP high density polyethylene).	PASS
	6-month Implantation Study in Sheep model	A 6-month implantation study was conducted in sheep model to assess the local tissue response as well as long-term safety of the device. The leads were implanted in the sheep within its neural foramen at the dorsal root ganglion (DRG). There were two groups in the sheep study – a 45-day group and a 180-day group. The effect of stimulation of DRG was assessed in the 45-day group with active leads. In the 180-day group, the long-term biocompatibility of the leads at the DRG site was assessed with a non-stimulating device. Safety was determined in the study by evaluating adverse events related to the use of the device including neurological evaluation of the animals, general health of the animals, hematology and clinical chemistry, gross necropsy and histology findings of the animals. No device-related adverse reactions were noted in the study.	
Carcinogenicity (ISO 10993-3)	An adequate carcinogenicity risk assessment was provided.		

- ^a Components tested: INS, Leads, and Soft Tissue Anchor (Lead Extension and Port Plug were not tested as they are identical in processing and materials to the Lead and the INS (header assembly))
- ^b Components tested: Stylets, Delivery Needles, Delivery Sheaths, Tunneling Tools, and INS Sizer
- * Among the external communicating device components, following components were tested in the rabbit pyrogen test - Delivery Sheaths, Delivery Needles, and Guidewire
- ^c Component tested: Connector Cable

C. Sterility and Packaging

The sterile components of the Spinal Modulation Axium Neurostimulator system are terminally sterilized using a 100% ethylene oxide (EO) sterilization process to provide a minimum sterility assurance level (SAL) of 10^{-6} . Validation of the sterilization process is in compliance with ANSI/AAMI/ISO 11135-1:2007 *Sterilization of health care products – Ethylene oxide – Part 1: Requirements for development, validation, and routine control of a sterilization process for medical devices*.

Sterilant residuals conform to the maximum allowable limits of EO and ethylene chlorohydrin (ECH) residuals specified in ISO 10993-7: 2008 *Biological Evaluation of Medical Devices – Part 7: Ethylene Oxide Sterilization Residuals*.

The bacterial endotoxin levels on the sterile components of the Spinal Modulation Axium Neurostimulator system are determined using Limulus Amebocyte Lysate (LAL) testing and demonstrated to be in compliance with the bacterial endotoxin limits specified in the USP Chapter <161> *Transfusion and Infusion Assemblies and Similar Medical Devices* and FDA's Guidance for Industry - Pyrogen and Endotoxins Testing: Questions and Answers (June 2012).

Packaging and shelf- life validation tests were completed in compliance with ISO 11607-1:2009 *Packaging for Terminally Sterilized Medical Devices. Part 1: Requirements for materials, sterile barrier systems and packaging systems*. Shelf life for the sterile system components has been established as two (2) years from the date of manufacturing.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study (ACCURATE) to establish a reasonable assurance of safety and effectiveness of stimulation of the DRG with the Axium Neurostimulator System as an aid in the management of severe chronic intractable pain of the lower limbs in adult patients with Complex Regional Pain Syndrome (CRPS) types I and II under IDE # G110186. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients in the ACCURATE study were enrolled and randomized between August 23, 2013 and July 28, 2014. The database for this PMA reflected data collected through October 2, 2015 and included 152 patients. There were 22 investigational sites.

The study was a prospective, randomized, controlled, unblinded, multi-centered clinical study comparing the Axium Neurostimulator System (Axium group) to a legally marketed spinal cord stimulation (SCS) system from a single manufacturer (Control group) (i.e., the RestoreSensor or RestoreUltra SCS devices manufactured by Medtronic, Inc.). Note that the Control device is approved for use in the treatment of chronic, intractable pain of the trunk and limbs. Note also that the Axium Neurostimulator System group received electrical stimulation at the DRG while the Control group received electrical stimulation at the dorsal column of the spinal cord.

Additionally, programming features were selected in the Control devices in order to be as comparable as possible to the Axium Neurostimulator System. For purposes of ensuring comparable features to assess this endpoint, the RestoreSensor Control device had an accelerometer feature that can adjust stimulation based on the patient's needs and preferences in different body positions (including stimulation to maintain paresthesia) deactivated. The Restore Ultra device did not have the feature.

Subjects were not blinded as to their device assignment. Subjects were randomized in a 1:1 ratio to the Axium and Control arms. The primary objective of the study was to demonstrate that a composite endpoint of safety and effectiveness of the Axium Neurostimulator System as compared to (i.e., non-inferior or superior) the legally-marketed SCS comparator for the treatment of chronic intractable pain associated with Complex Regional Pain Syndrome (CRPS) and Peripheral Causalgia. Note that although the ACCURATE study enrolled subjects with CRPS and peripheral causalgia, the indications for use utilized the updated terms of CRPS I and CRPS II. Since the study protocol uses the terms CRPS and peripheral causalgia and not CRPS I and CRPS II, the study summary in this document will use the terms CRPS and peripheral causalgia.

The study included a “Trial Neurostimulator Phase” (Subject received between 3 to 30 days of temporary trial neurostimulation, or TNS Phase), an “Implantable Neurostimulator Phase” (implantable neurostimulator, or INS Phase), and a “Follow-up Phase”. Only subjects who had a $\geq 50\%$ reduction in pain during TNS phase and expressed a desire to have an INS implant moved on to the INS phase. The initial planned sample size was 152 subjects (76 Axium and 76 Controls). An unblinded sample size re-estimation (SSR) based on the “Promising Zone” methods of Mehta and Pocock (2010) was conducted by an independent statistician when 50% of the expected primary endpoint information was available. The SSR found that no sample size increase was needed.

A Data Safety Monitoring Board (DSMB) monitored the study.

1. Clinical Inclusion and Exclusion Criteria

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

- Subject is male or female between the ages of 22 and 75 years.
- Subject is able and willing to comply with the follow-up schedule and protocol.
- Subject has chronic, intractable pain of the lower limb(s) for at least 6 months.
- Subjects are diagnosed with complex regional pain syndrome (CRPS) and/or peripheral causalgia.
- Subjects have a minimum VAS ≥ 60 mm in the area of greatest pain in the lower limb(s).
- Subject has failed to achieve adequate pain relief from at least 2 prior pharmacologic treatments from at least 2 different drugs classes.

- Subject has had stable neurologic function in the past 30 days.
- In the opinion of the Investigator, the subject is psychologically appropriate for the implantation of an active implantable medical device.
- Subject is able to provide written informed consent.

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

- Back pain is the greatest region of pain as measured on the baseline VAS.
- Female subject of childbearing potential is pregnant/nursing, plans to become pregnant or is unwilling to use approved birth control.
- Subject has exhibited escalating or changing pain condition within the past 30 days as evidenced by Investigator examination.
- Subject is currently involved in medically related litigation, including workers compensation.
- Subject has had corticosteroid therapy at an intended site of stimulation within the past 30 days.
- Subject's pain medication(s) dosage(s) are not stable for at least 30 days.
- Subject has had radiofrequency treatment of an intended target DRG within the past 3 months.
- Subject has previously failed spinal cord stimulation therapy.
- Subject currently has an active implantable device including ICD, pacemaker, spinal cord stimulator or intrathecal drug pump or subject requires magnetic resonance imaging (MRIs) or diathermy.
- Subject has pain only within a cervical or thoracic distribution.
- Subject has cognitive, physical or sensory impairment that, in the opinion of the Investigator, may limit their ability to operate the device.
- Subject currently has an indwelling device that may pose an increased risk of infection.
- Subject currently has an active systemic infection.
- Subject has, in the opinion of the Investigator, a medical comorbidity that contraindicates placement of an active medical device.
- Subject has participated in another clinical investigation within 30 days.
- Subject has a coagulation disorder or uses anticoagulants that, in the opinion of the Investigator, precludes participation.
- Subject has been diagnosed with cancer in the past 2 years.
- Imaging (MRI, CT, x-ray) findings within the last 12 months that, in the Investigator's opinion, contraindicates lead placement.
- Subject is a prisoner.

2. Follow-up Schedule

All subjects had a temporary trial neurostimulator (TNS) for a period of three to 30 days, similar to that used in current clinical practice. If the subject was a treatment success at the end of TNS (i.e. had a $\geq 50\%$ reduction in pain as measured by a 100 mm visual analogue scale and expressed a desire to have a

permanent implant), they were scheduled for the fully implantable neurostimulator (INS) procedure.

Post INS placement, subjects were seen for device programming as needed to customize their stimulation parameters. Approximately one week following the INS implant the subjects had a wound check visit. Regularly scheduled study follow-up visits were required at 1-, 3-, 6-, 9-, 12 months, and annually until the study is closed. Primary and secondary endpoints were assessed through the 3 month follow-up visit. Postoperatively, the objective parameters measured during the study included the assessments listed in Table 6 and Table 7 below. Adverse events and complications were recorded at all visits.

The key time-points are shown below in the tables summarizing safety and effectiveness.

Table 6: ACCURATE Study Visit Schedule (Baseline to 1 Month Post-Implant)

	Screening/ Baseline	TNS	Post-TNS Placement	End of TNS	INS Implant	Post-INS Placement	1 Month ± 14 days
	TNS Phase ¹			INS Phase ¹			
Informed Consent	X						
Inclusion/Exclusion MRI/CT/X-ray	X						
Baseline Pregnancy Test Medical History/ Physical Exam Neurological Exam Medications (all)	X						
Subject Questionnaire Form A: Pain Distribution, Pain (VAS), SF-36, BPI, POMS	X						X
Pain Diary	X						X
Procedure Evaluation X-rays/Fluoroscopy		X			X		
Subject Questionnaire Form B: Pain Distribution, Pain (VAS)				X			
Physical and Neurological Exam				X			X
Paresthesia Assessment			X ²	X		X ²	X
Programming			X ³	X		X ³	X
Subject Satisfaction				X			
Pain Medications				X			X

Telephone Follow-up (prior to visit)							X
Adverse Events & Protocol Deviation (if needed)	X	X	X	X	X	X	X

¹ The post- TNS and post-INS phases do not require unscheduled visits (e.g. Subject Questionnaire B) unless it is determined that more assessments are warranted based on the subjects condition. Only those unscheduled visits that occur after the 1-month visit will be subject to the unscheduled visit requirements. There may be programming forms in the unscheduled interval that are really post-revision/replacement or required to assess an AE in which are not true unscheduled visits (e.g. do not require Subject Questionnaire B).

² The Paresthesia Assessment is only required to be completed once during both the post-TNS and post-INS phase.

³ Multiple programming forms during post-TNS and post-INS phase are allowed

Table 7: ACCURATE Study Visit Schedule (3 Months to Study End)

	3 Months ± 14 days	6 months ± 28 days	9 months ± 28 days	12 months ± 28 days	24 – 60 months ± 90 days	Unscheduled Visits¹	Revision/ Replace Procedure
Physical/Neurological Exam	X	X	X	X	X		X ³
Pain Medications	X	X	X	X	X		
Subject Questionnaire Form A: Pain Distribution, Pain (VAS), SF-36, BPI, POMS	X	X	X	X	X		
Subject Questionnaire Form B: Pain Distribution, Pain (VAS)						X ¹	
Pain Diary	X	X	X	X			
Telephone Follow-up (prior to visit)	X	X	X	X			
Paresthesia Assessment	X	X	X	X	X		
Programming	X	X	X	X	X	X	X ³
Subject Satisfaction	X	X		X			
Revision/Replacement Procedure: X-rays/Fluoro							X ³
Explant Procedure: X-rays/Fluoro							
Study Exit					X ²		
Adverse Events & Protocol Deviations (if needed)	X	X	X	X	X	X	X

¹ The post- TNS and post-INS phases do not require unscheduled visits (e.g. Subject Questionnaire B) unless it is determined that more assessments are warranted based on the subjects condition. Only those unscheduled visits that occur after the 1-month visit will be subject to the unscheduled visit requirements. There may be programming forms in the unscheduled interval that are really post-revision/replacement or required to assess an AE in which are not true unscheduled visits (e.g. do not require Subject Questionnaire B).

² The Study Exit form is required at the time of study exit or 60 months as appropriate.

³ Replacement procedures that include external components (TNS, patient programmer, connector cable) do not require pre/post X-rays, physical or neurological exam, or programming. In addition, pre-x-rays were not always attainable (e.g., TNS leads pulled out at subject's home) and were not considered deviations

3. Clinical Endpoints

The primary endpoint was a composite safety and efficacy endpoint, assessed through three months post-implant (including the Trial Stimulation (TNS) and the Implant (INS) phases). Safety and efficacy were determined by the percentage of subjects that were free from a stimulation-induced neurological deficit and achieved at least 50% pain relief in the lower limbs, in the region of greatest baseline pain, in both the TNS and INS phases of the trial. Subjects were required to remain on stable pain medications; as seen in Table 28, changes in pain medication were minimal.

A stimulation induced neurological deficit was defined as a measureable motor or sensory deficit on the neurological examination, within the appropriate concordant anatomy, that is induced by stimulation and does not persist in the absence of stimulation within a 24-hour timeframe. Changes in motor and sensory scales were classified into three categories: Change ≤ -2 points (worsening), $-1 \leq \text{Change} \leq +1$ (no clinically meaningful change, and Change $\geq +2$ (improvement). Subjects' pain intensity was measured via a 100 mm visual analogue scale (VAS) with 100 mm representing the "Worst Imaginable Pain" and 0 mm representing "No Pain".

The Statistical Analysis Plan specified the use of the modified-intention-to-treat (MITT) analysis dataset for analyses of primary and secondary endpoints. The MITT analysis data set includes all subjects that were randomized and received a trial neurostimulator. The primary composite endpoint data was also analyzed using the intention-to-treat subjects (ITT) (i.e., all subjects who met the enrollment criteria and received a randomization assignment.) and per-protocol subjects (PP) (i.e., all randomized subjects who have valid data at baseline and the 3-month follow-up, and have no major protocol deviations that would potentially affect study outcomes).

Individual Subject Success

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

- Experienced at least 50% lower limb pain relief (VAS Score Reduction) in their primary area of pain at the end of the trial phase (TNS), and expressed a desire to go on to INS implant, and
- Received at least 50% lower limb pain relief (VAS Score reduction) in their primary area of pain at the 3-Month visit post implant (INS), and
- Did not experience a stimulation-induced neurological deficit through three months as adjudicated by the Data Safety Monitoring Board (DSMB).

A subject was considered a primary composite endpoint failure if the subject:

- Did not receive at least 50% lower limb pain relief (VAS Score reduction) in their primary area of pain at the end of the trial phase (TNS), or

- Did not receive at least 50% lower limb pain relief (VAS Score reduction) in their primary area of pain at the 3-Month visit post implant (INS), or
- Did receive at least 50% lower limb pain relief (VAS Score reduction) in their primary area of pain at the end of the trial phase (TNS), but chose not to receive the implantable neurostimulator (INS), or
- Experienced a stimulation-induced neurological deficit through three months as adjudicated by the DSMB, or
- Exited the study due to a device- or procedure-related adverse event through three months as adjudicated by the DSMB, or
- Exited the study due to the need for a revision, replacement or explant procedure.

A subject was considered missing for the primary composite endpoint analysis if the subject:

- Exited the study after the initiation of the TNS procedure but prior to INS implant for any reason other than,
 - achieved less than 50% improvement in VAS scores at the End of TNS visit (i.e. primary-endpoint failure), or
 - achieved at least 50% improvement in VAS scores but chose not to move on to INS procedure (i.e. primary-endpoint failure), or
 - had a device- or procedure-related adverse event as adjudicated by the DSMB (i.e. primary-endpoint failure).
- Exited the study after the INS implant for any reason other than a device- or procedure-related adverse event through three months as adjudicated by the DSMB.

