Protocol Title: High-FreQUEncy Nerve Block for PoST-Amputation Pain: QUEST IDE Trial (A Pivotal Study)

16 November 2020

Study Protocol
003-0001, Version 2.1
ClinicalTrials.gov Identifier: NCT02221934

Study Sponsor:
Neuros Medical, Inc.
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CLINICAL PROTOCOL AMENDMENT

G130203/S021

Version 2.1

DEVICE: ALTIUS® SYSTEM, IMPLANTABLE HIGH-FREQUENCY NERVE BLOCK DEVICE

16 November 2020

APPROVALS:

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DOCUMENT HISTORY:

REVISION	DATE	DESCRIPTION OF CHANGE
Version 2.1	18 November 2020	Proposed modifications to the investigational plan to increase the number of investigational centers and allowing alternative method for determining subject eligibility and telephone consenting, in order to limit the need for subjects to physically come to the study center for baseline screening.

Investigator Responsibilities

Prior to participation in the Neuros Medical High Frequency Nerve Block (HFNB) QUEST IDE Study, the appointed Principal Investigator(s) at the Investigational Site (hereafter referred to as "Principal Investigator" or "PI") must obtain written approval from his/her Institutional Review Board (IRB). This approval must be in the PI's name and a copy sent to the Sponsor or their representative along with the IRB-approved Informed Consent Form, HIPAA (Health Insurance Portability and Accountability Act) Authorization (if a separate document) and the signed Clinical Study Agreement, prior to the first shipment of the investigational study devices.

The Principal Investigator must also:

- Conduct the study in accordance with the study protocol, the signed Clinical Study Agreement and Good Clinical Practices, the Code of Federal Regulations 21 CFR Parts 812, 50, 54, 56, 45 CFR Part 46, MDD 93/42/EC, and ISO 14155, as applicable.
- Agree to participate in appropriate device and protocol training prior to study initiation.
- Assure that informed consent and HIPAA Authorization is obtained from each subject prior to enrollment, using the FDA, IRB and Sponsor approved forms.
- Assure that the study is not commenced until IRB/EC and FDA IDE approval have been obtained.
- Provide all required data and agree to source document verification of study data with patient's medical records.
- Allow staff from the Sponsor and its authorized representatives, as well as representatives from regulatory agencies such as the US FDA, to review, inspect and copy any documents pertaining to this clinical investigation.
- Provide a copy of a Financial Disclosure form that summarizes financial interest in the Neuros Medical HFNB System.
- Complete all Case Report Forms and study documentation and relevant imaging assessments (as required) promptly to the Sponsor or its authorized representative for data management.

The Principal Investigator may delegate one or more of the above functions to an associate or Sub-Investigator. However, the Principal Investigator retains overall responsibility for proper conduct of the study, including obtaining and documenting patient informed consent, compliance with the study protocol, and the collection of all required data.

Investigator Signature

I have read and understand the contents of this protocol. I agree to follow and abide by the guidelines set forth in this document.

_____

Investigator Name (print)

_____ _____

Investigator Signature Date

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Protocol Synopsis

Protocol Title: High-FreQUEncy Nerve Block for PoST-Amputation Pain: QUEST IDE Trial	
Protocol Number: 003-0001	
ClinicalTrials.gov Identifier: NCT02221934	
Study Overview	
Objectives	**Primary objective:** To evaluate the safety and effectiveness of the Altius® System High Frequency Nerve Block (HFNB) treatment for the management of post-amputation pain. **Secondary objective:** To determine the impact of Altius HFNB treatment for post-amputation pain on health outcomes, including measurement health-related quality of life and use of pain medications.
Intended Indication For Use	The Altius System is intended for the management of intractable lower limb pain of amputees 21 years of age or older who have demonstrated one adequate response to anesthetic injection for regional nerve blockade. Neuros intends to submit safety and effectiveness data in a Pre-Market Approval (PMA) application after all enrolled and actively participating subjects reach their Month-12 Visit.
Test Device	The Neuros Medical, Inc. (Neuros) Altius System consisting of an implantable Generator with rechargeable battery, Cuff Electrode, Extension, and external devices (Patient Controller, Charger, Programmer Wand, and Programmer Application). This system was previously evaluated in IDE Pilot study G110168.
Test and Control Treatment	Randomized subjects who are implanted with the Neuros Altius System will be programmed to receive Test treatment ($\mathbf{T_t}$) or Control treatment ($\mathbf{C_t}$). Subjects will be randomized 1:1 to receive either Test treatment ($\mathbf{T_t}$) or Control treatment ($\mathbf{C_t}$). During the Randomized Testing phase, study subjects will activate the test device as needed but remain blinded to which treatment is delivered ($\mathbf{T_t}$ or $\mathbf{C_t}$). The control (sham) treatment ($\mathbf{C_t}$) will be above sensory threshold but delivered at an extremely low frequency. It is anticipated that this treatment will be too minimal to be therapeutic while the sensation from this treatment should provide subjects a similar expectation of efficacy as receiving the Test treatment ($\mathbf{T_t}$).

Study Design	
Study Design	Multi-site, double-blinded, randomized, sham-controlled study with two (2) parallel groups.
Planned Number of Subjects	Up to one hundred and eighty (180) subjects implanted with Neuros Altius System.
Planned Number of Sites	Up to thirty-five (35) investigational sites in the U.S.A., each comprised of a physician in a pain-related specialty (i.e. anesthesiologist) and an implanting surgeon. Sites will have a combination of experience and anticipated patient treatment rates to support timely completion of the investigational study.
Outcome Measures	• Numerical Rating Scale (NRS) • Pain Medication Use • Brief Pain Inventory (BPI) • Short Form Health Survey (SF-12) • EuroQol (EQ-5D) • Patient-Global Impression of Change (PGIC)
Primary Efficacy Endpoint	The primary hypothesis for this study is that the responder rate is significantly higher for subjects who receive Test treatment (Tt) than Control treatment (Ct) during the Randomized Testing phase of the study. Study success will be determined by a superiority test on the difference between responder rates in the Test and Control group. A responder is defined per the IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) criteria as someone who demonstrates a 50% reduction in an NRS pain score from pre-treatment to post-treatment for more than 50% of all pain episodes in which the treatment was used.
Secondary Efficacy Endpoints	*Secondary Endpoints for Intended Labeling Claims:* • Opioid Pain Medication Use [Morphine Equivalent Dose (MED)] at Month-3 • Brief Pain Inventory (BPI) at Month-3 • Short Form Health Survey (SF-12) Physical Component Summary (PCS) at Month-3 • Short Form Health Survey (SF-12) Mental Component Summary (MCS) at Month-3 • EuroQol (EQ-5D) at Month-3

	Secondary Efficacy Endpoints Not Intended for Labeling Claims: • Pain Relief after 2 Hours • Pain Days per Week • Non-Opioid Analgesic Pain Medication Use through Month-12 • Opioid Pain Medication Use [Morphine Equivalent Dose (MED)] through Month-12 • Brief Pain Inventory (BPI) through Month-12 • EuroQol (EQ-5D) through Month-12 • Short Form Health Survey (SF-12) Physical Component Summary (PCS) through Month-12 • Short Form Health Survey (SF-12) Mental Component Summary (MCS) through Month-12 • Patient Global Impression of Change (PGIC) • Session Success Rate • Composite Responder Rate (Reduction in pain AND absence of increase in medication usage) *Additional Outcome Assessments:* • Technical Success rate (Successful Device Placement and Activation) • Prosthetic Use
Primary Safety Endpoint	The primary safety endpoint will be the incidence of all serious adverse events, including Serious Adverse Events (SAEs), Serious Adverse Device Effects (SADEs), and Unanticipated (Serious) Adverse Device Effects (UADEs), from the time of injection through three (3) months post-implant. The primary safety endpoint will be determined at the conclusion of the Randomized Testing phase of the study, after all active participants complete the Month-3 Visit.
Secondary Safety Endpoints	The secondary safety endpoint will include the incidence of all adverse events including non-serious adverse event (AE), non-serious adverse device effects (ADE), serious adverse events (SAE), serious adverse device effects (SADE), and unanticipated adverse device effects (UADE), from time of injection through the Month-12 visit, will be determined. In addition, AEs and SAEs occurring post informed consent through initiation of implant procedure will be presented. This assessment will be reported in both the Enrolled-not-Implanted and the Enrolled-and-Implanted populations.