Study Success

Study success was defined as the percentage of subjects who met each success criteria in the Axium group and the Control group, using a 10% non-inferiority margin. If non-inferiority was achieved at a one-sided alpha of 0.05, a one-sided superiority test was performed at the significance level of 0.025.

Secondary Endpoint – Non-powered

Subjects reported whether or not they felt paresthesia when stimulation was on as a non-powered secondary endpoint. At the 3- month study visit subjects responded “Yes” or “No” to the question “During the past month, did you feel paresthesia in your lower limbs when stimulation was on?” Subjects were categorized into two groups based on their response: Group 1 - Subjects with paresthesia and Group 2 - Subjects without Paresthesia.

At the time of the trial and implant procedures, all subjects were asked to confirm that they were feeling stimulation (i.e. sensation of paresthesia) in the targeted area of pain in order to confirm placement of the implanted leads. Post-procedure, stimulation settings were then programmed based upon physician judgment to optimize the appropriate therapy for each study subject. In addition, all study subjects were able to adjust the intensity level of the therapy, within a physician-prescribed range, with their patient programmers.

Note that the clinical relevance of this result is unknown. The instructions for use for the Control device instructed that subjects be programmed to receive paresthesia. In addition, the number of subjects that did not have paresthesia is very small and this endpoint was not adequately powered to detect the difference in pain relief for subjects who reported feeling versus not feeling paresthesia. A placebo controlled trial would be necessary to rule out the possibility that the effect is greater than placebo.

Tertiary Endpoints

The following are the study Tertiary endpoints:

- SF-36 Quality of Life Questionnaire at 3, 6, and 12-months
- Profile of Mood States (POMS) at 3, 6, and 12-months
- Brief Pain Inventory (BPI) at 3, 6, and 12-months
- Subject Satisfaction at 3, 6, and 12-months:
Subjects completed a satisfaction scale at the End of TNS visit, and at three, six, and 12-months. The first three items were evaluated on an 11-point numeric scale with 0 indicating “Not Satisfied/Not Likely” and 10 indicating “Very Satisfied/Very Likely” . The last item was measured on a 7-point scale from “Much Worse” to “Much Better.”
 - Please rate your satisfaction with the pain relief provided by the stimulation.
 - Please rate your satisfaction with the therapy in general.
 - Please rate how likely you would be to undergo this therapy again based on your experience thus far.
 - Please rate the change in your pain compared to before the device was implanted.
- Stimulation Specificity at 3-months:
The baseline pain diagrams completed by the subjects were compared to the subjects’ paresthesia maps completed at the end of the follow-up visit. The pain and paresthesia diagram forms had identical diagrams of the human body on which subjects marked where they felt pain and paresthesia coverage. The stimulation specificity endpoint was evaluated at all scheduled visits by determining whether a subject felt paresthesia in anatomical regions that were reported as having no pain at baseline.

B. Accountability of PMA Cohort

The ACCURATE study enrolled and randomized 152 subjects (76 Axium subjects and 76 Control subjects) at 22 investigational sites. As of October 2, 2015, when the database was locked for this report, the average months implanted for subjects that received an INS was 12.6 (\pm 3.5) months in the Axium group, and 12.0 (\pm 2.3) months in the Control group. The cumulative INS months of implanted experience for subjects that received an INS device in the Axium group was 768 months (64 cumulative years), and in the Control group was 649.2 months (54.1 cumulative years).

The Statistical Analysis Plan (SAP) specified the use of the modified-intention-to-treat (MITT) analysis dataset for analyses of primary and secondary endpoints. Missing data sensitivity analyses, Intention-to-treat (ITT) and per-protocol (PP), were conducted to assess the robustness of the primary endpoint analysis.

The MITT analysis data set includes all 146 subjects (73 Axium, 73 Control) that were randomized and received a trial neurostimulator. Six subjects in the ITT analysis data set (3 in the Axium group and 3 in the Control group) were randomized, did not go on to have a TNS procedure, withdrew from the study prior to the TNS procedure, and are not included in the MITT analysis set. One Control subject in the MITT analysis data set had a TNS procedure but withdrew from the study prior to undergoing the end of TNS study visit. Since the subject withdrew due to a device-related adverse event, the subject is counted as a treatment failure. One Axium subject in the MITT data set had an INS procedure but withdrew from the study prior to the 3-month study visit. Since the subject withdrew due to a device-related adverse event, the subject is counted as a treatment failure. Another Axium subject in the MITT data set exited the study prior to their INS procedure due to a device-related adverse event post-TNS procedure. Since this subject withdrew due to a device related adverse event, the subject is counted as a treatment failure.

Seven subjects (four in the Axium group and three in the Control group) in the MITT analysis data set have no evaluable data for the study endpoints and are counted as missing because they withdrew from the study prior to the 3-month study visit, and did not meet any prospectively defined criteria for treatment failure/success at the time of study withdrawal.

The ITT population includes all 152 randomized subjects, 76 subjects in each group. The Per Protocol (PP) analysis set includes all randomized subjects who have valid data at baseline and the 3-month follow-up, and have no major protocol deviations that would potentially affect study outcomes. Major protocol deviations were defined prior to database lock.

The Control group had 16 major protocol deviations in 15 subjects. Twelve deviations were due to noncompliant programming, three deviations were due to performing the neurological examination without stimulation turned on, and one

deviation was due to the neurological examination not being done at a follow-up visit. The Axiom group had 1 subject with one major protocol deviation due to an incomplete neurological exam at a follow-up visit. These deviations did not change the conclusions drawn from the primary composite endpoint.

See Figure 2 below for a flow chart describing the subject accountability. Note in Figure 2, there are three subjects with missing visits at 12 months. One subject moved to another state. The site is in communication with the individual and the subject plans to return to the site for another visit at a time that is convenient and has not exited the study. One subject is lost to follow-up. The site has attempted to contact the subject and has sent a certified letter. There has been no response from the subject. One subject missed the 12-month visit but still is enrolled in the study and will be seen at the site as soon as a visit can be scheduled out of window for the 12-month assessment.

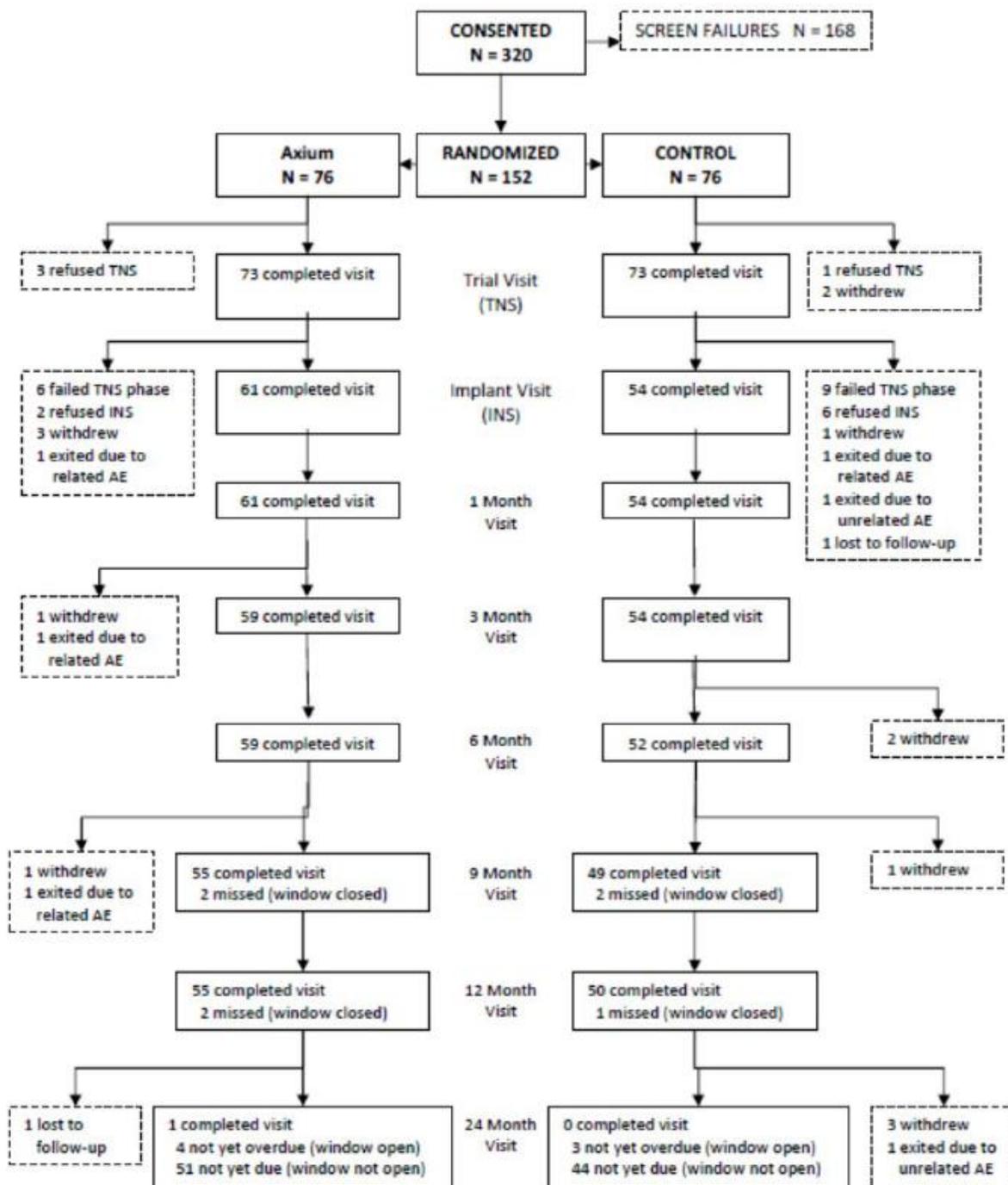


Figure 2: Subject Accountability

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a study of this type performed in the US. Table 8 presents information on key subject characteristics. No statistically significant differences were found among the baseline characteristics between the Axium group and the Control group. The average age of the subjects in the Axium and Control groups was 52.4 years and 52.5 years, respectively. The distribution of female gender in the Axium and Control groups was 51.3% and 51.3% respectively. Race was predominately white (94.7% and 92.1% Axium and Control, respectively). On average, subjects had an average BMI of 30.5 (Axium) and 28.9 (Control).

The distribution of Complex Regional Pain Syndrome (CRPS) (Axium 57.9% and Control 56.6%) and Peripheral Causalgia (Axium 42.1% and Control 43.4%) was similar between the groups. Subjects' medical history and prior surgeries were comparable for both groups, with average duration of lower extremity pain at 7.5 years (Axium) and 6.8 years (Control).

Table 8: Baseline Demographics and Characteristics

Baseline Characteristics	Axium N = 76	Control N = 76	p-value
Gender (% Female)	39/76 (51.3%)	39/76 (51.3%)	1.0000 ^{††}
Age in Years ± SD (Min., Max.)	52.4 ± 12.7 (23.9, 75.8)	52.5 ± 11.5 (25.4, 75.9)	0.9363 [*]
BMI (kg/m²) ± SD (Min., Max.)	30.5 ± 7.2 (16.9, 54.0)	28.9 ± 6.0 (17.4, 44.6)	0.1266 [*]
Duration of Lower Limb Pain in years ± SD (Min., Max.)	7.5 ± 7.5 (1.0, 39.0)	6.8 ± 7.6 (0.7, 51.0)	0.5571 ^{**}
Primary Diagnosis (n/N (%))			
Complex Regional Pain Syndrome	44/76 (57.9%)	43/76 (56.6%)	0.8698 ^{††}
Peripheral Causalgia	32/76 (42.1%)	33/76 (43.4%)	

*T-test, **Wilcoxon test, † Fisher exact test, †† Chi-square test

Baseline Lower Limb Pain Medications

Subjects' baseline lower limb pain medications were comparable between the Axium and Control groups (see Table 9). Opioids, anticonvulsants and nonsteroidal anti-inflammatory drugs (NSAIDs) were the most frequent medication classes taken by the subjects at the baseline visit. Opioids were taken by 60.5% (Axium) and 67.1% (Control) of subjects. Anticonvulsant medications were taken by 47.4% (Axium) and 46.1% (Control) of subjects. NSAIDs were taken by 48.7% (Axium) and 31.6% (Control) of subjects. There were no statistically significant differences in the use of lower limb pain medications, with the exception of NSAIDs.

Table 9: Baseline Pain Medication Usage for Lower Limb Pain by Medication Class

	Axium n/N (%)	Control n/N (%)	p-value
Analgesics	5/76 (6.6)	5/76 (6.6)	1.0000 ^{††}
Anticonvulsants	36/76 (47.4)	35/76 (46.1)	0.8709 ^{††}

	Axium n/N (%)	Control n/N (%)	p-value
Antidepressant	10/76 (13.2)	11/76 (14.5)	0.8142 ^{††}
Anxiolytics	2/76 (2.6)	1/76 (1.3)	1.0000 [†]
Hypnotics	0/76 (0.0)	0/76 (0.0)	N/A
Muscle Relaxant	6/76 (7.9)	5/76 (6.6)	0.7542 ^{††}
NSAIDs (OTC & prescription)	37/76 (48.7)	24/76 (31.6)	0.0315 ^{††}
Opioids (incl. synthetic and semisynthetic derivatives)	46/76 (60.5)	51/76 (67.1)	0.3987 ^{††}
Sedative	2/76 (2.6)	0/76 (0.0)	0.4967 [†]
Local Anesthetic	10/76 (13.2)	8/76 (10.5)	0.6156 ^{††}
Other	2/76 (2.6)	3/76 (3.9)	1.0000 [†]

†Fisher exact test, ††Chi-square test

Lower Limb Pain History

The subjects' lower limb pain history is summarized in Table 10. The distribution of Complex Regional Pain Syndrome (CRPS) (Axium 57.9% and Control 56.6%) and Peripheral Causalgia (Axium 42.1% and Control 43.4%) was similar between the groups. All subjects' diagnoses were confirmed by the Medical Monitor during his review.

The diagnostic criteria required for a diagnosis of CRPS were taken from the 1994 consensus statement from the International Association for the Study of Pain (IASP) (van Eijs et al., 2010). The CRPS diagnostic criteria were met when the following were present:

- Continuing pain that is disproportionate to any inciting event.
- At least 1 symptom reported in at least 3 of the following categories:
 - Sensory: Hyperesthesia or allodynia.
 - Vasomotor: Temperature asymmetry, skin color changes, skin color asymmetry.
 - Sudomotor/edema: Edema, sweating changes, or sweating asymmetry.
 - Motor/trophic: Decreased range of motion, motor dysfunction (e.g., weakness, tremor, dystonia), or trophic changes (e.g., hair, nail, skin).
- At least 1 sign at time of evaluation in at least 2 of the following categories.
 - Sensory: Evidence of hyperalgesia (to pinprick), allodynia (to light touch, temperature sensation, deep somatic pressure, or joint movement).
 - Vasomotor: Evidence of temperature asymmetry (>1°C), skin color changes or asymmetry.
 - Sudomotor/edema: Evidence of edema, sweating changes, or sweating symmetry.
 - Motor/trophic: Evidence of decreased range of motion, motor dysfunction (e.g., weakness, tremor, dystonia), or trophic changes (e.g., hair, nail, skin).

- No other diagnosis better explaining the signs and symptoms.

For peripheral causalgia, the diagnosis required that the subjects' chronic pain was due to damage to a nerve (Fishman et al., 2010). The pain was required to be in an anatomical area consistent with the innervation pattern of the damaged nerve (or nerves), and generally, in a hyperalgesic state. In some cases, the nerve damage progressed with secondary changes manifesting themselves. However, this was not a diagnostic requirement. Nerve damage typically resulted from blunt trauma (injury) or other types of injury such as post-surgical nerve cutting or lesioning.

Subjects' average duration of lower extremity pain is 7.5 years (Axium) and 6.8 years (Control). Subjects reported previous attempts to relieve lower extremity pain. Physical therapy, massage therapy, surgery, and injections (epidural steroid injections, sacroiliac joint injections and selective nerve blocks) were most frequently reported.

A primary region of pain targeted for treatment was identified by the investigators for each subject based on their baseline VAS pain assessment. The region with the highest VAS score consistent with the subjects' diagnoses was selected as the primary region of pain. Nine anatomical regions of the lower extremity were defined and subjects rated their pain intensity for each region on the 100mm VAS scale at baseline and at each scheduled visit. The distribution of primary regions of pain was comparable for the Axium and Control groups.

No statistically significant differences were observed in Lower Extremity Pain History indicating similar baseline characteristics; the two groups are balanced based on the randomization scheme.

Table 10: Lower Limb Pain History

Pain History Parameter	Axium N=76	Control N=76
Primary Diagnosis (n/N (%))		
Complex Regional Pain Syndrome	44/76 (57.9)	43/76 (56.6)
Peripheral Causalgia	32/76 (42.1)	33/76 (43.4)
P-value	0.8698 ^{††}	
Duration of CRPS Diagnosis (years)		
N	43	43
Mean (SD)	1.8 (4.1)	1.1 (2.1)
Median	0.4	0.2
Min. Max.	-0.0, 22.1	0.0, 9.9
P-value	0.5416 ^{**}	
Duration of PC Diagnosis (years)		
N	32	33
Mean (SD)	1.6 (5.1)	0.8 (2.7)
Median	0.0	0.0
Min. Max.	-0.0, 24.8	-0.0, 11.6
P-value	0.5401 ^{**}	
Duration of Lower Limb Pain (years)		
N	76	76

Pain History Parameter	Axium N=76	Control N=76
Mean (SD)	7.5 (7.5)	6.8 (7.6)
Median	5.0	4.5
Min. Max.	1.0, 39.0	0.7, 51.0
P-value	0.5571**	
Primary Region of Pain (n/N (%))		
Region 2 (right groin)	4/76 (5.3)	2/76 (2.6)
Region 3 (left groin)	4/76 (5.3)	7/76 (9.2)
Region 4 (right buttock)	1/76 (1.3)	2/76 (2.6)
Region 5 (left buttock)	2/76 (2.6)	2/76 (2.6)
Region 6 (right leg)	14/76 (18.4)	16/76 (21.1)
Region 7 (left leg)	8/76 (10.5)	11/76 (14.5)
Region 8 (right foot)	21/76 (27.6)	19/76 (25.0)
Region 9 (left foot)	22/76 (28.9)	17/76 (22.4)
P-value (Regions 2-5 vs. Regions 6/7 vs. Regions 8/9)	0.5228 ^{††}	
Previous Attempts to Relieve Lower Limb Pain (not mutually exclusive n/N (%))		
Massage therapy	39/76 (51.3)	33/76 (43.4)
Occupational therapy	18/76 (23.7)	13/76 (17.1)
Physical therapy	68/76 (89.5)	63/76 (82.9)
Lumbar sympathetic blocks	33/76 (43.4)	24/76 (31.6)
Facet blocks	6/76 (7.9)	5/76 (6.6)
Surgery for lower limb pain	40/76 (52.6)	40/76 (52.6)
Local anesthetic injection	33/76 (43.4)	26/76 (34.2)
Intradiscal electrothermal therapy (IDET)	1/76 (1.3)	1/76 (1.3)
Intrathecal injection	0/76 (0.0)	3/76 (3.9)
Drug pumps (e.g. intrathecal for chronic pain)	1/76 (1.3)	0/76 (0.0)
TENS unit	31/76 (40.8)	31/76 (40.8)
Sacroiliac joint injection	7/76 (9.2)	9/76 (11.8)
Epidural steroid injection	27/76 (35.5)	30/76 (39.5)
Pulsed or constant radiofrequency near the target DRG	4/76 (5.3)	5/76 (6.6)
Selective nerve blocks	27/76 (35.5)	23/76 (30.3)
Other	38/76 (50.0)	30/76 (39.5)

**Wilcoxon test, ^{††}Chi-square test

Implant Characteristics

The following four subgroups were defined: CRPS Type I - Unilateral, CRPS Type I - Bilateral, peripheral causalgia (aka CRPS II) - Unilateral, peripheral causalgia - Bilateral. Table 11 presents the number of Axium subjects in each subgroup, the number of leads implanted per subject in each sub-group, and the number of subjects in each sub-group with permanent leads at each spinal level. Table 12 presents the number of Control subjects in each subgroup, the number of leads implanted per subject in each sub-group, and the number of subjects in each sub-group with permanent leads at each spinal level.

Table 11: Leads Implanted in the Axium Group by Primary Diagnosis and Unilateral/Bilateral Pain - Axium

	Unilateral CRPS n/N (%)	Bilateral CRPS n/N (%)	Unilateral PC n/N (%)	Bilateral PC n/N (%)
Number of Subjects Implanted at INS	23/61 (37.7)	11/61 (18.0)	17/61 (27.9)	10/61 (16.4)
Number of Leads Implanted per Subject				
1 lead	7/23 (30.4)	0/11 (0.0)	6/17 (35.3)	0/10 (0.0)
2 leads	15/23 (65.2)	8/11 (72.7)	7/17 (41.2)	8/10 (80.0)
3 leads	1/23 (4.3)	1/11 (9.1)	3/17 (17.6)	0/10 (0.0)
4 leads	0/23 (0.0)	2/11 (18.2)	1/17 (5.9)	2/10 (20.0)
Level of Lead(s) Implanted Per Subject (not mutually exclusive)*				
T10	0/23 (0.0)	0/11 (0.0)	0/17 (0.0)	0/10 (0.0)
T11	1/23 (4.3)	0/11 (0.0)	0/17 (0.0)	0/10 (0.0)
T12	0/23 (0.0)	0/11 (0.0)	3/17 (17.6)	0/10 (0.0)
L1	4/23 (17.4)	2/11 (18.2)	5/17 (29.4)	0/10 (0.0)
L2	4/23 (17.4)	2/11 (18.2)	6/17 (35.3)	3/10 (30.0)
L3	7/23 (30.4)	2/11 (18.2)	3/17 (17.6)	1/10 (10.0)
L4	12/23 (52.2)	5/11 (45.5)	8/17 (47.1)	3/10 (30.0)
L5	12/23 (52.2)	7/11 (63.6)	7/17 (41.2)	6/10 (60.0)
S1	0/23 (0.0)	0/11 (0.0)	1/17 (5.9)	0/10 (0.0)
S2	0/23 (0.0)	0/11 (0.0)	0/17 (0.0)	0/10 (0.0)

* “Not mutually exclusive” refers to the fact that subjects may have up to 4 leads implanted in the Axium group. Subjects may have one or more leads implanted at one level or at multiple lead levels and are counted in multiple lead level categories. One lead may be implanted per DRG.

Table 12: Leads Implanted in the Control Group by Primary Diagnosis and Unilateral/Bilateral Pain

	Bilateral CRPS n/N (%)	Bilateral PC n/N (%)	Unilateral CRPS n/N (%)	Unilateral PC n/N (%)
Number of Subjects Implanted at INS	22/54 (40.7)	12/54 (22.2)	11/54 (20.4)	9/54 (16.7)
Number of Leads Implanted per Subject				
1 lead	1/22 (4.5)	0/12 (0.0)	2/11 (18.2)	1/9 (11.1)
2 leads	21/22 (95.5)	12/12 (100.0)	9/11 (81.8)	8/9 (88.9)
Level of Lead(s) Implanted Per Subject (not mutually exclusive)*				
T1	0/22 (0.0)	0/12 (0.0)	0/11 (0.0)	0/9 (0.0)
T2	0/22 (0.0)	0/12 (0.0)	0/11 (0.0)	0/9 (0.0)
T3	0/22 (0.0)	0/12 (0.0)	0/11 (0.0)	0/9 (0.0)
T4	0/22 (0.0)	0/12 (0.0)	0/11 (0.0)	0/9 (0.0)

	Bilateral CRPS n/N (%)	Bilateral PC n/N (%)	Unilateral CRPS n/N (%)	Unilateral PC n/N (%)
T5	0/22 (0.0)	0/12 (0.0)	0/11 (0.0)	0/9 (0.0)
T6	0/22 (0.0)	0/12 (0.0)	0/11 (0.0)	0/9 (0.0)
T7	0/22 (0.0)	0/12 (0.0)	0/11 (0.0)	1/9 (11.1)
T8	0/22 (0.0)	2/12 (16.7)	2/11 (18.2)	0/9 (0.0)
T9	2/22 (9.1)	2/12 (16.7)	3/11 (27.3)	3/9 (33.3)
T10	7/22 (31.8)	3/12 (25.0)	4/11 (36.4)	1/9 (11.1)
T11	8/22 (36.4)	2/12 (16.7)	1/11 (9.1)	1/9 (11.1)
T12	6/22 (27.3)	5/12 (41.7)	4/11 (36.4)	5/9 (55.6)

* “Not mutually exclusive” refers to the fact that subjects may have up to 2 leads implanted in the Control group. Subjects may have one or more leads implanted at one level or at multiple lead levels and are counted in multiple lead level categories.

Axium Programming Parameters

Table 13 presents a summary of the average amplitude, frequency and pulse width programmed settings for all Axium subjects over time. The median frequency was 20 Hz at all-time points; the median pulse width was 300 μ s at all time points except 12 months when it was 255 μ s. The median amplitude varied from 575 μ A to 687.5 μ A at the different time points. The median impedance ranged from 1225.5 Ω to 1355.0 Ω at the different time points.

Table 13: Summary of Axium Programmed Settings Based on Active Leads

	1 Month	3 Month	6 Month	9 Month	12 Month
Number of Subjects	61	59	59	55	55
Number of Active Leads	124	118	117	107	110
Frequency/Rate Range (Hz)					
N	123	118	117	107	110
Mean	22.5	20.8	20.0	19.0	19.0
SD	6.4	7.1	6.8	5.5	5.1
Median	20	20	20	20	20
Minimum	10	10	10	8	10
Maximum	40	48	48	40	36
Pulse Width (μs)					
N	124	118	117	107	110
Mean	312.4	308.9	315.4	295.6	289.8
SD	148.6	145.9	166.0	140.7	133.8
Median	300	300	300	300	255
Minimum	100	100	60	90	90
Maximum	1000	1000	1000	1000	1000

	1 Month	3 Month	6 Month	9 Month	12 Month
Amplitude (μA)					
N	122	118	116	107	107
Mean	892.3	915.4	836.4	764.6	827.4
SD	703.9	822	721.9	630.9	657.1
Median	687.5	675	650	575	650
Minimum	150	75	100	100	75
Maximum	4400	6000	4600	3950	4000
Impedance (Ω)					
N	116	116	114	107	110
Mean	1321.2	1431.7	1504.7	1583.9	1458.9
SD	527.9	571.4	700.4	792.8	714.5
Median	1225.5	1329.5	1324.5	1355.0	1256.5
Minimum	645	589	586	572	547
Maximum	5000	4795	5000	5000	4962

D. Safety and Effectiveness Results

1. Safety Results

As pre-specified in the Statistical Analysis Plan, the study primary composite endpoint data was analyzed using a modified intention to treat (MITT) analysis which included all subjects that were randomized and received a trial neurostimulator. The analysis of safety in the composite endpoint was based on 146 (73 Axium and 73 Control) evaluable subjects at the 3-month time point. The analysis of safety also included the intent-to-treat (ITT) population of 152 subjects (76 Axium and 76 Control) available for the 3 month evaluation and 105 subjects (55 Axium and 50 Control) available at 12 months. None of the study subjects experienced a primary composite endpoint safety event (stimulation induced neurological deficit) through 12 months and up to the date of the database lock.

The overall motor examination results indicate that most of the subjects in both groups experienced no change in their motor examination at three months (96.6% Axium and 100% Control had no change). None of the subjects in the Axium or Control groups experienced a worsening of motor scores. Improvement in the overall motor score occurred in three subjects in the Axium group and none of the subjects in the Control group.

The overall sensory examination results indicate that most of the subjects in both groups experienced no change in their sensory examination at three months (98.3% Axium and 98.1% Control had no change). None of the subjects in the Axium or Control group experienced a worsening of sensory scores. Improvement in sensory scores occurred in one subject in the Axium group, and two subjects in the Control group.

Serious Adverse Events

A total of 21 serious adverse events occurred in 19 subjects, four events in four subjects (Axium 1, Control 3) during the TNS phase, and 17 events in 15 subjects (Axium 7, Control 8) in the INS phase. The overall difference in the rate of SAEs between the groups was not statistically different (Axium 10.5%, Control 14.5%, $p=0.6248$); the rate during the TNS phase (Axium 1.3%, Control 3.9%, $p=0.62$), and INS phase (Axium 9.2%, Control 10.5%, $p=1.0$) also were not statistically different. See Table 14 below. There were no unanticipated AEs or deaths in the study.

Table 14: Percent of Subjects with SAEs

	Axium N=76	Control N=76	P-value
SAE during TNS Phase	(1/76) 1.3%	(3/76) 3.9%	0.6200
SAE during INS Phase	(7/76) 9.2%	(8/76) 10.5%	1.0000
Total	(8/76)10.5%	(11/76) 14.5%	0.6248

Fourteen of the serious adverse events resolved (6 with and 8 without sequelae). In the Control group, there were five unrelated SAEs and one device/procedure related SAE still ongoing at the time of the database lock on Oct. 2, 2015. In the Axium group there was one unrelated SAE still ongoing.

Eighteen of the 21 SAEs were unrelated to the implant procedure, device or stimulation therapy. Two of the SAEs in the Control group were definitely related to the implant procedure and/or device:

- One Control subject had an infection following the TNS procedure that required explantation of the system.
- A second Control subject had an infection following the INS procedure that required explantation of the system.

One Axium subject experienced an episode of atrial fibrillation in the recovery room following the INS implant that was adjudicated as possibly related to a pre-existing condition, the implant procedure or the device.

Table 15 and Table 16 present the serious adverse events (SAEs) reported for subjects in both the Axium and Control groups through the TNS and INS phases. The total rate of SAEs in the Axium group was not significantly different than the Control group.