Intent-to-Treat	The primary analysis for the primary efficacy endpoint will be analyzed on a modified intention-to-treat basis (mITT). In the mITT analysis, all subjects who were implanted with the investigational device, randomized and received treatment will be included in the analysis. Subjects who did not satisfy the eligibility criteria, were implanted with the investigational device but are not randomized or were implanted and did not receive treatment will not be included in the mITT analysis.
Study Schedule	**Eligibility** • Baseline (Start electronic diary [eDiary]) • Injection Evaluation **Implant** • Implant Surgery (by Surgeon) **Randomization and Parameter Optimization** • Device Activation • Programming Adjustment **Randomized Testing** • Month-1 Start of Primary Endpoint • Follow-up Post-Operation Day (POD 42) • Follow-up Post-Operation Day (POD 56) • Month-3 Conclusion of Primary Endpoint **Follow-Up** • Programming Adjustment (if needed) • Month-6 • Month-9 • Month-12 Subject Study Completion **Long-Term Follow-Up (Optional)** • Follow-up (as needed, no less than every 12 months)

Inclusion Criteria	1. Subject shall have a unilateral amputated lower limb for no less than 12 months. If amputation needed revision within 12 months, patient could be enrolled if investigator documents that the amputation site has healed and subject's symptoms have stabilized. 2. Post-amputation pain shall be chronic (persistent over 6 months) and resistant to pain medications with a documented history within the subject's medical records. 3. Subject shall have frequent and recurring pain defined as no less than 4 episodes of pain ≥ 5 (NRS) per week on average (to be confirmed with baseline pain diary). 4. Subject's typical pain episode should last no less than 60 minutes. 5. Subject shall demonstrate response to two injections, one regional nerve block and the other saline. Response to the regional nerve block is defined as greater than or equal to a 50% pain reduction by NRS at 20 minutes from administration of Lidocaine. An allowable, non-therapeutic response to saline is defined as less than 30% pain reduction by NRS 15 minutes after administration. NRS must be ≥ 5 before first injection. 6. Subject's regimen of drug therapy for pain shall be stable for no less than 4 weeks prior to implant and shall not change without approval of investigator until after their Month-3 visit. Subject shall sign a pain medication "contract" to confirm acceptance of guidelines for the use of pain medication. 7. Subject agrees not to replace or alter their prosthetic (if applicable) until after their Month-3 (primary endpoint) visit. 8. Subject is able to independently read and complete all questionnaires provided in English and use electronic diary during study. 9. Subject is willing and able to provide informed consent and comply with all procedures and assessments required by study protocol. 10. Subject, and caregiver if applicable, is able and willing to be available for study visits throughout the duration of the study, e.g., no planned relocation of residence or extended vacation during the study that would prevent compliance with study visit schedule. 11. Subject shall be 21 years of age or older (FDA definition of non-pediatric) and legally able to provide written informed consent.

Exclusion Criteria	1. Subject is currently implanted with any active implantable device including but not limited to: pacemaker, implantable cardiac defibrillator, implantable neurostimulator (e.g. peripheral or spinal cord stimulator), or implantable drug pump. 2. Subject has a source of pain other than post-amputation pain (incl. dysesthesia, cancer-related, visceral, angina, migraine, causalgia) which in the opinion of the investigator may interfere with the reporting of post-amputation pain. 3. Subject has medical contraindications to surgery, including but not limited to cardiovascular, pulmonary, renal, liver or hematological disorders, active inflammation, medical contraindication for general anesthesia (e.g., severe cardiopulmonary disease), compromised immune state (due to concomitant disease or medications such as chemotherapy or immunosuppressants), or anticoagulant medication that cannot be discontinued for perioperative period. 4. Uncontrolled diabetes as defined by HbA1c > 8.0. 5. Spasticity in their residual limb such that the subject cannot achieve volitional full range of motion (ROM) of joints on involved side. 6. Subject has skin graft or severe scarring over targeted implant site or any anatomical conditions that would prevent placement of the Altius System components. 7. Subject demonstrates an inability to discern differences in pain severity, report pain intensity and related information, or complete a pain diary. 8. Subject has a suspected or known allergy to any materials of the Altius System in tissue contact or Lidocaine (necessary for injection screen). 9. Subject has received therapeutic regional nerve block (e.g. anesthetic with steroid, and/or opioids) for post-amputation pain within 30 days prior to baseline visit. 10. Subject's usual seated posture includes sitting on the end of their stump. 11. Subject is a woman who is not using adequate contraception, is pregnant or breastfeeding, or intends to become pregnant during the course of the study. 12. Subject is currently participating or intends to participate in another investigational drug or device clinical study that may

	influence or interfere with the data that will be collected for this study. 13. Subject has a condition requiring MRI studies or diathermy after device implantation. 14. Subject has a history of any alcohol or substance abuse or dependence which has required prior medical treatment or intervention. Subject has active alcohol or substance abuse. 15. Subject has a condition that, in the opinion of the investigator, would interfere with study compliance (incl. unresolved issues of secondary gain) or subject's safety. 16. Subject has a life expectancy of less than 24 months. 17. Subject is diagnosed with or has untreated psychological conditions: borderline personality disorder, major depression disorder characterized by hospitalization within the prior year for a major depressive episode. 18. Subject has current diagnosis of any progressive neurological disease such as multiple sclerosis, chronic inflammatory demyelinating polyneuropathy, rapidly progressive diabetic peripheral neuropathy, or any tumor of the nervous system. 19. Subjects with active local or systemic infection, prior recurrent bacterial infection, those who are immunocompromised or have high risk of infection due to other comorbidities.

Statistical Methods	
Primary Statistical Hypothesis	H_o: $P_T = P_C$ vs. H_A: $P_T \neq P_C$, where P is the proportion of responders (responder rate).
Statistical Test Method and Decision Criteria	Cochran-Mantel-Haentzel chi-square test adjusting for clinical site with a 2x2 table of responders and non-responders to Test treatment (**T_t**) and Control treatment (**C_t**). Reject H_o in favor of H_A when $p \leq 0.05$ using two-sided significance level.
Sample Size Calculation Inputs	• Probability of type I error, α=0.05 • Probability of type II error, β=0.10 • Power, 1-β = 0.90 • Test, two-tailed • Expected responder rate to Test treatment (Tt), PT = 0.50 • Expected responder rate to Control treatment (Ct), PC = 0.25 • Inflation factor (IF) for three interim analyses, IF = 1.09 • Percent attrition = 0.10 Total sample size, based on the above parameters using a normal approximation multiplied by an inflation factor for group sequential design (PASS 15) is N = 180
Interim Analysis and Decision Criteria	Three interim analysis for futility will be conducted at: N = 20, N = 40, and N = 80 subjects implanted and have reached their Month-3 Visit (primary endpoint). Group sequential design will be used with beta spent parameters: 0.006, 0.00615, 0.0102, and 0.1 for futility. The interim analyses will result in one of the following two scenarios for the study: A. Enrollment continues uninterrupted and reaches the planned maximum. B. Enrollment is stopped and the study is terminated due to futility.

1 Introduction

1.1 Therapeutic Mechanism of Action

The possibility of blocking nerve conduction by electric current instead of chemical agents has been explored through the past decades (see review by Kilgore and Bhadra 2004). Recent research has provided further scientific evidence and technical details on conduction block using high-frequency alternating current. These studies demonstrated, via computer simulation and animal experiments, that continuous application of alternating current within the 5-50 kHz frequency range could result in a reliable and reversible conduction block in motor, sensory, and autonomic nerves (Bhadra et al 2007, Bhadra and Kilgore 2005, Tai et al 2011, Waataja et al 2011).

The mechanism of action of the proposed therapy using high-frequency nerve block (HFNB) is completely different from that of other electrical stimulation techniques for pain management, such as Peripheral Nerve Stimulation or Spinal Cord Stimulation. These modalities rely on activation of certain sensory nerves to interact with pain signals in the central nervous system rather than blockage of pain signal in the peripheral nervous system, and thus have less predictable effects than a direct nerve block (Barlas and Lundeberg 2006, Mobbs et al 2007, Hsu and Cohen 2013).

The rationale is to use this “electrical Lidocaine” to block the pain signal at a location just proximal to the neuroma in a peripheral nerve by HFNB generated by an implanted waveform generator and delivered to the affected nerve via an implanted electrode.

1.2 Pre-Clinical Studies

The research group led by Dr. Kevin Kilgore at Case Western Reserve University (CWRU) has published a series of pre-clinical studies on electrical nerve block since 2004. They demonstrated conclusively that HFNB produces a true conduction block in peripheral nerves, established the basic parameters for nerve block through a series of randomized in-vivo experiments and defined optimal parameters of device design to achieve effective block (Bhadra and Kilgore 2005, Ackermann et al 2009, Gerges et al 2010, Ackermann et al 2011). These pre-clinical studies laid a solid foundation for the clinical testing of this promising new technology.

Nerve conduction block by high-frequency alternating current was initially investigated in motor nerves using a rat nerve-muscle preparation. The results showed that complete and reversible conduction block could be achieved by alternating current in the frequency range of 5-50 kHz (Bhadra and Kilgore 2005). Conduction block was later demonstrated in sensory nerves in a cat sural nerve model, in which compound action potential (CAP) of the nerve was used to indicate conduction block instead of muscle force (Lahowetz 2007). The results showed that sensory nerves undergo electrical block in a manner similar to motor nerves. All sizes of myelinated sensory fibers can be blocked using the appropriate amplitude of high-frequency alternating current. It is possible to selectively block the larger sensory fibers in isolation from smaller fibers by adjusting the amplitude of high-frequency alternating current. In addition to the effects on myelinated sensory fibers, direct evidence on conduction block in unmyelinated C fibers by high-

frequency alternating current has also been provided in a more recently published study (Waataja et al 2011).

The influence of frequency of the waveform on conduction block was assessed in randomized in-vivo experiments (Bhadra and Kilgore 2005). The setup for these experiments is shown in **Figure 1**. The frequency range tested was 10-30 kHz. A complete and reversible conduction block was achieved in all 6 animals at all 6 frequencies tested. The voltage range for complete block across all frequencies was 2-10 V_{pp}. The linear regression between block threshold amplitude (in voltage) and frequency showed an R^2 value of 0.7 ($p<0.0001$); higher frequencies required higher amplitudes to achieve complete block.

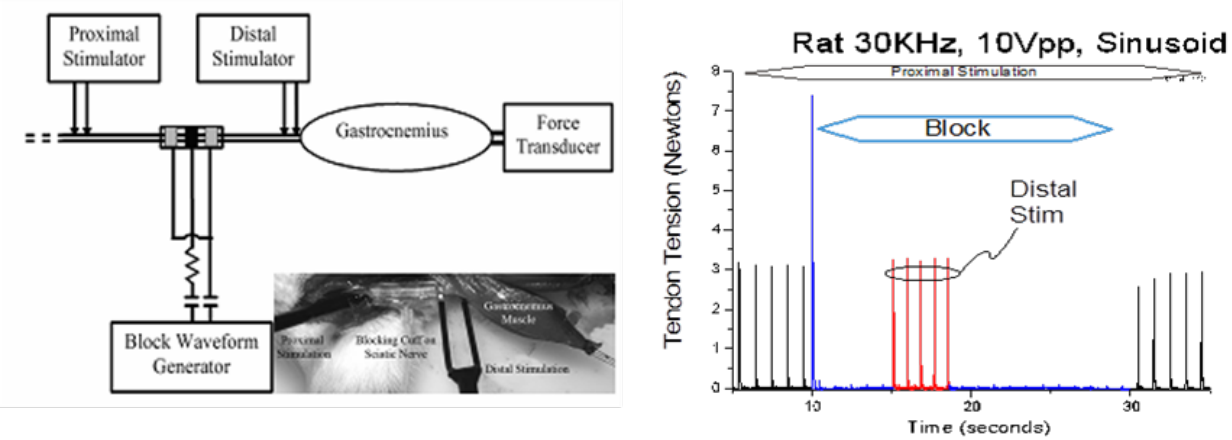

Figure 1. Experimental setup for pre-clinical HFNB testing and a typical recording

These findings from non-mammalian and small mammalian animals were recently confirmed in primate animals by the collaborative investigations of researchers from CWRU and Northwestern University. The study demonstrated that robust and reversible conduction block by high-frequency alternating current is feasible in the large-diameter nerves (up to 4 mm) in a non-human primate model. Block thresholds were in the range of 2-10 V_{pp} for a frequency range of 20-40 kHz and are only slightly higher than the amplitude range reported for the 1-mm diameter nerve in small animals (Ackermann et al 2011).

1.3 First-in-Human Study

A first-in-human study was conducted to prove the feasibility of HFNB in reducing chronic post-amputation pain in a small group of subjects during a short period of therapy. The study was conducted at the Ohio Pain Clinic affiliated with Kettering Health Network (KHN) under IRB approval. A total of five (5) lower-limb amputees were enrolled. The main inclusion criteria were chronic and severe pain in an amputated limb and significant pain reduction after local anesthetic injection for temporary nerve block.

A nerve cuff electrode, as shown in **Figure 2,** was placed on each target nerve during an outpatient surgery under general anesthesia. One cuff electrode with a diameter between 9 and 12 mm was placed on the sciatic nerve for each of the three (3) above-knee amputees, while two

(2) cuff electrodes with diameters between 5 and 10 mm were placed on the tibial and common peroneal nerves in the two (2) below-knee amputees. The leads from the electrodes were tunneled subcutaneously and exited at the lateral side of the thigh to terminate on a connector taped on the skin.

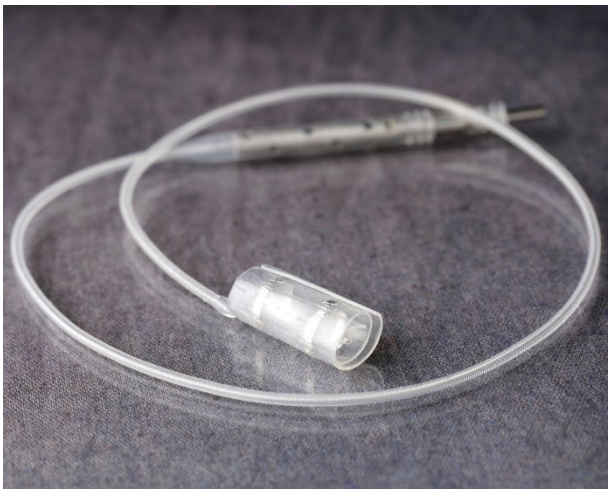

Figure 2. Nerve cuff electrode

This electrode is of a "self-sizing" design to prevent compression on the nerve trunk while ensuring intimate contact with the nerve (Naples et al 1988). It consists of platinum contacts embedded in silicone substrates and adopts a bipolar configuration with an inter-polar distance close to the cuff inner diameter (Ackermann et al 2009). The long-term safety and stability of performance for the electrode-lead system has been demonstrated in multiple human studies, in which the leads crossed multiple joints in both lower and upper extremities without breakage after long-term uses (Polasek et al 2009, Fisher et al 2009, Brelen et al 2010).

An external waveform generator was connected to the implanted nerve cuff electrode during the first in-clinic testing one week after surgery. Various frequencies in the range of 5-30 kHz were tested for the effect on the chronic pain and accompanying sensations at various voltages. Subjects attaining significant and consistent pain reduction during the in-clinic testing were given the portable generator for home therapy between the clinical visits. Subjects were also required to keep a daily diary on pain intensity, device use, and pain medication intake.

Among the five (5) subjects tested, four (4) attained pain relief during in-clinic testing, while two (2) of them used the therapy at home for a brief period with significant pain reduction. For all subjects, the implanted electrodes were explanted on Day 29 after implantation according to the IRB-approved protocol for a non-permanent implant study. No adverse device effects occurred during the study. The visual inspection during the explant surgery did not find any noticeable tissue damage in the nerve under the cuff electrode or surrounding tissues. The neurological exam conducted post explant surgery did not find detectable deterioration of sensory or motor function in any subject.

The most important finding of this study is that a brief application of 10-30 minutes of HFNB can result in an extended period of pain reduction lasting tens of minutes or even hours. This means

the device does not have to deliver the energy to the nerve continuously to attain extended pain reduction, a huge benefit for the implementation of the therapy by an implantable battery-powered generator as the final product. The most important lesson learned from this study is the episodic nature of post-amputation pain can affect the implementation of a short-term study when subjects have low baseline spontaneous pain at a prescheduled visit for testing and setting up appropriate therapeutic parameters for home use. In conclusion, the feasibility of using high-frequency nerve block in reducing chronic post-amputation pain is demonstrated without any adverse events by this first-in-human study, warranting further long-term studies.

1.4 Pilot Clinical Study

A Pilot study on electrical nerve block for post-amputation pain was conducted as a follow-on to the first-in-human study, which showed short-term efficacy and safety of High Frequency Nerve Block (HFNB) in five (5) subjects for 28 days. The objective of the open-label Pilot study was to assess the long-term efficacy and safety of the therapy in a larger patient population, specifically, a 3-month primary endpoint with up to 12-month follow-up in 10 subjects.