Table 15: Distribution of Serious Adverse Events through the TNS Phase

Subsystem Code/Preferred Code	Axium N=76		Control N=76	
	Events N	Subjects n (%)	Events N	Subject n (%)
Total Serious Adverse Events (based on ITT)	1	1 (1.3)	3	3 (3.9)
Total Serious Adverse Events (based on At	1	1 (1.3)	3	3 (3.9)

Subsystem Code/Preferred Code	Axiom N=76		Control N=76	
	Events N	Subjects n (%)	Events N	Subject n (%)
Risk)[†]				
Blood Components / Abnormal Blood Chemistry	1	1 (1.3)	0	0 (0.0)
Lower Extremity / Bilateral Lower Leg Pain	0	0 (0.0)	1	1 (1.3)
Substance Related Disorders / Overdose	0	0 (0.0)	1	1 (1.3)
Wound Issue / Wound Infection	0	0 (0.0)	1	1 (1.3)

[†] Subjects at risk means are all randomized subjects, n=76 in each group

Table 16: Distribution of Serious Adverse Events through the INS Phase

Subsystem Code/Preferred Code	Axiom N=76		Control N=76	
	Events N	Subjects n (%)	Events N	Subject n (%)
Total Serious Adverse Events (based on ITT)	7	7 (9.2)	10	8 (10.5)
Total Serious Adverse Events (based on At Risk)¹	7	7 (11.5)	10	8 (14.8)
Degenerative Joint Disease / Arthritis ²	2	2 (2.6)	0	0 (0.0)
Bone / Bone Infection ³	1	1 (1.3)	0	0 (0.0)
Cardiac / Arrhythmia and Irregularities	1	1 (1.3)	0	0 (0.0)
Injury / ADL ⁴	1	1 (1.3)	0	0 (0.0)
Intestinal / Nausea and/or Vomiting	1	1 (1.3)	0	0 (0.0)
Joint or Muscle / Surgery	1	1 (1.3)	0	0 (0.0)
Blood Pressure / Hypertension	0	0 (0.0)	1	1 (1.3)
Dermatologic ⁵	0	0 (0.0)	1	1 (1.3)
Eyes or Ears or Nose or Throat (EENT) ⁶	0	0 (0.0)	1	1 (1.3)
Infection / Cellulitis	0	0 (0.0)	1	1 (1.3)
Infection / Systemic Infection or General or Unknown	0	0 (0.0)	1	1 (1.3)
Intestinal / Diverticulitis	0	0 (0.0)	1	1 (1.3)
Liver / Cirrhosis or Fatty Liver	0	0 (0.0)	1	1 (1.3)
Substance Related Disorders / Substance Dependence or Withdrawal	0	0 (0.0)	1	1 (1.3)
Trunk or Ribs / Trunk or Rib Pain	0	0 (0.0)	1	1 (1.3)
Wound Issue / Wound Infection	0	0 (0.0)	1	1 (1.3)

1. Subjects at risk means all subjects that underwent an INS procedure, (Axiom n=61, Control n=54).
2. One subject reported worsening of left shoulder arthritis. The subject was treated with left shoulder hemiarthroplasty for arthritis, cuff tear and biceps tendonitis. During the surgery a degenerative osteocartilagenous cyst was removed. A second subject had baseline ongoing condition of neck pain with previous cervical radiofrequency thermocoagulation. Three months post INS implant, the subject reported having surgery (ACF and discectomy at C4-5 and C5-6) due to cervical spondylosis with radiculitis.
3. Subject reported osteomyelitis of right great toe. The subject's right toe was run over by a cart while working and the right toe started to become red/black. The subject then went to the hospital and was admitted. The subject presented to the hospital with worsening swelling with a ½ cm diameter deep ulceration and discharge of the right great toe. The subject was started on IV antibiotics (vancomycin) and underwent a great right toe amputation at the MTPJ level.
4. The subject reported a chainsaw cutting incident in which he broke his left leg (tibia bone near the knee).
5. The subject was noted to have an ulcer of the left plantar foot (neuropathic foot ulcer sub left 1st metatarsal heal with a dry neurotic base and large periwound keratosis). The subject has a medical history

of diabetes. The subject was treated with an excisional debridement of the ulcer and application of a Aquacel AG dressing.

6. The subject reported loss of vision in the right eye. The subject did not receive any treatment from the investigator but it was noted that the subject was being evaluated and treated by an ophthalmologist.

Adverse Events by Relatedness to Implant Procedure, Device or Stimulation Therapy

Adverse events were classified by the DSMB as device-, procedure-, and/or stimulation-related. Note that the categories of device related, procedure related and stimulation related are not mutually exclusive. For some events the DSMB adjudicated an event as related to multiple categories such as device and procedure related, or device and stimulation related, etc.

As seen in Table 17, which represents the ITT population, the rates of device- and stimulation-related events were not statistically different between the groups. However, procedure-related AEs were more frequent in the Axium group (52 events in 35 of 76 subjects (46.1% of subjects)) than the Control group (29 events in 20 of 76 subjects (26.3% of subjects)) (p=0.0177).

Table 17: Definitely Related Adverse Event Rates – ITT Population

Adverse Event Characteristic	Axium N=76		Control N=76		P-value
	Events	Subjects n (%)	Events	Subjects n (%)	
Relatedness to Neurostimulator System/ Device	39	28 (36.8%)	24	20 (26.3%)	0.2217
Relatedness to Implant Procedure	52	35 (46.1%)	29	20 (26.3%)	0.0177
Relatedness to Stimulation Therapy	10	8 (10.5%)	10	10 (13.2%)	0.8025

In analyzing the procedure-related adverse events the MITT data analysis set (all subjects that had a TNS procedure; Axium = 73 subjects and Control = 73 Subjects)) is used since it represents data specifically related to subjects’ and physicians experience with Axium device implantation procedures. The number of leads implanted presented in Table 18 includes the leads implanted during the TNS and INS procedures the subject underwent. For example, if a subject had four DRG leads implanted at TNS, and four DRG leads at INS, the subject would be counted in the table as having eight leads implanted. The subjects excluded from the MITT data analysis set were not exposed to any implant procedure; therefore, the MITT data set is the most relevant for looking at procedure related AEs. As shown in Table 18, the number of subjects with procedure related events in the Axium group is associated with the number of leads implanted per subject. This may be expected since individual needle sticks are required to implant each Axium lead during a procedure (up to four leads), in contrast to the fewer needle sticks typically used to implant one or two leads during a Control procedure. The results show an increasing linear relationship between the number of Axium leads implanted and the number of subjects with procedure-related events,

ranging from zero events in two subjects with one lead implanted, to eight events in eight subjects with six leads implanted. There is no apparent increasing linear relationship between the number of leads implanted and the number of Control subjects with procedure-related events.

Table 18: Subjects with Definitely Related Procedure Adverse Events by Leads Implanted

Number of Leads Implanted	Axium		Control	
	Subjects Implanted n/N (%)	Subjects with Adverse Events n/N (%)	Subjects Implanted n/N (%)	Subjects with Adverse Events Nn/N (%)
1 lead	2/73 (2.7)	0/2 (0.0)	3/73 (4.1)	2/3 (66.7)
2 leads	16/73 (21.9)	5/16 (31.3)	20/73 (27.4)	4/20 (20.0)
3 leads	10/73 (13.7)	3/10 (30.0)	7/73 (9.6)	3/7 (42.9)
4 leads	26/73 (35.6)	13/26 (50.0)	38/73 (52.1)	9/38 (23.7)
5 leads	4/73 (5.5)	2/4 (50.0)	2/73 (2.7)	1/2 (50.0)
6 leads	9/73 (12.3)	9/9 (100.0)	3/73 (4.1)	1/3 (33.3)
7 leads	2/73 (2.7)	0/2 (0.0)	0/73 (0.0)	--
8 leads	4/73 (5.5)	3/4 (75.0)	0/73 (0.0)	--
Total	73/73 (100.0)	35/73 (47.9)	73/73 (100.0)	20/73 (27.4)

Table 19 presents the distribution and time course of all definitely related adverse events by time course (regardless of seriousness). The most frequently occurring procedure related adverse events in the Axium group were pain at the incision site and post-procedure back pain. The most frequently occurring device related adverse events in Axium subjects were lead migration/loss of stimulation, INS pocket pain, and lead breakage. The most frequently occurring stimulation related adverse event in the Axium group was over-stimulation.

The most frequently occurring procedure related adverse events in the Control group were pain at the incision site, post-procedure back pain, and wound infection. The most frequently occurring device related adverse events in Control subjects were lead migration/loss of stimulation, INS pocket pain, and wound infection. The most frequently occurring stimulation related adverse event in the Control group was over-stimulation.

Table 19: Time Course of Definitely Related Adverse Events

Subsystem Code/Preferred Code	Through TNS Phase		INS to 30 days		>30 days to 3 Months		>3 Months to 6 Months		>6 Months to 12 Months		>12 Months	
	AX	C	AX	C	AX	C	AX	C	AX	C	AX	C
Total Adverse Events	28	20	22	16	11	10	13	3	9	5	3	0
Subjects At Risk	76	76	61	54	61	54	59	54	59	52	55	50
INS Pocket / INS Pocket Pain	0	0	2	0	2	3	4	0	2	1	0	0
Lead / Migration -Loss of Stimulation	3	5	3	2	0	0	2	0	1	1	0	0
Wound Issue / Pain at Incision Site	0	1	5	2	1	2	1	0	0	0	0	0
Lead / Breakage	0	0	0	0	1	0	3	0	2	0	0	0
Back / Back Pain	4	4	0	1	0	1	0	0	1	0	0	0

Subsystem Code/Preferred Code	Through TNS Phase		INS to 30 days		>30 days to 3 Months		>3 Months to 6 Months		>6 Months to 12 Months		>12 Months	
	AX	C	AX	C	AX	C	AX	C	AX	C	AX	C
Side Effect / Procedure Medication	3	2	1	0	0	0	0	0	0	0	0	0
Unknown device component / Loss Stimulation	0	0	0	0	2	0	1	0	1	0	0	0
Stimulation / Overstimulation	0	1	1	2	0	0	0	1	1	1	1	0
Wound Issue / Erythema or Drainage or Inflammation	1	0	2	1	0	0	0	0	0	0	0	0
Allergic Reaction / Procedure Medications or dressings	2	0	1	0	0	0	0	0	0	0	0	0
Stimulation / Understimulation	1	0	1	0	1	0	0	0	0	0	0	0
Lower Extremity / Unilateral Lower Leg Pain	1	1	1	0	0	0	0	0	0	0	0	0
Fever / Fever or Pyrexia	1	0	1	0	0	0	0	0	0	0	0	0
Lead / Migration - Observation only	1	0	0	0	0	0	1	0	0	0	0	0
Lead / Severed	2	0	0	0	0	0	0	0	0	0	0	0
Procedural complications / Dural puncture	2	0	0	0	0	0	0	0	0	0	0	0
Foot / Foot Pain	0	0	0	1	0	1	1	0	0	0	0	0
Patient Programmer / Loss of Stimulation	0	0	0	0	0	0	0	0	0	2	1	0
Back and Lower Extremity / Back Pain and Unilateral Radiation into Upper Leg	1	0	0	0	0	1	0	0	0	0	0	0
Head and Neck /Headache	1	1	0	0	0	0	0	0	0	0	0	0
Lower Extremity/ Unilateral Upper Leg Pain	0	1	1	0	0	0	0	0	0	0	0	0
Sensory Deficit / Sensory Deficit Subjective - Bilateral	0	0	0	1	1	0	0	0	0	0	0	0
Blood Loss / More than Expected	0	0	1	0	0	0	0	0	0	0	0	0
Connector cable / Loss of stimulation	1	0	0	0	0	0	0	0	0	0	0	0
Dermatologic	1	0	0	0	0	0	0	0	0	0	0	0
Fluid Volume Balance / Edema - other	1	0	0	0	0	0	0	0	0	0	0	0
Head and Neck / Restlessness or Agitation	1	0	0	0	0	0	0	0	0	0	0	0
INS / Battery depletion	0	0	0	0	1	0	0	0	0	0	0	0
Joint or Muscle / Pulled or Strained Muscle or Muscle Cramp	1	0	0	0	0	0	0	0	0	0	0	0
Lead / Retained Lead(s)	0	0	0	0	0	0	0	0	0	0	1	0
Lower Extremity / Bilateral Lower Leg Pain	0	0	0	0	1	0	0	0	0	0	0	0
Reproductive / Vaginal or Yeast Infection	0	0	1	0	0	0	0	0	0	0	0	0

Subsystem Code/Preferred Code	Through TNS Phase		INS to 30 days		>30 days to 3 Months		>3 Months to 6 Months		>6 Months to 12 Months		>12 Months	
	AX	C	AX	C	AX	C	AX	C	AX	C	AX	C
Sensory Deficit / Sensory Deficit Measureable - Unilateral	0	0	1	0	0	0	0	0	0	0	0	0
Urinary / Urinary Urgency	0	0	0	0	1	0	0	0	0	0	0	0
Wound Issue / Deep	0	0	0	0	0	0	0	0	1	0	0	0
Wound Issue / Wound Infection	0	2	0	2	0	0	0	2	0	0	0	0
Muscle Spasms / Muscle Spasm	0	0	0	0	0	2	0	0	0	0	0	0
Urinary / Urinary Hesitance	0	1	0	1	0	0	0	0	0	0	0	0
Knee / Knee Pain	0	0	0	1	0	0	0	0	0	0	0	0
Sensory Deficit / Sensory Deficit Subjective - Unilateral	0	1	0	0	0	0	0	0	0	0	0	0
Substance Related Disorders / Substance Dependence or Withdrawal	0	0	0	1	0	0	0	0	0	0	0	0
Wound Issue / Incisional cellulitis	0	0	0	1	0	0	0	0	0	0	0	0

Axiom Device Complaints

When a site reported a device performance issue, a Complaint was submitted to the Spinal Modulation (SMI) Quality system, and when appropriate, the device component that had the performance issue was returned to SMI for analysis. In addition, all adverse events that were reported by investigators and adjudicated by the DSMB as related to the implant procedure, the device, or stimulation therapy were evaluated for whether a complaint should be reported as well. Table 58 presents a summary of complaints by complaint category. The complaint summary lists all events reported into the SMI quality system as complaints. The events are categorized into five main areas:

- Hardware-related complaints refer to non-procedural events related to the product, including the Clinical and Patient Programmers, stimulators, leads, accessories, and packaging.
- Intra-operative complaints are segmented into two categories:
 - o Events that are probably or likely related to the procedure
 - o Physiological events that occurred during the operative procedure
- Post-operative events occurred after the TNS or INS procedure during normal use of the therapy. The complaints have been segmented into two categories:
 - o Physiological
 - o Device-related

A total of 59 of 73 Axium subjects experienced a complaint (80.8%). Note that not all complaints were associated with an adverse event. In the trial, 43.8% (67/153) of all Axium complaints were associated with an adverse event. The most frequently reported device complaints were kinked sheaths (21 events in 19 subjects, 26% of subjects) and connector-cable related events (21 events in 19 subjects, 26% of subjects). Lead migration requiring a replacement procedure occurred in 6.8% of subjects (5/73). Two subjects (2.7%) had lead breakage during an explant procedure that resulted in lead fragments being retained in the body, two subjects had a dural puncture during implant (2.7%), and one subject (1.4%) had a loss of urinary sensation. See Table 20 below for a summary of complaints associated with the Axium device.