The study was initiated in May 2012 following IDE approval by the FDA and protocol approval by the designated Institutional Review Board. The clinical study was performed at the Ohio Pain Clinic affiliated with Kettering Health Network in Dayton, Ohio. The Principal Investigator is Amol Soin, MD, an interventional pain physician. Seven (7) subjects who received home therapy had passed 3-month primary endpoint; among them, five (5) subjects had passed 6-month follow-up, and 1 subject completed 12-month follow-up. As of 04 November 2019, three (3) subjects remain active in the long-term follow-up phase and continue to employ the study device per device logs.

1.4.1 *Subject Population*

Patients suffering from severe and chronic post-amputation pain were screened according to the study eligibility criteria. Subjects with phantom pain and residual limb (stump) pain were included per the criteria. Among all of the inclusion criteria, attaining significant pain relief after nerve block injection just proximal to the neuroma, was the strongest predictor of response to HFNB.

The population of this Pilot study represented a good distribution of the characteristics of amputees and post-amputation pain. Specifically, it includes both dysvascular and trauma etiologies, both above and below knee amputees, both stump and phantom pain, and both persistent and episodic pain.

Subjects for the study were recruited by physician referral and newspaper advertisement during a period of 10 months. Among the 24 initial contacts, 15 subjects signed consent, and a final set of 10 subjects proceeded to surgical implantation, the participant limit specified by the IDE. Seven (7) subjects who received home therapy completed the 3-month primary endpoint.

1.4.2 *Electrode Implantation*

The placement of the cuff electrode was performed under general anesthesia. The procedure was completed in approximately 30 minutes in all subjects and no surgical complications were reported. The leads from the electrodes were tunneled subcutaneously, exited at the lateral side of the thigh, and terminated on an external connector taped on the skin. An external cable was

used to connect the percutaneous lead to a portable waveform generator for implementing the therapy.

1.4.3 *As-Needed Therapy*

Each of the seven (7) subjects who attained pain relief during the in-clinic testing was assigned an external generator with a specific parameter setting. These subjects used the therapy on an "as needed" basis for pain relief by pushing a button on the external generator. They recorded the pain intensity, on a 0-10 Numerical Rating Scale (NRS), immediately before and after each 30-minute therapy session in a diary. The diary entries were verified for consistencies against the electronic log in the external generator during subsequent clinical visits.

1.4.4 *Primary Outcome*

All of the seven (7) subjects who received as-needed therapy were responders per the predefined success criterion on the primary outcome of achieving ≥ 50% pain reduction in ≥ 50% therapy sessions by 3-month endpoint. Pain reduction after each therapy session and across all 7 subjects decreased on average by 4.3 per session. In general, pain relief lasted for several hours after each therapy session. The therapeutic efficacy was sustained through the follow-up period of 4-12 months.

1.4.5 *Safety Assessment*

No changes of residual motor and sensory function were observed during physical examination up to the last follow-up visit for all subjects. No device-related unanticipated adverse events occurred during the study. Beside dislodgement and loss of function for one (1) electrode in one (1) subject with a special anatomical condition, all other devices functioned as intended in all other subjects throughout the as-needed therapy period through 12-month study endpoint.

1.4.6 *Conclusion*

In summary, this Pilot study generated preliminary evidence on the efficacy and safety of the electrical nerve block therapy, which justifies the planning for a larger-scale confirmatory study for the market approval of the device.

2 Device Description

The Neuros Medical® Altius® System includes a Cuff Electrode (**Figure 3**), Generator with an integrated rechargeable battery, Patient Controller, Charger with charging coil, Programmer Application and Programmer Wand. The Cuff Electrode will be connected to an implanted Generator which is programmed by means of a Programmer Application on a Windows PC. The Windows PC wirelessly communicates with the Generator through a Programmer Wand.

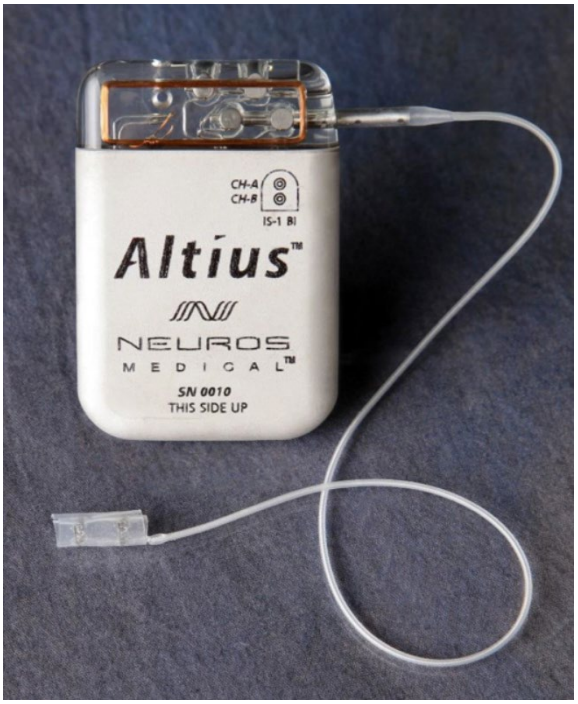

Figure 3. Implantable Generator and Nerve Cuff Electrode

A treatment session is launched by using the Patient Controller. The treatment may be considered patient-controlled analgesia (PCA), which is based upon the patient's need for pain control. The patient will use the Charger to recharge the battery contained within the Generator.

2.1 Cuff Electrode

The Cuff Electrode is comprised of platinum contacts embedded in silicone substrates similar to other implantable nerve electrodes that are commercially available. The electrode is "self-curling" and "self-sizing". This prevents nerve trunk compression while sustaining contact with nerve tissue. The Cuff Electrode has a bipolar configuration with an inter-polar distance close to the inner diameter of the cuff. It has been used for permanent implant in two earlier investigational studies. Long-term safety and stability of the electrode has been demonstrated in these human studies (Polasek et al 2009, Fisher et al 2009).

2.2 Generator

The implantable waveform Generator consists of electronic components and a rechargeable battery. The treatment delivered by the Generator is activated by a hand-held Patient Controller. The Generator is periodically recharged using an external Charger.

2.3 Patient Controller

The Patient Controller is used by a patient to start or stop a treatment session. The communication between the Patient Controller and the implanted Generator is realized via a digitally modulated magnetic field. Communication is possible within a distance of 0-2 inches.

2.4 Charger

The Charger consists of a keypad with a button for subjects to start or stop a charge session along with visual and audio indicators to report the status of the charging process. The communication between the charger and the implanted Generator is performed by charge link which performs a transcutaneous energy transmission.

2.5 Programmer Application

The Programmer Application provides a graphical user interface which operates on a Windows PC. The Programmer Application, with a Programming Wand, is used to set and retrieve dose parameters and log information from the Generator.

2.6 Programmer Wand

A Programmer Wand is used to retrieve or send the dose parameters to the implanted Generator. It consists of a keypad with buttons to set and retrieve dose parameters. It has visual indicators which report the response to the commands. The communication between the wand and the Generator is by telemetry. To communicate, a wand is aligned over the implanted Generator, and kept within a distance of 1.5 inches.

2.7 Device Labeling

The Altius System components shall bear a label with the name and place of business of Neuros Medical and the following statement: "CAUTION--Investigational device. Limited by Federal (or United States) law to investigational use."

3 Study Objective

3.1 Primary Objective

The primary objective is to evaluate the safety and effectiveness of the Altius® System High-Frequency Nerve Block (HFNB) treatment for the management of post-amputation pain.

3.2 Secondary Objective

The secondary objective is to determine the impact of Altius HFNB treatment for post-amputation pain on health-related quality of life outcomes and medication use.

4 Study Design

The study protocol will begin only after the study has received FDA Investigational Device Exemption (IDE) and local Institutional Review Board (IRB) approval.

4.1 Overview

This study is a double-blinded, randomized, sham-controlled study with two parallel groups.

4.2 Scale and Duration

A subject's study participation will span approximately 12 months through the study completion visit (**Figure 4**). The primary efficacy endpoint will be evaluated at the Month-3 visit at the conclusion of an 8-week Randomized Testing phase. During the Randomized Testing phase, subjects will receive either Test treatment ($\mathbf{T}_t$) or Control treatment ($\mathbf{C}_t$). The Control (sham) treatment ($\mathbf{C}_t$) will be above sensory threshold but delivered at extremely low frequency. It is anticipated that this treatment will be too minimal to be therapeutic while the sensation from this treatment should provide subjects a similar expectation of efficacy as receiving the Test treatment ($\mathbf{T}_t$). Following the Randomized Testing phase, subjects will transition to a Follow-Up phase for an additional nine (9) months for collecting supplementary data related to safety and efficacy. During the Follow-Up phase all subjects will receive Test treatment ($\mathbf{T}_t$). After the 12-month follow-up, subjects may continue into a long-term follow-up phase which will continue until the End-of-Trial declaration, either product approval or study discontinuation by the Sponsor.