Table 20: Axium Complaints Summary

Category	Number of Complaints	Number of Subjects with a Complaint	Percentage of Subjects with a Complaint
Hardware-related	52	43	58.9%
Clinical Programmer	14	11	15.1%
Impedance Measurement	4	4	5.5%
Frozen Clinical Programmer Screen	3	3	4.1%
Communication	2	2	2.7%
Clinical Programmer Charging	2	2	2.7%
Misalignment Clinical Programmer Screen	1	1	1.4%
Programmer Battery	1	1	1.4%
Clinical Programmer Software Hard Reset	1	1	1.4%
Patient Programmer	10	9	13.7%
Patient Programmer Charging	5	5	6.8%
Frozen Patient Programmer Screen	3	3	4.1%
Communication	2	2	2.7%
TNS	2	2	2.7%
TNS Label Adhesion	2	2	2.7%
Lead Migration Requiring Revision	5	5	6.8%
During Trial Phase	2	2	2.7%
Post-implant (<30 days)	2	2	2.7%
Post-implant (>30 days)	1	1	1.4%
Connector Cable	21	19	26.0%
Connector Cable-Block	12	11	14.5%
Connector Cable-Hood	6	6	8.2%
Connector Cable-Damaged	2	2	2.7%
Connector Cable-Clip	1	1	1.4%
Intra-operative events (procedural related)	43	41	56.2%
Kinked Sheath	21	19	26.0%
Stylet Reinsertion into Lead	7	7	9.6%
Lead Damaged at Implant	3	3	4.1%
Lead Fragments	2	2	2.7%
Dural Puncture	2	2	2.7%
Lead Movement Without Clinical Effect	2	2	2.7%
Kinked Lead	1	1	1.4%
Tyvek tears	1	1	1.4%
Foot drop	1	1	1.4%
User product preference	1	1	1.4%

Category	Number of Complaints	Number of Subjects with a Complaint	Percentage of Subjects with a Complaint
Sciatica	1	1	1.4%
Lower Extremity numbness	1	1	1.4%
Post-operative events (physiological)	41	36	49.3%
Incisional discomfort after INS	9	7	9.6%
Post-procedure lower extremity discomfort	9	6	7.9%
Fever	3	3	4.1%
Incisional Erythema	3	3	4.1%
Allergic reaction to dressing	2	2	2.7%
Incisional discomfort after TNS	2	2	2.7%
Low back pain after TNS	2	2	2.7%
Nausea after TNS	1	1	1.4%
Impedance Measurement	1	1	1.4%
Headache	1	1	1.4%
Inadequate pain relief/positional changes	1	1	1.4%
Rash after TNS	1	1	1.4%
Programming	1	1	1.4%
Tinea Cruris	1	1	1.4%
Discomfort at extension connection site	1	1	1.4%
Discomfort at INS site	1	1	1.4%
Electrical sensation	1	1	1.4%
Lesion over INS pocket	1	1	1.4%
Post-operative events (device related)	15	14	19.2%
Low Impedance	4	3	4.1%
INS Replacement	2	2	2.7%
Lead Movement Requiring Reprogramming	2	2	2.7%
Lead Fracture	2	2	2.7%
High Impedance	1	1	1.4%
Loss of therapy	1	1	1.4%
Loss of sense of urination	1	1	1.4%
Pocket stimulation after INS	1	1	1.4%
Lead Movement Without Clinical Effect	1	1	1.4%
Intra-operative events (physiological)	2	2	2.7%
New onset Atrial Fibrillation at INS procedure	1	1	1.4%
Excess blood loss at INS procedure	1	1	1.4%
Total Complaints	153		

All Adverse Events

Investigators reported all adverse events whether or not the event was serious or related to the study devices, implant procedures, or stimulation therapy. Table 21 presents the distribution of all adjudicated adverse events reported and adjudicated at the time of the database lock. There were 241 adverse events in 62 subjects (81.6%) in the Axium group and 161 adverse events in 55 subjects (72.4%) in the Control group ($p = 0.2575$). There were 24 un-adjudicated adverse events in 17 subjects at the time of the database lock. None were reported as serious adverse events by the investigators, and two events of INS pocket pain were classified as possibly related to the device and/or procedure by the investigators.

Table 21: Distribution of All Adverse Events

Subsystem Code/Preferred Code	Axiom N=76		Control N=76	
	Events N	Subjects n (%)	Events N	Subjects n (%)
Total Adverse Events (based on ITT)	241	62 (81.6)	161	55 (72.4)
Total Adverse Events (based on At Risk)	241	62 (81.6)	161	55 (72.4)
INS Pocket / INS Pocket Pain	11	11 (14.5)	6	5 (6.6)
Lead / Migration -Loss of Stimulation	10	9 (11.8)	9	9 (11.8)
Dermatologic	9	6 (7.9)	5	5 (6.6)
Injury / ADL	9	8 (10.5)	3	3 (3.9)
Back / Back Pain	8	8 (10.5)	10	9 (11.8)
Wound Issue / Pain at Incision Site	8	7 (9.2)	6	6 (7.9)
Eyes or Ears or Nose or Throat (EENT)	7	6 (7.9)	11	8 (10.5)
Lead / Breakage	6	5 (6.6)	0	0 (0.0)
Side Effect / Procedure Medication	5	3 (3.9)	5	4 (5.3)
Injury / Fall or Trip or Slip or Twist	5	5 (6.6)	4	4 (5.3)
Sinus / Sinus Infection or Sinusitis	5	5 (6.6)	4	3 (3.9)
Foot / Foot Pain	5	5 (6.6)	3	2 (2.6)
Lower Extremity / Unilateral Upper Leg Pain	5	5 (6.6)	3	3 (3.9)
Intestinal / Nausea and/or Vomiting	5	5 (6.6)	1	1 (1.3)
Allergic Reaction / Procedure Medications or dressings	5	4 (5.3)	0	0 (0.0)
Unknown device component / Loss of Stimulation	5	5 (6.6)	0	0 (0.0)
Stimulation / Overstimulation	4	4 (5.3)	5	5 (6.6)
Head and Neck / Headache	4	3 (3.9)	2	2 (2.6)
Joint or Muscle / Bursitis	4	4 (5.3)	1	1 (1.3)
Knee / Knee Pain	4	4 (5.3)	1	1 (1.3)
Upper Respiratory Symptoms / Upper Respiratory Symptoms	3	3 (3.9)	4	4 (5.3)
Joint or Muscle / Pulled or Strained Muscle or Muscle Cramp	3	3 (3.9)	3	2 (2.6)
Substance Related Disorders / Substance Dependence or Withdrawal	3	3 (3.9)	3	3 (3.9)
Lower Extremity / Bilateral Lower Leg Pain	3	3 (3.9)	2	2 (2.6)
Wound Issue / Erythema or Drainage or Inflammation	3	3 (3.9)	2	2 (2.6)
Degenerative Joint Disease / Arthritis	3	3 (3.9)	1	1 (1.3)
Upper Extremity / Upper Extremities Pain	3	3 (3.9)	1	1 (1.3)
Urinary / Urinary Tract Infection	3	3 (3.9)	1	1 (1.3)
Blood Components / Abnormal Blood Chemistry	3	3 (3.9)	0	0 (0.0)
Bone / Bone Fracture	3	3 (3.9)	0	0 (0.0)
Fever / Fever or Pyrexia	3	3 (3.9)	0	0 (0.0)
Motor Deficit / Motor Deficit Subjective - Unilateral	3	3 (3.9)	0	0 (0.0)
Stimulation / Understimulation	3	3 (3.9)	0	0 (0.0)
Sensory Deficit / Sensory Deficit Subjective - Unilateral	2	2 (2.6)	3	2 (2.6)
Gastric / Gastroenteritis or Stomach Flu	2	2 (2.6)	2	2 (2.6)
Lower Extremity / Unilateral Lower Leg Pain	2	2 (2.6)	2	2 (2.6)

Subsystem Code/Preferred Code	Axium N=76		Control N=76	
	Events N	Subjects n (%)	Events N	Subjects n (%)
Lung / Bronchitis	2	2 (2.6)	2	2 (2.6)
Back and Lower Extremity / Back Pain and Unilateral Radiation into Lower Leg	2	2 (2.6)	1	1 (1.3)
Gastric / Abdominal Pain	2	2 (2.6)	1	1 (1.3)
Lung / Respiratory Infection	2	2 (2.6)	1	1 (1.3)
Sensory Deficit / Sensory Deficit Subjective - Bilateral	2	2 (2.6)	1	1 (1.3)
Trunk or Ribs / Trunk or Rib Pain	2	2 (2.6)	1	1 (1.3)
Cardiac / Arrhythmia and Irregularities	2	2 (2.6)	0	0 (0.0)
Fluid Volume Balance / Edema - lower extremities	2	2 (2.6)	0	0 (0.0)
Intestinal / Constipation	2	2 (2.6)	0	0 (0.0)
Intestinal / Diarrhea	2	2 (2.6)	0	0 (0.0)
Joint or Muscle / Inflammation of Muscle	2	2 (2.6)	0	0 (0.0)
Joint or Muscle / Joint Sprain	2	2 (2.6)	0	0 (0.0)
Lead / Migration - Observation only	2	2 (2.6)	0	0 (0.0)
Lead / Severed	2	2 (2.6)	0	0 (0.0)
Pancreas / Diabetes Mellitus	2	2 (2.6)	0	0 (0.0)
Procedural complications / Dural puncture	2	2 (2.6)	0	0 (0.0)
Blood Pressure / Hypertension	1	1 (1.3)	3	3 (3.9)
Neck or Cervical / Neck or Cervical Pain	1	1 (1.3)	3	3 (3.9)
Reflex / Reflex Change or Abnormality	1	1 (1.3)	3	3 (3.9)
Back and Lower Extremity / Back Pain and Unilateral Radiation into Upper Leg	1	1 (1.3)	2	2 (2.6)
Patient Programmer / Loss of Stimulation	1	1 (1.3)	2	2 (2.6)
Foot or Ankle or Toe / Plantar fasciitis	1	1 (1.3)	1	1 (1.3)
Hip Joint / Hip Joint Pain and Discomfort	1	1 (1.3)	1	1 (1.3)
Infection / Systemic Infection or General or Unknown	1	1 (1.3)	1	1 (1.3)
Joint or Muscle / Sacroiliitis	1	1 (1.3)	1	1 (1.3)
Liver / Cirrhosis or Fatty Liver	1	1 (1.3)	1	1 (1.3)
Lung / COPD (Chronic Obstructive Pulmonary Disease)	1	1 (1.3)	1	1 (1.3)
SI Joint / SI Joint Pain and Discomfort	1	1 (1.3)	1	1 (1.3)
Sleep Disorders / Insomnia	1	1 (1.3)	1	1 (1.3)
Autoimmune Disorder / Celiac disease	1	1 (1.3)	0	0 (0.0)
Blood Loss / More than Expected	1	1 (1.3)	0	0 (0.0)
Bone / Bone Infection	1	1 (1.3)	0	0 (0.0)
Connector cable / Loss of stimulation	1	1 (1.3)	0	0 (0.0)
Fluid Volume Balance / Dehydration	1	1 (1.3)	0	0 (0.0)
Fluid Volume Balance / Edema - other	1	1 (1.3)	0	0 (0.0)
Foot or Ankle or Toe / Foot or Feet Problem - Other	1	1 (1.3)	0	0 (0.0)
Gall Bladder / Cholelithiasis or Gallstones	1	1 (1.3)	0	0 (0.0)
Gastric / Dyspepsia or Indigestion	1	1 (1.3)	0	0 (0.0)
Head and Neck / Restlessness or Agitation	1	1 (1.3)	0	0 (0.0)
INS / Battery depletion	1	1 (1.3)	0	0 (0.0)
Infection / Viral Infection	1	1 (1.3)	0	0 (0.0)
Injury / Motor Vehicle Accident	1	1 (1.3)	0	0 (0.0)
Intestinal / Irritable Bowel Syndrome	1	1 (1.3)	0	0 (0.0)

Subsystem Code/Preferred Code	Axium N=76		Control N=76	
	Events N	Subjects n (%)	Events N	Subjects n (%)
Joint or Muscle / Surgery	1	1 (1.3)	0	0 (0.0)
Lead / Retained Lead(s)	1	1 (1.3)	0	0 (0.0)
Lung / Pneumonia	1	1 (1.3)	0	0 (0.0)
Prostate / Prostate Cancer	1	1 (1.3)	0	0 (0.0)
Psychosocial Disorders / Depressive Disorders	1	1 (1.3)	0	0 (0.0)
Reproductive / Vaginal or Yeast Infection	1	1 (1.3)	0	0 (0.0)
Sensory Deficit / Sensory Deficit Measureable - Unilateral	1	1 (1.3)	0	0 (0.0)
Spine / Degenerative Disc Disease Progression	1	1 (1.3)	0	0 (0.0)
Surgery / TURP	1	1 (1.3)	0	0 (0.0)
Upper Extremities / Upper Extremity Sensory Deficit - Unilateral	1	1 (1.3)	0	0 (0.0)
Urinary / Urinary Urgency	1	1 (1.3)	0	0 (0.0)
Whole Body / Chronic Pain Syndrome	1	1 (1.3)	0	0 (0.0)
Wound Issue / Deep	1	1 (1.3)	0	0 (0.0)
Wound Issue / Wound Infection	0	0 (0.0)	7	5 (6.6)
Cardiac / Cardiac Chest Pain	0	0 (0.0)	3	3 (3.9)
Muscle Spasms / Muscle Spasm	0	0 (0.0)	2	2 (2.6)
Urinary / Urinary Hesitance	0	0 (0.0)	2	1 (1.3)
Back and Lower Extremity / Back Pain and Bilateral Radiation into Lower Leg	0	0 (0.0)	1	1 (1.3)
Gastric / Acid Reflux	0	0 (0.0)	1	1 (1.3)
Head and Neck / Migraine	0	0 (0.0)	1	1 (1.3)
Hormones / Decreased Testosterone	0	0 (0.0)	1	1 (1.3)
Infection / Cellulitis	0	0 (0.0)	1	1 (1.3)
Intestinal / Diverticulitis	0	0 (0.0)	1	1 (1.3)
Joint or Muscle / Trigger Finger or Stenosing Tenosynovitis	0	0 (0.0)	1	1 (1.3)
Kidney / Kidney Problems - Other	0	0 (0.0)	1	1 (1.3)
Lipid Metabolism / Hypercholesterolemia or High Cholesterol or Hyperlipidemia	0	0 (0.0)	1	1 (1.3)
Lung / Asthma	0	0 (0.0)	1	1 (1.3)
Skin / Melanoma	0	0 (0.0)	1	1 (1.3)
Sleep Disorders / Fatigue or Sleepiness or Somnolence	0	0 (0.0)	1	1 (1.3)
Substance Related Disorders / Overdose	0	0 (0.0)	1	1 (1.3)
Upper Extremities / Carpal tunnel	0	0 (0.0)	1	1 (1.3)
Wound Issue / Abscess	0	0 (0.0)	1	1 (1.3)
Wound Issue / Incisional cellulitis	0	0 (0.0)	1	1 (1.3)

Device Replacements, Revisions and Explants through 12 Months

Table 22 summarizes the frequency of replacements of external device components (i.e., TNS, TNS connector cable, and patient programmer) through 12 months.

Table 22: Replacement of External Components

	Axium		Control	
	TNS	INS	TNS	INS
Number of External Component Replacement Procedures	11	11	0	5
Replacement of External Components				
Connector Cable	10	0	0	0
Patient Programmer	0	11	0	5
TNS and Patient Programmer	1	0	0	0

A summary of the device replacements, revisions, and explants is presented in Table 23. Note that Axium leads are not able to be revised (e.g., same lead moved to an alternate location), but Control leads may be revised. If an Axium lead has an issue, the lead must be replaced with a new lead.

Table 23: Subsequent Replacement, Revision, or Explant Procedures through 12 Months

	Axium	Control
INS or INS Lead Replacement/Revisions	8	4
TNS Lead Revision	0	1
INS System Replacement/Revision	5	1
TNS System Replacement/Revision	4	3
INS/TNS Lead Addition	4	0
INS System Explant	5	4

2. Effectiveness Results

As pre-specified in the Statistical Analysis Plan (SAP), the study primary composite endpoint data was analyzed using a modified intention to treat (MITT) analysis which included all subjects that were randomized and received a trial neurostimulator. The analysis of effectiveness was based on 146 (73 Axium and 73 Control) evaluable subjects at the 3-month time point. Intention-to-treat (ITT) and per-protocol (PP) analyses were also performed.

See Figure 3 below for a disposition of subjects by analysis data set. One Control subject in the MITT analysis data set had a TNS procedure but withdrew from the study prior to undergoing the end of TNS-study visit. Since the subject withdrew due to a device-related adverse event, the subject is counted as a treatment failure based on the definitions of treatment success and failure, as pre-specified in the SAP. One Axium subject in the MITT data set had an INS procedure but withdrew from the study prior to the 3-month study visit. Since the subject withdrew due to a device-related adverse event, the subject is counted as a treatment failure based on the definitions of treatment success and failure, as pre-specified in the SAP. Another Axium subject in the MITT data set exited the study prior to their INS procedure due to a device-related adverse event post-TNS procedure. Since this subject withdrew due to a device related adverse event, the subject is counted as a treatment failure based on the definitions of treatment success and failure, as pre-specified in the SAP. Seven subjects (four in the Axium group and three in the Control group) in the MITT analysis data set have no evaluable data for the study endpoints at three months and are counted as

missing because they withdrew from the study prior to the 3-month study visit, and did not meet any prospectively defined criteria for treatment failure/success at the time of study withdrawal. Six subjects in the ITT analysis data set (three in the Axium group and three in the Control group) were randomized, did not go on to have a TNS procedure, withdrew from the study prior to the TNS procedure, and are not included in the MITT analysis set.