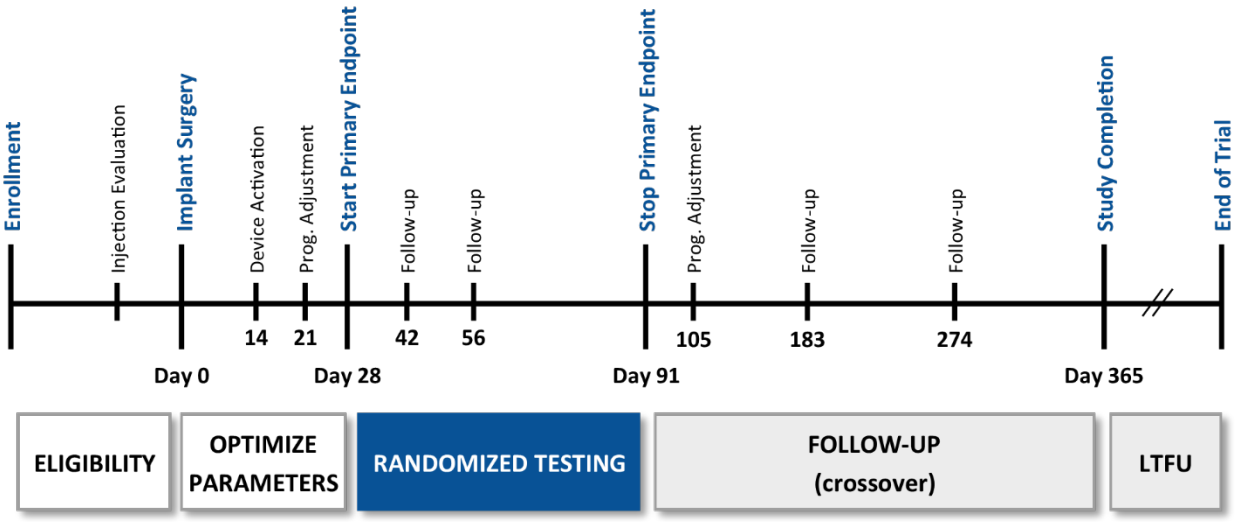

Figure 4. Study Schedule Overview

4.3 Study Variables

The primary variable to be measured during this study will be pain intensity reported by the subject. The pain intensity will be measured by the 0-10 Numerical Rating Scale (NRS). The validity of the NRS has been well demonstrated by its positive and significant correlation with other measures of pain intensity such as the Visual Analog Scale (VAS) (Jensen et al 1986, Kremer et al 1981, Wilkie et al 1990). The sensitivity to treatments that are expected to have an impact on pain intensity has also been demonstrated (Keefe et al 1981, Paice and Cohen 1997). The NRS is also extremely easy to administer and score, so it can be used with a greater variety of subjects than is possible with the VAS (Jensen et al 1986, Paice and Cohen 1997, Jensen et al 2001). The use of the NRS in clinical studies on pain interventions has also been recommended by The

Initiative on Methods, Measurements, and Pain Assessment in Clinical Trials (IMMPACT) (Dworkin et al 2005, Dworkin et al 2010).

Secondary variables to be measured during this study will include pain interference to the activities of daily living (ADL) reported by the subject. The pain interference will be assessed by Brief Pain Inventory (BPI), more specifically, the section in the BPI that assesses pain interference with: general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life (Cleeland and Ryan 1994). This portion of the BPI assesses the impact of pain on function and quality of life. The validity of the BPI in chronic pain studies has been demonstrated (Keller et al 2004). The use of the BPI in clinical studies on pain interventions has also been recommended by the IMMPACT (Dworkin et al 2005, Dworkin et al 2010).

In addition to pain intensity and interference, data on the use of pain medication and prosthetics will also be collected by diary and questionnaires to corroborate the findings from the primary and secondary variables.

4.4 Assessment Instruments

Study assessments were selected to evaluate: symptom relief, functionality, quality of life, and global rating of improvement. The assessments shall be detailed in the informed consent document for this study and will be fully explained to participants prior to study enrollment. The assessment shall be administered during study visit. The assessments include:

- Numerical Rating Scale (NRS)
- Brief Pain Inventory (BPI)
- Short Form Health Survey (SF-12)
- EuroQol (EQ-5D)
- Patient-Global Impression of Change (PGIC)

4.5 Justification of Study Design

This study design is similar to the majority of IDE pivotal studies approved for neuromodulation devices for treating neurogenic pain, such as occipital nerve stimulation for migraine (e.g. NCT00286078 listed on ClinicalTrials.gov). For these studies, implantation surgery for sham treatment in a Control group is used for blinding. The length of a three (3) month controlled phase represents reasonable compromise between the scientific study pursuits, which prefer longer period of parallel comparison, and ethical considerations, which prefer a shorter period of withholding a potentially beneficial treatment.

5 Subject Selection

Individuals will be selected to participate in this study based on the inclusion and exclusion criteria described below. Individuals will not be excluded on the basis of gender, ethnicity, religious beliefs, nationality or any other reasons that may be viewed as discriminatory.

5.1 Study Population

Participants in this study shall have post-amputation pain. People suffering from chronic severe post-amputation pain will be screened by the eligibility criteria shown below (5.2 Inclusion Criteria and 5.3 Exclusion Criteria). The most critical criteria will be the injection evaluation: potential study subjects must show significant pain relief after nerve block injection proximal to the neuroma. This has proven to be a strong predictor of the subject's response to electrical nerve block in the Pilot study.

Implantation of the Altius System in Subjects on Anticoagulation Therapy

In the judgement of the enrolling and implanting physicians at the site and appropriate treating physicians, there must be consensus on appropriateness for inclusion of the subject in the study and on the plans for management of individualized peri-procedural anticoagulation therapy based on most recent published best practice guidelines at the time of implant.

5.2 Inclusion Criteria

Study participants must meet all of the following inclusion criteria:

1. Subject shall have a unilateral amputated lower limb for no less than 12 months. If the amputation needed revision within 12 months, patient could be enrolled if investigator documents that the amputation site has healed and subject's symptoms have stabilized.
2. Post-amputation pain shall be chronic (persistent over 6 months) and resistant to pain medications with a documented history within the subject's medical records.
3. Subject shall have frequent and recurring pain defined as no less than 4 episodes of pain ≥ 5 (NRS) per week on average (to be confirmed with baseline pain diary).
4. Subject's typical pain episode should last no less than 60 minutes.
5. Subject shall demonstrate response to two injections, one regional nerve block and the other saline. Response to the regional nerve block is defined as greater than or equal to a 50% pain reduction by NRS at 20 minutes from administration of Lidocaine. An allowable, non-therapeutic response to saline is defined as less than 30% pain reduction by NRS 15 minutes after administration. NRS must be ≥ 5 before first injection.
6. Subject's regimen of drug therapy for pain shall be stable for no less than 4 weeks prior to implant and shall not change without approval of investigator until after their Month-3 visit. Subject shall sign a pain medication "contract" to confirm acceptance of guidelines for the use of pain medication.
7. Subject agrees not to replace or alter their prosthetic (if applicable) until after their Month-3 (primary endpoint) visit.
8. Subject is able to independently read and complete all questionnaires provided in English and use electronic diary during study.

9. Subject is willing and able to provide informed consent and comply with all procedures and assessments required by study protocol.
10. Subject, and caregiver if applicable, is able and willing to be available for study visits throughout the duration of the study, e.g., no planned relocation of residence or extended vacation during the study that would prevent compliance with study visit schedule.
11. Subject shall be 21 years of age or older (FDA definition of non-pediatric) and legally able to provide written informed consent.

5.3 Exclusion Criteria

Study participants must not meet any of the following exclusion criteria:

1. Subject is currently implanted with any active implantable device including but not limited to: pacemaker, implantable cardiac defibrillator, implantable neurostimulator (e.g. peripheral or spinal cord stimulator), or implantable drug pump.
2. Subject has a source of pain other than post-amputation pain (incl. dysesthesia, cancer-related, visceral, angina, migraine, causalgia) which in the opinion of the investigator may interfere with the reporting of post-amputation pain.
3. Subject has medical contraindications to surgery, including but not limited to cardiovascular, pulmonary, renal, liver or hematological disorders, active inflammation, medical contraindication for general anesthesia (e.g., severe cardiopulmonary disease), compromised immune state (due to concomitant disease or medications such as chemotherapy or immunosuppressants), or anticoagulant medication that cannot be discontinued for perioperative period.
4. Uncontrolled diabetes as defined by HbA1c > 8.0.
5. Spasticity in their residual limb such that the subject cannot achieve volitional full range of motion (ROM) of joints on involved side.
6. Subject has skin graft or severe scarring over targeted implant site or any anatomical conditions that would prevent placement of the Altius System components.
7. Subject demonstrates an inability to discern differences in pain severity, report pain intensity and related information, or complete a pain diary.
8. Subject has a suspected or known allergy to any materials of the Altius System in tissue contact or Lidocaine (necessary for injection screen).
9. Subject has received therapeutic regional nerve block (e.g. anesthetic with steroid, and/or opioids) for post-amputation pain within 30 days prior to baseline visit.
10. Subject's usual seated posture includes sitting on the end of their stump.