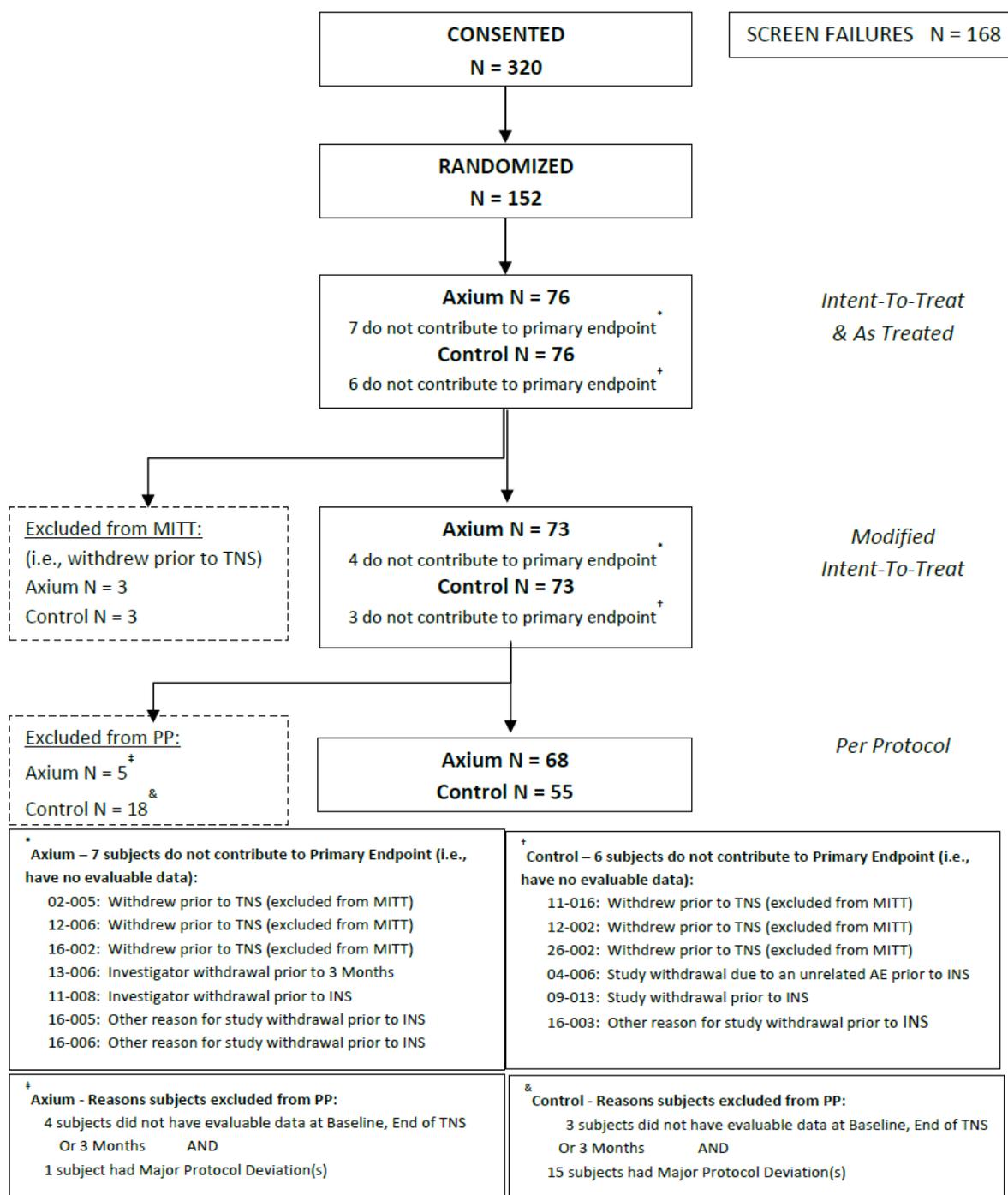


Figure 3: Subject Disposition by Analysis Data Set

Primary Composite Endpoint

The results of the primary endpoint (MITT analysis) are presented in Table 24. As shown in Table 24, treatment success in the Axium group at 3 months was 81.2% and treatment success in the Control group was 55.7% at three months. None of the study subjects experienced a primary composite endpoint safety event (stimulation induced neurological deficit). The results demonstrate the non-inferiority ($p < 0.0001$) and superiority ($p = 0.0004$) of Axium therapy over the Control therapy for the primary composite endpoint as defined in the Statistical Analysis Plan.

Table 24: Primary Composite Endpoint Treatment Success through 3 Months

Primary Endpoint Component	Axium	Control
Number of Subjects - MITT analysis data set	73	73
Number of Subjects-Primary endpoint analysis [†]	69	70
Overall primary endpoint success		
n/N (%)	56/69 (81.2)	39/70 (55.7)
95% CI	(69.9, 89.6)	(43.3, 67.6)
Success rate difference (%) and 95% CI (Blackwelder)	25.4 (13.0, 100.0)	
P-value (non-inferiority $\delta = 10\%$)	<0.0001	
P-value (superiority)	0.0004	

[†] Subjects excluded since they do not have evaluable data: Axium=4, Control=3. Seven subjects in the MITT analysis have no evaluable data for the study endpoints because they withdrew from the study prior to the 3-month study visit, and did not meet any prospectively defined criteria for treatment failure/success at the time of study withdrawal. Therefore, the number of subjects in the MITT analysis that have evaluable data for the analysis of this endpoint is 69 subjects in the Axium group, and 70 subjects in the Control group.

Figure 4 and Figure 5 below show the percent improvement at the 3-month follow-up as compared to baseline for the Axium subjects and the Control subjects.

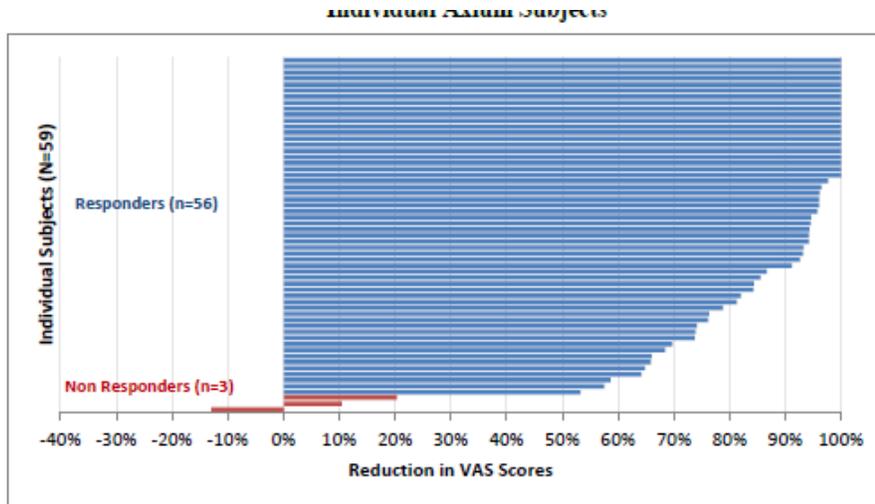


Figure 4: Percent Improvement in Pain from Baseline to 3 Months Post INS Implant Individual Axiom Subjects[‡]

[‡] Fifteen responders decreased their pain medications; three responders increased their pain medications

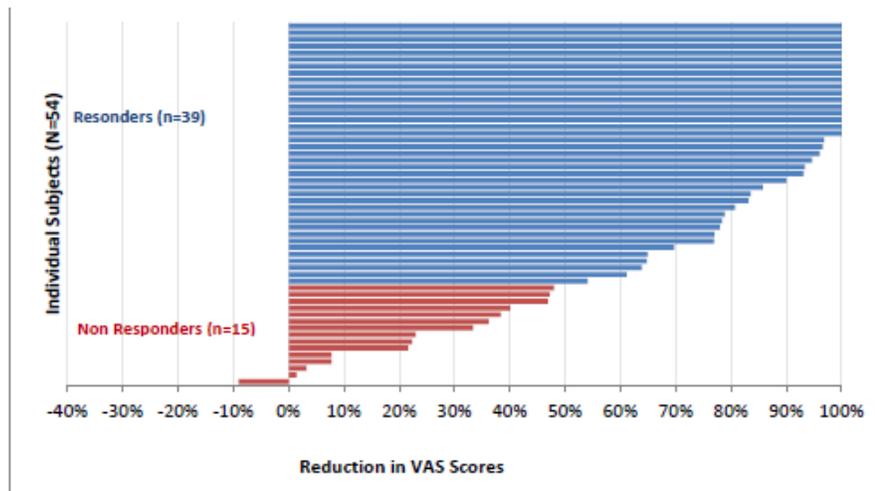


Figure 5: Percent Improvement in Pain from Baseline to 3 Months Post INS Implant Individual Control Subjects[†]

[†] Ten responders decreased their pain medications; three responders increased their pain medications

Supplemental Effectiveness Analysis - VAS Pain Score

A post-hoc analysis was performed to assess pain relief over time. VAS scores were assessed at each scheduled study visit. Pain level was measured using a 100 mm visual analogue scale (VAS) with 100 mm representing the “Worst Imaginable Pain” and 0 representing “No Pain.” Figure 6 presents the mean pain ratings with the 95% confidence intervals over time. At baseline, pain scores were equivalent between Axium and Control groups (80.6 and 80.7, respectively). At 3 months and 12-months the Axium group rated their pain as being lower than the Control group (13.1 vs. 23.8 at three months and 15.0 vs. 26.5 at 12 months).

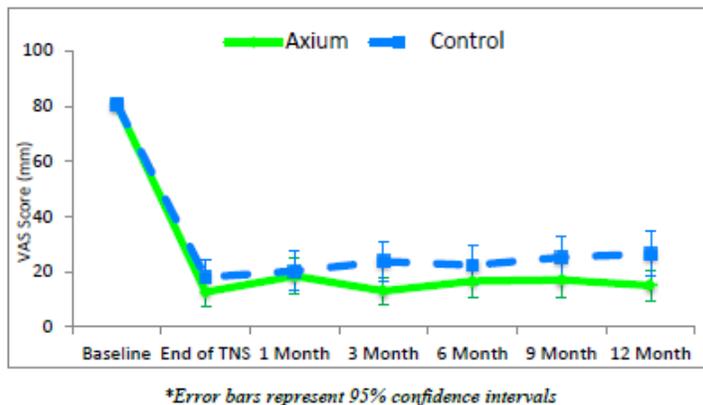


Figure 6: Average Pain Ratings (VAS Scores) over Time

Figure 7 presents average percent pain relief, as measured by the mean percent reduction in VAS scores, over time. The Axium group demonstrated a numerically greater percent reduction than the Control group at the three month interval (84.1% vs. 70.9%) and at 12 months (81.4% vs. 66.5%). These data are complementary to the primary endpoint analyses that demonstrated statistical non-inferiority and superiority in treatment success at 3 months for the Axium group.

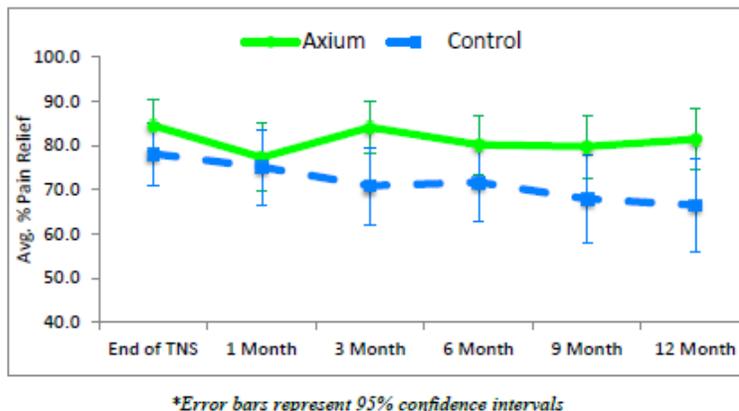


Figure 7: Average Percent Pain Relief (% VAS Reduction) over Time

Pre-specified Primary Composite Endpoint Sensitivity Analyses

All sensitivity analyses, including analyses of the ITT and PP data sets, subjects who received the implantable neurostimulator (INS), and missing data, confirmed the results of the primary analysis. In all cases, non-inferiority and superiority were met, indicating the robustness of the results for the 3- month data. The primary composite endpoint conclusions of non-inferiority ($p \leq 0.0001$) and superiority were met in each sensitivity analysis. See Figure 8 below.

- Intention-to-Treat (ITT)

The primary non-inferiority ($p < 0.0001$) and superiority ($p = 0.0004$) objectives were met using the intention-to-treat data analysis set (see Table 25).

Table 25: Primary Composite Endpoint Success through 3 Months – ITT

Primary Endpoint Component	Axium	Control
Number of Subjects - ITT analysis data set	76	76
Number of Subjects-Primary endpoint analysis [†]	69	70
Overall primary endpoint success		
n/N (%)	56/69 (81.2)	39/70 (55.7)
95% CI	(69.9, 89.6)	(43.3, 67.6)
Success rate difference (%) and 95% CI (Blackwelder)	25.4 (13.0, 100.0)	
P-value (non-inferiority $\delta = 10\%$)	<0.0001	
P-value (superiority)	0.0004	

[†] Subjects excluded since they do not have valid data: Axium=7, Control=6

- Per Protocol (PP) Analyses

The primary non-inferiority ($p < 0.0001$) and superiority ($p = 0.0007$) objectives were met using the PP data analysis set (see Table 26).

Table 26: Primary Composite Endpoint Success through 3 Months – PP

Primary Endpoint Component	Axium	Control
Number of Subjects - PP analysis data set	68	55
Overall primary endpoint success		
n/N (%)	55/68 (80.9)	30/55 (54.5)
95% CI	(69.5, 89.4)	(40.6, 68.0)
Success rate difference (%) and 95% CI (Blackwelder)	26.3 (12.8, 100.0)	
P-value (non-inferiority $\delta = 10\%$)	<0.0001	
P-value (superiority)	0.0007	

- Subjects who Received the Implantable Neurostimulator (INS)

As prespecified in the SAP, since the non-inferiority of the primary endpoint was demonstrated, an analysis of the subset of subjects who received the INS was performed (see Table 27).

Table 27: Primary Composite Endpoint Success through 3 Months – INS Subjects Only

Primary Endpoint Component	Axium	Control
Number of Subjects – Subjects in analysis [†]	68	55
Overall primary endpoint success		
n/N (%)	56/60 (93.3)	39/54 (72.2)
95% CI	(83.8, 98.2)	(58.4, 83.5)
Success rate difference (%) and 95% CI (Blackwelder)	21.1 (9.8, 100.0)	
P-value (non-inferiority $\delta = 10\%$)	<0.0001	
P-value (superiority)	0.0011	

[†] Subjects excluded because of invalid data: Axium = 1 and Control = 0.

- Missing Data

The sensitivity analyses on the primary composite endpoint to assess the impact of missing data on the results included the following:

- All subjects with missing data counted as failures.
- All subjects with missing data counted as successes.
- Worst case scenario (including all Control subjects with missing data as successes and all Axium subjects with missing data as failures).
- Best case scenario (including all Control subjects with missing data as failures and all Axium subjects with missing data as successes).
- All subjects with $\geq 50\%$ reduction at end of TNS but chose not to have a TNS treated as missing.
- Tipping point analysis – setting all missing values to either success or failure.

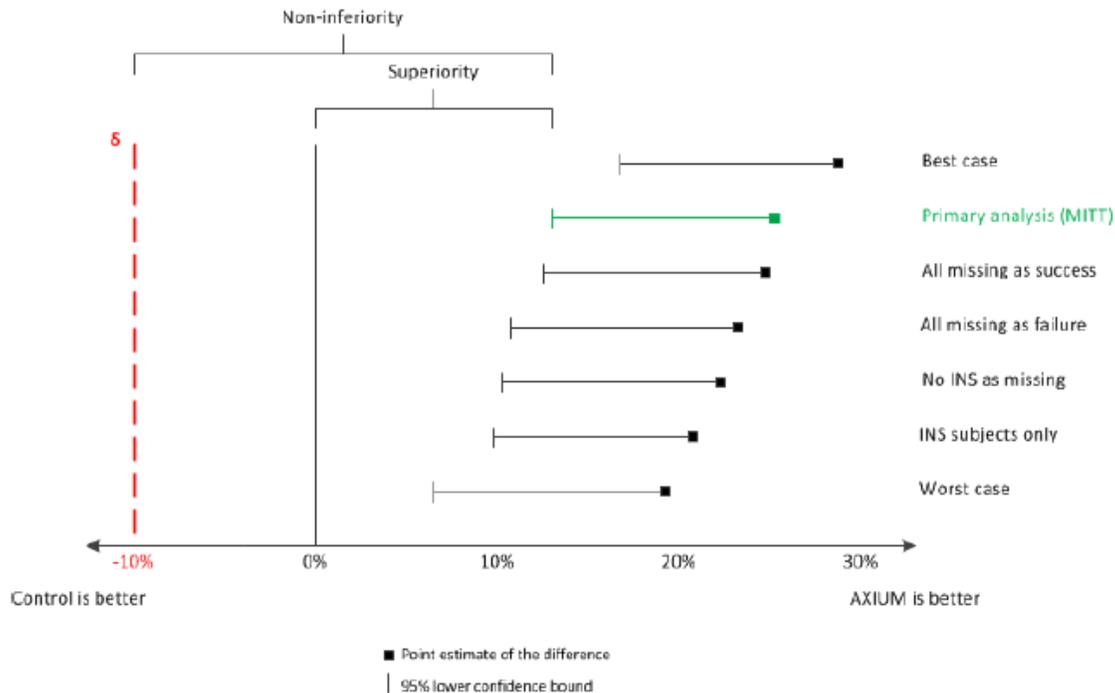


Figure 8: Sensitivity Analyses

Additional Sensitivity Analysis - Medication Changes

An additional sensitivity analysis was done to assess the effects of subject’s that had medication increases (i.e., increased their maximum daily dose of medication, added adjunctive medications or increased the frequency of adjunctive lower limb pain medications) from baseline through three months post INS implant. These subjects were also identified as having a protocol deviation. There were a total of 12 subjects (4 Axium, 8 Control) that had medication increases. Two of Axium subjects (2/4) and three of the Control subjects (3/8) already were counted as treatment failures for other reasons. The difference in treatment success between the Axium and Control groups met both the non-inferiority ($p < 0.0001$) and superiority hypotheses ($p < 0.0001$). See Table 28 below.

Table 28: Primary Composite Endpoint Sensitivity Analysis with Subjects with Medication Increases Classified as Treatment Failure

Primary Endpoint Component	Axium	Control
Number of Subjects – MITT	73	73
Number of Subjects-Primary endpoint analysis [†]	69	71
Overall primary endpoint success		
n/N (%)	54/69 (78.3)	35/71 (49.3)
95% CI	(66.7, 87.3)	(37.2, 61.4)
Success rate difference (%) and 95% CI (Blackwelder)	29.0 (16.2, 100.00)	
P-value (non-inferiority $\delta = 10\%$)	< 0.0001	
P-value (superiority)	< 0.0001	

[†] Subjects excluded since they do not have valid data: Axium=4, Control=2

One Control subject was a missing value in the primary composite endpoint because the subject withdrew prior to the INS implant and did not meet any pre-specified failure criteria (the subject met the success criteria at the end of TNS). However, that subject did have a pain medication increase after randomization and prior to withdrawal from the study. Therefore, since this analysis treats subjects that increased pain medications as treatment failures, the Control group sample size is 71 in this analysis and only two Control subjects do not have evaluable data.

Additional Sensitivity Analysis – Average VAS Scores from Subject Diary Responses

An additional assessment was done to assess the variability in pain severity based on the subjects’ VAS ratings done once a day for seven days prior to each scheduled study visit through three months. Subjects rated their “pain right now” and their “worst pain in the last 24 hours” on a 100 mm VAS scale.

Table 29 presents the average of subjects’ diary VAS scores over the seven days prior to each visit.

Table 29: Average VAS Scores Based on Subject Diary Responses – 3 Months

	Baseline		1 Month		3 Months	
	Axium	Control	Axium	Control	Axium	Control
Number of Subjects	76	76	61	54	59	54
Average Pain 'Right Now' Per Subject Diary						
N	76	76	56	53	54	51

	Baseline		1 Month		3 Months	
	Axium	Control	Axium	Control	Axium	Control
Mean	68.5	65.6	22.0	18.9	17.8	23.0
SD	19.3	17.5	22.2	18.4	18.4	22.0
Median	73.3	65.9	13.5	10.9	13.9	14.0
Min	13.3	13.1	0.0	0.0	0.0	0.0
Max	100.0	100.0	81.6	75.0	75.6	72.9
Average 'Worst Pain' Per Subject Diary						
N	76	76	56	53	54	51
Mean	80.8	78.6	32.3	33.1	28.6	36.8
SD	13.8	13.6	25.9	24.4	24.6	27.1
Median	81.6	78.5	26.8	30.1	24.8	36.6
Min	40.4	40.4	0.0	0.0	0.0	0.0
Max	100.0	100.0	87.7	89.6	96.9	100.0

Non-powered Secondary Endpoint - Pain Relief for Subjects “With” and “Without” Paresthesia

This non-powered secondary endpoint characterizes pain relief for subjects with and without paresthesia. As shown in Table 30, nine subjects in the Axium group and four subjects in the Control group reported a complete absence of paresthesia at three months post implantation. All nine subjects in the Axium group and two of the four subjects in the Control group were treatment successes.

At the time of the trial and implant procedures, all subjects were asked to confirm that they were feeling stimulation (i.e. sensation of paresthesia) in the targeted area of pain in order to confirm placement of the implanted leads. Post-procedure, stimulation settings were then programmed based upon physician judgment to optimize the appropriate therapy for each study subject. In addition, all study subjects were able to adjust the intensity level of the therapy, within a physician-prescribed range, with their patient programmers.

Note that the clinical relevance of this result is unknown. The study was a non-inferiority trial, designed to assess device effectiveness in the presence of paresthesia. The instructions for use for the Control device requires the Control device be programmed for subjects to receive paresthesia. In addition, the number of subjects that did not have paresthesia is very small and this endpoint was not adequately powered to detect the difference in pain relief for subjects who reported feeling versus not feeling paresthesia. A placebo controlled trial would be necessary to rule out the possibility that the effect is greater than placebo.

Table 30: Characteristics of Axiom and Control Subjects Who Did Not Experience Paresthesia at 3 Months

	Axiom		Control	
	Subjects with Paresthesia	Subjects without Paresthesia	Subjects with Paresthesia	Subjects without Paresthesia
Number of Subjects	49	9	50	4
Percent Pain Relief at 3 Months				
N	49	9	50	4
Mean (SD)	82.1 (24.3)	93.6 (13.6)	71.3 (32.7)	65.6 (37.3)
Median	94.2	100.0	81.9	70.1

Tertiary Endpoints

The following tertiary endpoints were evaluated:

- SF-36 Quality of Life Questionnaire at 3, 6, and 12-months

The SF-36 is a self-reported health-related quality of life scale with 36 questions that yield scores on eight dimensions of quality of life including: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. These eight dimensions also are combined to provide two summary scales for physical health (PCS) and mental health (MCS). Improvements on the SF-36 scale are represented by higher scores. Table 31 presents the mean change from baseline in SF-36 scores to the 3-, 6-, and 12-month follow-up visits with 95% confidence intervals.

Table 31: Change in SF-36 Scores from Baseline through 12 Months

	Axiom			Control		
	Improvement from Baseline Mean (95% CI)			Improvement from Baseline Mean (95% CI)		
	3 Months	6 Months	12 Months	3 Months	6 Months	12 Months
SF-36 Quality of Life Questionnaire						
Physical Component Summary (PCS)	11.8 (9.8, 13.8)	11.1 (9.1, 13.1)	11.5 (9.0, 14.1)	9.4 (6.8, 12.0)	8.6 (6.3, 11.0)	8.0 (5.4, 10.6)
Mental Component Summary (MCS)	8.3 (5.4, 11.2)	6.6 (3.2, 10.0)	6.2 (2.9, 9.5)	4.8 (2.0, 7.6)	4.1 (1.3, 6.9)	3.6 (0.4, 6.7)
Physical Functioning (PF)	27.1 (21.3, 32.9)	26.2 (20.1, 32.2)	26.6 (19.5, 33.8)	19.5 (12.6, 26.3)	19.0 (12.1, 25.9)	17.7 (10.6, 24.7)
Role-Physical (RP)	38.9 (31.9, 46.0)	33.9 (26.4, 41.4)	30.4 (22.1, 38.7)	28.6 (19.8, 37.3)	28.1 (19.5, 36.7)	24.6 (15.2, 34.0)
Bodily Pain (BP)	32.7 (26.9, 38.5)	27.4 (21.6, 33.2)	27.4 (20.4, 34.3)	29.0 (22.0, 36.0)	19.0 (12.1, 25.9)	23.1 (15.1, 31.1)
General Health (GH)	10.9 (6.2, 15.6)	11.7 (6.3, 17.1)	13.0 (7.1, 18.8)	6.3 (2.2, 10.4)	2.3 (-2.5, 7.1)	2.9 (-2.3, 8.1)
Vitality (VT)	21.3 (15.5, 27.2)	17.5 (12.1, 22.9)	17.8 (11.1, 24.5)	14.5 (9.4, 19.6)	12.0 (6.7, 17.3)	10.0 (4.0, 16.0)
Social Functioning (SF)	28.9	24.5	23.0	19.8	18.3	13.1

	Axium			Control		
	Improvement from Baseline Mean (95% CI)			Improvement from Baseline Mean (95% CI)		
	3 Months	6 Months	12 Months	3 Months	6 Months	12 Months
	(20.8, 37.0)	(16.5, 32.5)	(14.7, 31.3)	(12.3, 27.2)	(10.6, 26.0)	(4.7, 21.5)
Role-Emotional (RE)	17.0 (9.1, 24.9)	14.7 (5.3, 24.0)	14.9 (5.6, 24.3)	15.2 (7.2, 23.2)	12.6 (4.8, 20.4)	11.0 (2.0, 20.0)
Mental Health (MH)	15.5 (10.7, 20.3)	11.9 (6.3, 17.5)	13.7 (8.2, 19.2)	8.1 (3.4, 12.8)	6.7 (1.8, 11.6)	8.6 (2.9, 14.3)

- Profile of Mood States (POMS) at 3, 6, and 12-months

The Axium group experienced greater improvement than the Control group in Total Mood Disturbance at three months (19.9 vs. 13.1 respectively, 95% CI -0.2, 13.7) and 12 months post INS implant (18.1 vs. 8.1, 95% CI 2.4, 17.4). Table 32 shows the improvement in POMS for Axium and Control groups through 12-months. Table 32 presents the mean improvement and 95% confidence intervals in POMS scores from baseline to three months, six months, and 12 months, for each study group. Note that improvement on the Vigor scale is represented by a decrease in scores, while all other scales represent improvement by an increase in scores.

Table 32: Change from Baseline in POMS Brief Score Through 12 Months

	Axium			Control		
	Improvement from Baseline Mean (95% CI)			Improvement from Baseline Mean (95% CI)		
	3 Months	6 Months	12 Months	3 Months	6 Months	12 Months
Profile of Mood States (POMS)						
Total Mood Disturbance	19.9 (14.3, 25.5)	18.1 (12.3, 23.9)	18.1 (12.8, 23.4)	13.1 (8.9, 23.9)	11.8 (7.2, 16.4)	8.1 (2.7, 13.5)
Tension	3.5 (2.5, 4.4)	3.1 (1.9, 4.3)	3.2 (2.2, 4.3)	3.1 (0.9, 2.9)	1.4 (0.2, 2.6)	1.5 (0.5, 2.5)
Depression	3.7 (2.4, 5.0)	3.4 (2.1, 4.7)	3.5 (2.2, 4.8)	2.0 (0.8, 3.2)	1.6 (0.6, 2.6)	0.8 (-0.5, 2.1)
Anger	3.3 (2.0, 4.6)	3.3 (2.1, 4.5)	2.3 (0.9, 3.7)	2.0 (0.9, 3.1)	1.8 (0.8, 2.8)	1.2 (0.2, 2.2)
Vigor	3.7 (2.3, 5.1)	-2.7 (-4.2, -1.2)	3.1 (1.9, 4.4)	-2.6 (-3.7, -1.5)	-3.3 (-4.7, -1.9)	-2.1 (-3.5, -0.6)
Fatigue	4.9 (3.3, 6.5)	4.5 (2.9, 6.1)	4.7 (3.1, 6.3)	3.5 (2.4, 4.6)	3.3 (2.1, 4.5)	2.7 (1.2, 4.2)
Confusion	0.8 (0.0, 1.6)	1.0 (0.2, 1.8)	1.3 (0.5, 2.1)	1.1 (0.3, 1.9)	0.5 (-0.4, 1.4)	-0.2 (-1.1, 0.7)

- Brief Pain Inventory (BPI) at 3, 6, and 12-month

Table 33 depicts the change from baseline in the BPI through 12-months.

Table 33: Change from Baseline in Brief Pain Inventory Through 12 Months

	Axium			Control		
	Improvement from Baseline Mean (95% CI)			Improvement from Baseline Mean (95% CI)		
	3 Months	6 Months	12 Months	3 Months	6 Months	12 Months
Brief Pain Inventory (BPI)						
Severity	4.2 (3.6, 4.9)	3.8 (3.2, 4.4)	3.8 (3.0, 4.5)	3.8 (3.2, 4.4)	3.6 (3.0, 4.2)	3.3 (2.5, 4.1)
Interference	4.2 (3.5, 4.9)	3.8 (3.1, 4.5)	3.9 (3.1, 4.6)	3.8 (3.1, 4.5)	3.1 (2.4, 3.8)	2.6 (1.9, 3.3)
Activity	4.5 (3.8, 5.1)	4.1 (3.4, 4.8)	4.1 (3.4, 4.9)	3.4 (2.6, 4.2)	2.8 (2.6, 4.2)	2.9 (2.1, 3.7)
Affective	3.8 (3.0, 4.6)	3.5 (2.7, 4.3)	3.5 (2.7, 4.3)	2.5 (1.8, 3.2)	2.6 (1.8, 3.4)	2.2 (1.4, 3.0)

- Subject Satisfaction at 3, 6, and 12-months

At 3, 6, and 12-months post INS implant, subjects rated their satisfaction with the degree of pain relief they received, the therapy in general, and the likelihood that they would undergo therapy again. Subjects in both groups reported a high degree of satisfaction. See Table 34 below for results.