11. Subject is a woman who is not using adequate contraception, is pregnant or breastfeeding, or intends to become pregnant during the course of the study.
12. Subject is currently participating or intends to participate in another investigational drug or device clinical study that may influence or interfere with the data that will be collected for this study.
13. Subject has a condition requiring MRI studies or diathermy after device implantation.
14. Subject has a history of any alcohol or substance abuse or dependence which has required prior medical treatment or intervention. Subject has active alcohol or substance abuse.
15. Subject has a condition that, in the opinion of the investigator, would interfere with study compliance (incl. unresolved issues of secondary gain) or subject's safety.
16. Subject has a life expectancy of less than 24 months.
17. Subject is diagnosed with or has untreated psychological conditions: borderline personality disorder, major depression disorder characterized by hospitalization within the prior year for a major depressive episode.
18. Subject has current diagnosis of any progressive neurological disease such as multiple sclerosis, chronic inflammatory demyelinating polyneuropathy, rapidly progressive diabetic peripheral neuropathy, or any tumor of the nervous system.
19. Subjects with active local or systemic infection, prior recurrent bacterial infection, those who are immunocompromised or have high risk of infection due to other comorbidities.

5.4 Subject Accountability

5.4.1 *Enrollment*

After completion of the consent process, the study subject is enrolled upon fully executing informed consent. All subjects enrolled in this study shall be accurately accounted and documented in study records.

5.4.2 *Subject Status and Replacement*

Enrolled-and-implanted refers to all subjects who have fully executed an informed consent prior to study participation, and subsequently received implant of the Altius System. Subjects are considered enrolled-and-implanted as soon as an implant procedure is attempted. Only subjects who are enrolled-and-implanted will count towards the sample size limit and these subjects cannot be replaced.

Enrolled-not-implanted refers to enrolled subjects who have fully executed the informed consent document, but have not been implanted with the Altius System. If a subject is determined by the investigator not to qualify for the study because they do not meet all of the inclusion criteria, including the injection evaluation, or are found to meet one or more of the exclusion criteria, the subject will be considered enrolled-not-implanted. Any subject that terminates from the study prior to the implant procedure will be considered enrolled-not-implanted. Subjects who are enrolled-not-implanted will not be counted towards the sample size limit and can be replaced.

5.4.3 *Termination of Subjects*

Subjects may terminate from this study for various reasons and at their own will. All subjects who terminate will follow the End-of-Trial procedures (§7.2 End-of-Trial) and the reason for termination will be documented in study records. A subject who has terminated the study prior to the End-of-Trial Declaration, for whatever reason, will be required to discontinue using the Altius System and will be asked to return all investigational components of the Altius system, including the Patient Controller and Charging System. Technical support and replacement of external device components will no longer be provided.

5.4.4 *Enrollment Controls*

The Sponsor will monitor enrollment to ensure a single institution does not enroll and implant more than approximately 20% of the overall study population. Enrollment will be monitored through regular review and status updates by the Sponsor. Each site will have a site-specific study enrollment goal developed through ongoing communication and review. Sites unable to meet enrollment may be withdrawn from further study participation.

6 Study Visits

6.1 Visits Schedule

The Study will consist of the following phases: Eligibility, Implant, Randomization and Parameter Optimization, Randomized Testing, Follow-Up, and Long-term Follow-up, as shown in **Table 1 - 3**.

Table 1. Study Schedule for Eligibility

Schedule	Day from Baseline
Eligibility	
Baseline (Start eDiary)	Day 0
Injection Evaluation (after 2 weeks or more of eDiary)	>14 days

Table 2. Study Schedule for Surgery through Long-Term Follow-Up

Schedule	Day from Implant
Implant	
Implant Surgery (by Surgeon)	Day 0
Randomization and Parameter Optimization	
Randomization and Activation	Day 14 ± 3
Programming Adjustment	Day 21 ± 3
Randomized Testing	
Month-1, Start of Primary Endpoint	Day 28 ± 3
Follow-up	Day 42 ± 7
Follow-up	Day 56 ± 7
Month-3, Conclusion of Primary Endpoint (and crossover)	Day 91 + 14
Follow-Up	
Programming Adjustment (as needed)	Day 105 ± 7
Month-6	Day 183 -14, +30
Month-9	Day 274 -14, +30
Month-12, Subject Study Completion	Day 365 ± 30
Long-Term Follow-Up (Optional)	
Follow-up (as needed, no greater than every 12 months)	Day +365 ± 30

Table 3. Study Schedule for Surgical Revision and Explant

Schedule	Day from Surgery
Explant	
Explant Surgery (by Surgeon)	Day 0
Post-Op Follow-up	Day 14 ± 7
Follow-up	Day 183 ± 30
Revision	
Revision Surgery (by Surgeon)	Day 0
Post-Op Follow-up	Day 14 ± 7

6.1.1 *Data Collection Schedule*

Data will be obtained through subject-reported outcomes or source documents. Primary endpoint data will consist of patient-reported outcomes (PRO) collected using Electronic Diaries (eDiaries). All other study data will be collected on case report forms (CRFs) by the investigator or designee. **Table 4** summarizes the study assessments.

Table 4. Assessments and Evaluations

Study Phase	Study Visit	Medical History	DASS	Urine Dipstick	Sensorimotor Eval	Injection	HbA1c*	Wound Eval	Programming	Blinding Questionnaire	Device Log	NRS (eDiary)	BPI	SF-12	EQ-5D	P-GIC	AE Assessment
Eligibility	Baseline											start					
	Injection Evaluation																as needed
Implant	Implant Surgery																as needed
Randomization & Parameter Optimization	Device Activation																as needed
	Programming Adjustment																as needed
Randomized Testing	Month-1								†								as needed
	Follow-up								†								as needed
	Follow-up								†								as needed
	Month-3																as needed
Follow-Up	Programming Adjustment (if needed)								as needed								as needed
	Month-6								as needed								as needed
	Month-9								as needed								as needed
	Month-12 Study Completion								as needed			end					as needed
Long-Term Follow-Up	Follow-up								as needed								as needed
Explant (if needed)	Explant Consultation †																as needed
	Explant Surgery																as needed
	Post-op Follow-up																as needed
	Month-6 Follow-up																as needed
Revision (if needed)	Revision Surgery																as needed
	Post-op Follow-up								as needed								as needed
	Programming Adjustment (if needed)								as needed								as needed
Unscheduled	Unscheduled Visit								as needed								as needed

† Programming Adjustments during the Randomized Testing Phase should only be made if necessary.
*HbA1c will be collected for diabetic subjects only. A blood sample within 3 months of scheduled injection may be used to meet HbA1c testing criteria.

6.2 Eligibility Phase

Subject recruitment activities may include direct advertising and physician to physician referral. No study procedures will be conducted prior to subject fully executing the informed consent. The evaluation of subject eligibility will include a Baseline Visit, Baseline eDiary Assessment, and Injection Evaluation Visit. A final eligibility determination, based on the inclusion and exclusion criteria, will be made at the end of the Injection Evaluation.

6.2.1 *Prosthesis and Pain Medication Lock*

Subjects are required to remain on a stable pain medication regimen with no prosthesis modifications from the Baseline Visit through their Month-3 (primary endpoint) Visit. Once pain medication is locked, modifications in the regimen of pain management medications (including any rescue medications for breakthrough pain) shall not change without approval of the investigator. Subjects shall sign a pain medication 'contract' to confirm acceptance of guidelines for managing their prescription(s) of pain medications and shall not seek any pain medications outside of the study. Any violation of this contract will be sufficient grounds for termination from the study. Note, if subjects request modification of their existing prosthesis during the initial eligibility phase and have completed eDiary compliance, they will need to repeat the eDiary reporting requirements.