Table 34: Subject Satisfaction through 12 Months

	Axium			Control		
	3 Months	6 Months	12 Months	3 Months	6 Months	12 Months
Subject Satisfaction						
How likely you would undergo the therapy again¹	9.0	8.7	8.9	9.1	8.7	8.5
Change in your pain as compared to before the device was implanted²						
Much Worse	0.0	0.0	0.0	0.0	0.0	2.1
Worse	0.0	1.7	1.8	1.9	0.0	0.0
A Little Worse	1.7	0.0	0.0	1.9	1.9	0.0
No change	0.0	5.1	3.6	3.7	5.8	4.2
A Little Better	6.8	6.8	3.6	11.1	9.6	12.5
Better	27.1	20.3	25.5	14.8	19.2	20.8
Much Better	64.4	66.1	65.5	66.7	63.5	60.4

¹ Scale 0-10 [0=Not Likely, 10=Very Likely]; the mean ratings are displayed.

² The percent of subjects that selected each response option is displayed

- Stimulation Specificity at 3 and 12-months

In the ACCURATE study, the stimulation specificity endpoint was evaluated at three months per the SAP and post-hoc at 12 months by determining whether a subject felt paresthesia in anatomical regions that were reported as having no pain at baseline. Subjects in the Control group were 2.3 times more likely to report feeling paresthesia in one or more non-painful areas when compared to subjects in the Axium group (35.2% vs.15.3%) at three months. At 12 months post INS implant, subjects in the Control group were 7.1 times more likely to report feeling paresthesia in one or more non-painful areas as

subjects in the Axium group (38.8% vs. 5.5%). Therefore, this endpoint showed that paresthesias in the Control Group were more likely to be experienced in the non-painful regions, as compared to the Axium group.

Results Over Time

This section provides the results of additional endpoints (assessments performed through one year). Since a multiplicity adjustment procedure was not pre-specified for these endpoints, the results are presented with 95% CIs instead of p-values.

- Primary Composite Endpoint – 12 Months (MITT)

Results for 12 months show that the Axium group continued to show a greater treatment success (74.2%) when compared to the Control group (53.0%). See Table 35 below.

Table 35: Primary Composite Endpoint Treatment Success through 12 Months – MITT

Primary Endpoint Component	Axium	Control
Overall Treatment Success at 12-Months		
n/N (%)	49/66 (74.2%)	35/66 (53.0%)
95% CI	(62.0, 84.2)	(40.3, 65.4)
Success rate difference (%) and 95% CI (Blackwelder)	21.2 (7.8, 100.0)	

- Pain Relief for Subjects “With” and “Without” Paresthesia Through 12-Months

A post-hoc analysis was performed to characterize pain relief for subjects with and without paresthesia through 12-months. At twelve months, 19 subjects in the Axium group and six subjects in the Control group reported a complete absence of paresthesia. Of the 19 subjects in the Axium group, 17 were treatment successes and three of the six subjects in the Control group were treatment successes.

At the time of the trial and implant procedures, all subjects were asked to confirm that they were feeling stimulation (i.e. sensation of paresthesia) in the targeted area of pain in order to confirm placement of the implanted leads. Post-procedure, stimulation settings were then programmed based upon physician judgment to optimize the appropriate therapy for each study subject. In addition, all study subjects were able to adjust the intensity level of the therapy, within a physician-prescribed range, with their patient programmers.

Table 36: Pain Relief for Subjects with and without Paresthesia – 12 Months

	Axium		Control	
	Subjects with Paresthesia	Subjects without Paresthesia	Subjects with Paresthesia	Subjects without Paresthesia
Number of Subjects	35	19	43	6
Percent Pain Relief at 3 Months				
N	35	19	43	6
Mean (SD)	81.4 (22.8)	86.0 (25.3)	70.2 (34.9)	48.1 (50.8)
Median	89.1	100.0	83	51.2

Note that the clinical relevance of this result is unknown. The study was a non-inferiority trial, designed to assess device effectiveness in the presence of paresthesia. The instructions for use for the Control device requires the Control device be programmed for subjects to receive paresthesia. In addition, the number of subjects that did not have paresthesia is very small and this endpoint was not adequately powered to detect the difference in pain relief for subjects who reported feeling versus not feeling paresthesia. A placebo controlled trial would be necessary to rule out the possibility that the effect is greater than placebo. However, the results show that pain relief can be experienced without feeling paresthesia, at least in some subjects.

- *Responder Rates Over Time – INS Subjects Only*

Responders are defined as subjects who achieve 50% or greater pain relief compared to baseline (as measured by the change in VAS scores). By definition, these analyses include only subjects who received an INS implant. Table 37 presents the $\geq 50\%$ improvement responder rates over time. As this table demonstrates, the Axium group had a numerically higher percent of subjects that had $\geq 50\%$ improvement in VAS scores at every time point. At three months post INS implant, 94.9% of subjects in the Axium group had $\geq 50\%$ improvement in VAS scores, and 72.2% of subjects in the Control group improved by $\geq 50\%$. At 12 months post INS implant, 89.1% of subjects in the Axium group had $\geq 50\%$ improvement in VAS scores, and 70% of subjects in the Control group improved by $\geq 50\%$.

Table 37: Responder Rates over Time (INS Only Subjects)

	BL		1 Month		3 Month		6 Month		9 Month		12 Month	
	AX	C	AX	C	AX	C	AX	C	AX	C	AX	C
Number of Subjects	76	76	61	54	59	54	59	52	55	49	55	50
Responder rate $\geq 50\%$ Improvement			50/61 (82.0)	41/54 (75.9)	56/59 (94.9)	39/54 (72.2)	51/59 (86.4)	41/52 (78.8)	46/55 (83.6)	34/49 (69.4)	49/55 (89.1)	35/50 (70.0)

Figure 9 presents the distribution of responder rates at three months post INS implant.

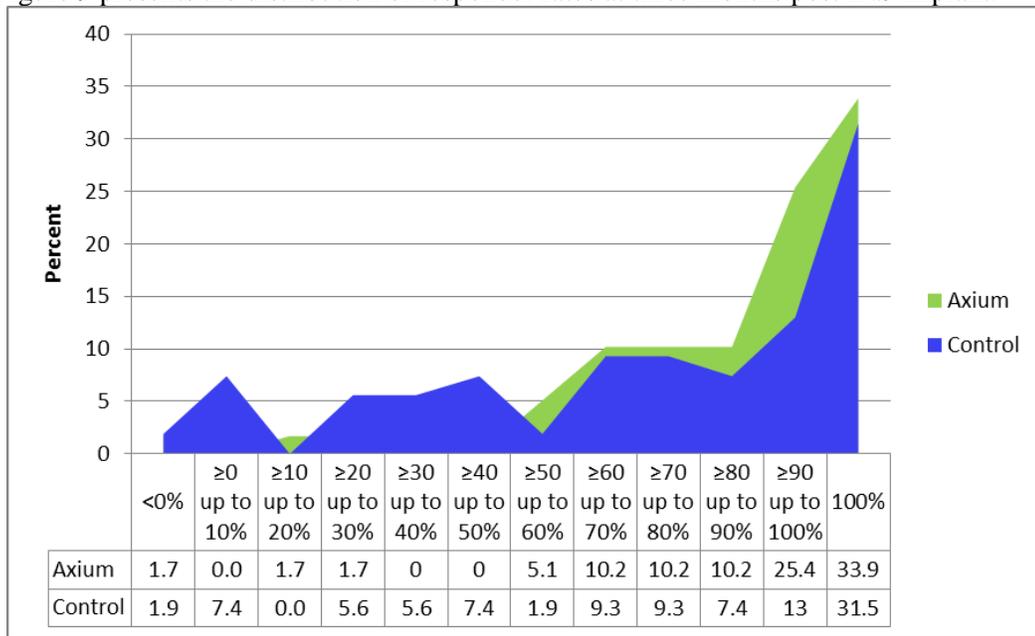


Figure 9: Distribution of Responder Rates at 3-months Post INS Implant

3. Subgroup Analyses

As prespecified in the SAP, the primary composite endpoint was analyzed by age, gender and primary diagnosis (MITT). Results are summarized below.

- Age
The primary non-inferiority endpoint was met both in subjects ≤ 53 years and > 53 years. The median age (53 years) was selected as the cut point for the age analysis. The primary composite endpoint conclusion of superiority was met for subjects ≤ 53 years. There was a trend for superiority for subjects > 53 years of age.
- Gender
The primary non-inferiority endpoints were met both in male and female subjects. The primary superiority endpoint also was met for female subjects.
- Diagnosis
The primary non-inferiority endpoints were met both for subjects diagnosed with CRPS and subjects diagnosed with Peripheral Causalgia. The primary superiority endpoint also was met for subjects diagnosed with CRPS and subjects diagnosed with Peripheral Causalgia.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 73 investigators of which 3 investigators had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Significant payment of other sorts: 1
- Significant equity interest held by investigator in sponsor of covered study: 3

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

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

A Panel Meeting was not held for this device.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Effectiveness for the Axium Neurostimulator System was based on a non-inferiority pivotal study. A total of 152 subjects were enrolled and randomized 1:1 with 76 subjects in the Axium group and 76 subjects in the Control group (a commercially available SCS system). Baseline assessments demonstrated a well-matched population with no statistical differences on demographic, lower extremity pain history and primary diagnosis. Of the 152 subjects randomized, 113 subjects (all subjects expected) completed the three month primary composite endpoint. A total of 105 subjects ($105/108 = 97.2\%$) of expected subjects completed the post-INS 12-month follow-up visit.

The primary objective of the study was to demonstrate safety and effectiveness with a composite endpoint at 3 months with two components defined as 1) a $\geq 50\%$ pain relief (as measured by VAS scores), and 2) the absence of any stimulation-induced neurological deficit. If a subject met this endpoint they were considered to be a treatment success for the ascertainment of the primary endpoint. The Axium group had a greater number of subjects achieving success (81.2%) as compared to the Control (55.7%). Using a predefined MITT analysis, the Axium group achieved statistical non-inferiority ($p < 0.0001$) and superiority ($p = 0.0004$) in treatment success compared to the Control. Similar results were found in the ITT and PP analyses and at the 12-month follow-up. Secondary and

tertiary endpoints were considered hypothesis generating and were not considered in the evaluation of effectiveness.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory studies as well as data collected in a clinical study conducted to support PMA approval as described above. The Axium group demonstrated a comparable safety profile to the Control in the following:

- In the pre-specified safety component of the primary composite endpoint there were no subjects in the Axium or the Control group who experienced stimulation induced neurological deficit.
- The overall difference in the rate of SAEs between the groups was similar and not clinically or statistically different (Axium 10.5%, Control 14.5%, $p=0.6248$); the rate during the TNS phase (Axium 1.3%, Control 3.9%, $p=0.62$), and INS phase (Axium 9.2%, Control 10.5%, $p=1.0$).
- There were no unanticipated safety events and no deaths in the trial.

Additionally, there were 241 adverse events in 62 subjects (81.6%) in the Axium group and 161 adverse events in 55 subjects (72.4%) in the Control group ($p=0.2575$).

There were differences between the Axium and Control groups in the number of subjects with procedure related events in the Axium group (35/76, 46.1%) was statistically significantly greater ($p=0.0177$) than that in the Control group (20/76, 26.3%) and appears to be associated with the number of leads implanted per subject. The results show an increasing linear relationship between the number of Axium leads implanted and the number of subjects with procedure-related events, ranging from zero events in two subjects with one lead implanted, to eight events in eight subjects with six leads implanted. This may be expected since individual needle sticks are required to implant each Axium lead during a procedure (up to four leads), in contrast to the fewer needle sticks typically used to implant one or two leads during a Control procedure. There is no apparent increasing linear relationship between the number of leads implanted and the number of Control subjects with procedure-related events.

C. Benefit-Risk Conclusions

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The study met its primary endpoint which was to demonstrate noninferiority/superiority as compared to a legally marketed Control spinal cord stimulation system using a composite endpoint with two components defined as 1) a $\geq 50\%$ pain relief (as measured by VAS scores) and 2) no stimulation-induced neurological deficit. Results were consistent at 12-months.

Additional factors to be considered in determining probable risks and benefits for the Axium Neurostimulation System included the following:

- Durability of the benefit, majority of test subjects having persistent reduction in pain at 12 months compared to control subjects (74.2% vs. 53%, $p < 0.0001$).
- Comparable total, device-related, stimulation-related, and serious adverse event rates between the test and the control groups.
- Higher incidence of procedure-related adverse events with mitigation in the form of a mandatory training program prior to actual patient implantation.
- Challenging disease process in the form of lower extremity pain in CRPS I and II with few medical, interventional pain, and surgical therapies that have demonstrated limited efficacy.

The following limitations were considered when determining probable risks and benefits for the Axium Neurostimulator System:

- The non-inferiority design of the clinical study did not blind subjects as to which device they had implanted. This may have resulted in investigator and patient bias and did not allow an assessment of the placebo response. Placebo response is well known in pain studies due to the subjective nature of the pain assessment and the duration of the response may be long lasting.
- The primary endpoint was pain in the area of greatest pain. This endpoint was chosen due to the dermatomal coverage of the targeted DRG. The Axium device is limited to lower limb pain while the Control device is indicated for the trunk and/or limb. Additionally, pain during activity, worst pain, and specific attributes of neuropathic pain (i.e., dermatome, response to temperature, palpation, quality, etc.) were not assessed.
- The primary endpoint was based on an in-clinic evaluation rather than a patient pain diary and thus, day-to-day variation in pain was not assessed.
- The purpose of the study was to study device effect on pain and all secondary and tertiary endpoints not specifically related to pain should be interpreted as hypothesis generating only.
- The Control group subjects received either the RestoreSensor or Restore Ultra SCS devices manufactured by Medtronic, Inc. and for purposes of ensuring comparable features to assess this endpoint, the RestoreSensor Control device had accelerometer feature that can adjust stimulation based

on the patient's needs and preferences in different body positions (including stimulation to maintain paresthesia) deactivated. The Restore Ultra device does not have the feature.

- Pain medications were kept stable through the three month assessment. However, changes in pain medication may have affected pain assessments following 3 months.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The results from the clinical study support a reasonable assurance of the safety and efficacy of the Axium Neurostimulator System, as well its long-term performance, when used in a manner consistent with its labeling and intended use. The evidence supporting the safety and effectiveness of the Axium Neurostimulator System is on a non-inferiority pivotal study. The results from comprehensive pre-clinical testing show that the Axium Neurostimulator System performs as intended. The analyses also support a clinical benefit to risk determination that is favorable.

XIII. CDRH DECISION

CDRH issued an approval order on February 11, 2016. The final conditions of approval cited in the approval order are described below.

Continued approval of this PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year from the date of approval of the original PMA. In addition to the Annual Report requirements, post-approval study (PAS) reports must be submitted for the PAS study every six (6) months during the first two (2) years of the study and annually thereafter.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

Fishman, SM, Ballantyne JC, Rathmell, JP Bonica's Management of Pain. Lippincott Williams & Wilkins, 2010.

Kramer J, Liem L, Russo M, Smet I, Van Buyten JP, Huygen F. Lack of body positional effects on paresthesias when stimulating the dorsal root ganglion (DRG) in the treatment of chronic pain. *Neuromodulation*. 2015 Jan;18(1):50-7. doi: 10.1111/ner.12217. Epub 2014 Aug 21.

Mehta, CR, Pocock, SJ. Adaptive increase in sample size when interim results are promising: A practical guide with examples. *Statistics in Medicine*. 2010; DOI: 10.1002/sim.4102.

van Eijs F, Stanton-Hicks M, Van Zundert J, Faber CG, Lubenow TR, Mekhail N, van Kleef M, Huygen F. Evidence-based interventional pain medicine according to clinical diagnoses. 16. Complex regional pain syndrome. *Pain Pract*. 2011 Jan-Feb;11(1):70-87. Epub 2010 Aug 27.