6.2.2 *Baseline Visit*

After completing the informed consent process, an initial eligibility assessment will be conducted to evaluate each candidate against the inclusion and exclusion criteria by means of subject interview and medical chart review. This evaluation will not include the baseline eDiary or injection evaluation. Consenting and initial eligibility determination may be assessed remotely utilizing a telemedicine platform used for clinical research purposes. Clinical sites are to remain compliant with their institutional requirements and IRB policy in order to continue recruiting, screening and enrolling subjects. Once subjects pass this initial phase of screening, study-related procedures (such as injections and implants) will occur when sites are able to safely bring the subjects into their practice.

Baseline evaluations and assessments include:

- Medical History
- Demographics
- Urine Dipstick (for woman of childbearing potential)
- Brief Pain Inventory (BPI)
- Short Form Health Survey (SF-12)
- EuroQol (EQ-5D)
- Depression Anxiety Stress Scales (DASS)

Subjects who have passed the initial eligibility assessment will be issued an eDiary device for recording pain intensity, medication and prosthetic use (if applicable). The eDiary will be returned to the Sponsor at subject's termination or completion of the study.

6.2.3 *Baseline eDiary*

A baseline eDiary will be collected for no less than 14 calendar days with 2 or fewer days of missing data. The eDiary will collect subject's responses to a few short questions regarding the severity, frequency, and duration of pain, medication consumption, and prosthetic use.

Baseline eDiary collection may last up to 4 weeks but must conclude with 14 days of data demonstrating compliant eDiary entry. From the start of eDiary data collection, the subject will be required to make daily entries. eDiary entries will be routinely uploaded to an electronic database via wireless data communication and will be reviewed for completeness. If necessary, the subject will be contacted by phone for corrective actions regarding incompliance or may return to the site for further training.

Subjects who do not demonstrate 14 days of compliant eDiary collection will be considered screen failures and will not proceed any further beyond this point; these subjects shall be documented as screen failures. Subjects whose eDiary confirm frequent and recurring pain episodes, as defined per the inclusion criteria, will proceed to the Injection Visit.

6.2.4 *Injection Evaluation Visit*

On the day of the injection evaluation, the subject should be asked to refrain from using rescue medication (opioids/narcotics) prior to the visit. Subjects may use routine medications the day of the injection evaluation. At the start of the injection evaluation, the subject's limb overall post-amputation pain must be ≥ 5 on a 0-10 numerical rating scale (NRS). If the subject's pain is < 5 they will be rescheduled.

Injection evaluations are to be performed without external prosthetic devices, wraps or socks on the affected limb. External prosthetic devices, including socks and wraps, may be reapplied at the conclusion of the injection evaluation visit.

Nerve localization techniques, such as ultrasound imaging, must be used to guide each injection. For above-knee amputees (AKA), the target injection site should be near the sciatic nerve as distal as possible; for below knee amputations (BKA), the target injection site should be near the bifurcation of the tibial and common peroneal nerves.

To assess the effect of placebo, 1 ml of saline will be injected prior to the anesthetic injection. The saline shall be administered near but slightly away from the target injection site. An allowable, non-therapeutic, response to saline will be defined as a pain reduction < 30% on a NRS 15 minutes after administration. Subjects who demonstrate a therapeutic response to saline will be documented as screen failures and will not proceed any further beyond this point.

If the subject successfully passes the saline injection, 15 ml 2% Lidocaine will be injected. A response to Lidocaine will be defined as a reduction of ≥ 50% on NRS at 20 minutes from administration relative to the pain intensity saline injection (level of pain before saline needle insertion). Subjects who do not respond to Lidocaine will be documented as screen failures and will not proceed any further beyond this point. Injection assessment will need to be repeated if there has been a minimum of six (6) months from the time of administration to the time of implant.

6.2.5 *Eligibility Determination*

Final eligibility will be determined by the investigator based on whether the study subject meets all inclusion criteria and none of the exclusion criteria, which include the successful completion of a baseline eDiary and injection evaluation.

6.3 Implant Phase

The implantable components of the Altius System include the Generator, Cuff Electrode, and Extension(s). The Altius system implant will be conducted per the "Altius® System for Amputation Pain Investigator Guide", as summarized in the subsequent section.

6.3.1 *Implant Surgery Visit*

During this outpatient surgical visit, the study surgeon will implant Cuff Electrode(s), Extension(s) and a Generator. The procedure will be conducted under general anesthesia and will take roughly one hour from first incision to surgical closure based on the Pilot Study. As part of regular medical care, female subjects of childbearing potential will undergo a urine dipstick test during the initial eligibility phase.

Cuff Electrode Implantation

The procedure for placing the Cuff Electrode on the previously severed nerve is similar to the conventional procedure for neuroma resection. Subjects implanted with the Altius System will receive either one Cuff Electrode or two Cuff Electrodes.

The target nerve(s) will be exposed proximal to the neuroma formation at the tip of the severed nerve(s). The nerve(s) will then be isolated from the surrounding tissue for a length of a few centimeters. The diameter of the nerve trunk will be measured to aid selection of a Cuff Electrode size.

The spiral Cuff Electrode will be gently opened and wrapped around the target nerve using two pairs of dressing forceps. The self-sizing spiral design assures proper contact for delivery of treatment without restriction or compression of the nerve.

The cable from the Cuff Electrode will then be tunneled subcutaneously for connection to the Generator. The Generator has two connector ports to accommodate up to two (2) Cuff Electrodes. An unused port of the Generator will be sealed with a port plug.

Extension Implantation

Extension(s) can be used to connect the Cuff Electrode to the Generator. The proximal IS-1 connector of the Extension should be inserted into the IS-1 connector port of the Generator. Following insertion, the setscrew within the Generator header should be tightened with the torque-limited wrench provided with the Generator.

Generator Implantation

The implantation location of the Generator will be similar to locations selected for neurostimulators. The location should be within easy reach of the subject for communication with and recharging of the device. The primary location for the subcutaneous pocket is the

anterior or lateral abdominal wall. Secondary location includes the anterior side of the thigh. The Generator will be placed in a subcutaneous pocket similar to a pacemaker or neurostimulator. The pocket depth should be no more than 1 cm (0.4 inches). The outside face of the Altius Generator (the side with "Altius") should face outward to allow recharging and communication with the device.

Implant Assessment

After implant of the Altius System, intraoperative communication will be established with the Generator and the system will be interrogated to verify Cuff Electrode impedances are within expected ranges.

Post-Surgical Care

As part of regular medical care, wound healing will be evaluated approximately two weeks after implant.

6.4 Randomization and Programming Phase

6.4.1 *Parameter Settings*

During the Randomized Treatment Phase subjects will be randomized to receive either Test ($\mathbf{T}_t$) or Control ($\mathbf{C}_t$) treatment. Test ($\mathbf{T}_t$) or Control ($\mathbf{C}_t$) treatment will be limited to the parameter ranges provided in **Table 5**.

Table 5. Parameter Ranges for Randomized Testing Phase

Treatment	Frequency	Amplitude	Ramp-up	On time[†]
Control ($\mathbf{C}_t$)	0.1 Hz	0-16V	1-5 minutes	8 minutes
Test ($\mathbf{T}_t$)	5kHz, 10kHz	0-16V	1-15 minutes	30 minutes

[†] On-Time duration includes the duration of Ramp-up

6.4.2 *Subject Group Assignment*

Study subjects will be randomized in a 1:1 ratio to receive either Test treatment ($\mathbf{T}_t$) or Control treatment ($\mathbf{C}_t$). Randomization will be stratified by clinical site with random permuted blocks to achieve approximate balance of treatment allocation within each site. Using a pre-generated randomization table, group assignments will be sequentially assigned. The block size will be concealed to site personnel.

6.4.3 *Device Activation Visit*

An office visit will be scheduled after the implant surgery to determine treatment parameters for Test treatment ($\mathbf{T}_t$) or Control treatment ($\mathbf{C}_t$). This visit will occur two weeks after implant to allow for an adequate healing period.

System Integrity Check

At the beginning of this visit, communication will be established with the Generator and the system will be interrogated to verify Cuff Electrode impedances are within expected ranges. To verify the integrity of the implanted system and determine sensory threshold, individual pulses (100 µsec biphasic) will be delivered. Sensory threshold will be evaluated by incrementally increasing the voltage of the single-pulse. Once system integrity is verified, the subject will proceed to Randomization.

If system integrity is not verified, the subject will not proceed to Randomization but will be scheduled for a subsequent visit to confirm the negative findings. During the subsequent visit, if integrity is verified the subject will proceed to Randomization and the study schedule will be adjusted accordingly. If the negative finding is confirmed, the subject will be scheduled for revision surgery.

Randomization

The subject will be randomized only after the system integrity has been confirmed. The next sequential randomization assignment will be obtained by the assigned Field Clinical Specialist (FCS) to determine the subject's assignment to Test treatment (**T_t**) or Control treatment (**C_t**).

It is important that subjects receiving Test treatment (**T_t**) or Control treatment (**C_t**) have a nearly identical experience during device programming. For this reason, a script will be read to the subject describing the parameter selection procedures.

Parameter Selection Procedures

Appropriate parameters for the treatment will be determined based on the subject's response to the assigned treatment, either Test treatment (**T_t**) or Control treatment (**C_t**). In this way, subjects will only experience one treatment, the treatment that they will receive for the duration of the Randomized Testing phase.

> Subjects randomized to Control (**C_t**) treatment: To find the subjects response to low-frequency stimulation, a series of 100µsec biphasic rectangular pulses will be delivered at a frequency of 0.1 Hz. The voltage will be gradually increased to a level that reliably produces a perceivable sensation. This voltage value will be used for the Control treatment (**C_t**).
>
> Subjects randomized to (**T_t**) Test Treatment: To find the subjects response to High-Frequency Nerve Block, a series of high-frequency waveforms will be delivered briefly to each subject. The voltage will be gradually increased to a level that produces a strong but tolerable transient sensation for the subject. This voltage value will be used for Test treatment (**T_t**).

The FCS will then program the corresponding parameters into the implanted Generator by using the Programmer Application. The parameters programmed into the Generator will be recorded in the Programming CRF, which will be stored separately from the other study documents and not accessible to the investigator unless necessary for safety-related unblinding. After the

parameters are programmed the subjects in both groups will be asked to complete the Blinding Questionnaire.

The subject will be trained on using the Patient Controller to initiate a treatment session based on their need for pain relief. The group assignment will be concealed to subjects and site personnel until the last implanted subject in the Study reaches their Month-12 visit.

6.4.4 *Subject Use of Treatment*

Each subject will use the device to deliver treatment based on their need for pain relief, similar to taking a dose of rescue medication for breakthrough pain. Specifically, when the need for pain treatment arises, the subject will activate the Generator with the Patient Controller and receive the prescribed treatment. All parameters for the treatment are preset in the Generator during the office visit and cannot be changed by the subject (as defined in **Table 5**). In addition, a preset lock-out period prevents continuous use of treatment since it is expected to have sustained effect for a few hours or longer, based on observations in the Pilot study.

The outcomes from the use of treatment will be recorded in the subject's eDiary. Specifically, pain intensity will be reported immediately preceding a treatment session and again after 30 minutes and 2 hours (120 minutes). Once per day, subjects will be requested to report their current pain plus worst, least, and average pain in the past 24 hours.

Subjects will also be instructed that they are permitted to take their rescue pain medication if the treatment by the device does not provide adequate pain relief. Each use of medication will be recorded in the eDiary, including medication name, dose, and time of administration.

6.4.5 *Programming Adjustment Visit*

The first follow-up visit will be scheduled one week ± 3 days after device activation. Adjustments of treatment parameters will be made during this visit to optimize treatment for the subjects receiving either treatment, Test ($\mathbf{T_t}$) or Control ($\mathbf{C_t}$).

Adjustments of the parameter settings can be made by the FCS based on subject's use of treatment or additional in-clinic evaluations. The voltage can be increased or decreased to optimize treatment effect or sensation during treatment. The duration of the ramp-up can also be adjusted based on feedback from the subject. The parameters used during the in-clinic evaluations and corresponding changes in the parameters will be recorded in the Programming CRF and stored by the Field Clinical Specialist.

Subject's use of their Generator is recorded in an electronic log stored on the Generator and the log will be retrieved during this visit. This machine-generated data will be used to assess the validity of the subject-reported data in the eDiary. In case of significant discrepancies between the two sets of data, corrective actions will be taken to improve the quality of data reporting.

6.5 Randomized Testing Phase

6.5.1 *Month-1 Visit*

The Month-1 Visit begins the Randomized Testing phase. During this visit the following assessments will be performed:

- Blinding Questionnaire
- Brief Pain Inventory (BPI)
- Short Form Health Survey (SF-12)
- EuroQol (EQ-5D)

Subjects must complete the Blinding Questionnaire prior to any parameter adjustments.

Adjustments of the parameter settings can be made by the FCS based on subject's use of treatment or additional in-clinic evaluations. The voltage can be increased or decreased to optimize treatment effect or sensation during treatment. The duration of the ramp-up can also be adjusted based on feedback from the subject. The parameters used during the in-clinic evaluations and corresponding changes in the parameters will be recorded in the Programming CRF, which will be stored separate from other study documentation.

Subject's use of their Generator is recorded in an electronic log stored on the Generator and the log will be retrieved during this visit. This machine-generated data will be used to assess the validity of the subject-reported data in the eDiary. In case of significant discrepancies between the two sets of data, corrective actions will be taken to improve the quality of data reporting.

6.5.2 *Follow-Up Visit(s)*

Subjects will be scheduled for two follow-up visits occurring every other week (POD 42 and POD 56). During these visits, adjustments of the parameter settings can be made by the FCS to optimize treatment.

Subject's use of their Generator is recorded in an electronic log stored on the Generator and the log will be retrieved during this visit. This machine-generated data will be used to assess the validity of the subject-reported data in the eDiary. In case of significant discrepancies between the two sets of data, corrective actions will be taken to improve the quality of data reporting.

6.5.3 *Month-3 Visit*

The Month-3 Visit concludes the Randomized Testing phase. During this visit the following assessments will be performed:

- Sensorimotor Assessment
- Blinding Questionnaire
- Brief Pain Inventory (BPI)
- Short Form Health Survey (SF-12)
- EuroQol (EQ-5D)
- Patient-Global Impression of Change (PGIC)

Subjects must complete the Blinding Questionnaire prior to any parameter adjustments.

Subjects who previously received Control treatment ($\mathbf{C}_t$) will be reprogrammed to receive Test treatment ($\mathbf{T}_t$). Subjects who previously received Test treatment ($\mathbf{T}_t$) will undergo parameter optimization. Subject's use of their Generator will be retrieved from the electronic log during this visit.

This visit concludes the subject's prosthesis and medication lock.

6.6 Follow-Up Phase

6.6.1 *Programming Adjustment Visit(s)*

If needed, subjects may be scheduled for a Programming Adjustment visit. It is expected that this visit will be primarily for subjects who were receiving the Control treatment (**C_t**) during the Randomized Testing phase and were converted to receive Test (**T_t**) treatment. Subject's use of their Generator will be retrieved from the electronic log during this visit.

6.6.2 *Month-6 Visit*

During this visit the following assessments will be performed:

- Blinding Questionnaire
- Brief Pain Inventory (BPI)
- Short Form Health Survey (SF-12)
- EuroQol (EQ-5D)
- Patient-Global Impression of Change (PGIC)

After the assessments and questionnaires are completed, the subject will undergo a programming adjustment, if requested. Subject's use of their Generator will be retrieved from the electronic log during this visit.

6.6.3 *Month-9 Visit*

If requested, the subject will undergo programming adjustments. Subject's use of their Generator will be retrieved from the electronic log during this visit.

6.6.4 *Month-12 Study Completion Visit*

A subject will reach study completion after their Month-12 study visit. Following study completion, the subjects may remain enrolled in the study and undergo safety reporting as defined in §16.3 Investigator Reporting Requirements. However, the subject will no longer have study visits scheduled to collect data relevant to the endpoints and scientific soundness of the study. Subjects will be asked at this visit if they wish to continue in long-term follow-up. For study participants choosing to continue, the participant will return to the study site every 12 months for long-term safety monitoring, but will otherwise undergo routine medical care.

During this visit the following assessments will be performed:

- Sensorimotor Assessment
- Brief Pain Inventory (BPI)
- Short Form Health Survey (SF-12)
- EuroQol (EQ-5D)
- Patient-Global Impression of Change (PGIC)

After the assessments and questionnaires are completed, the subject will undergo programming adjustments, if requested. Subject's use of their Generator will be retrieved from the electronic log during this visit. Subject will also return their pain diary (eDiary) at the end of this visit.

This concludes the study visit schedule and the subject will begin Long-term Follow-up if agreed.

6.7 Long-Term Follow-Up Phase (Optional)

6.7.1 *Long-term Follow-up Visits*

During Long-Term Follow-Up the study subjects will be asked to return to the study site every 12 months until End-of-Trial Declaration. Subjects will be instructed to report any device-related medical events or deficiencies throughout Long-Term Follow-Up. The subject will undergo a programming adjustment, if requested. Subject's use of their Generator is recorded in a device log stored on the implanted Generator and the device log will be downloaded during this visit.

6.8 Unscheduled Visits

If subjects have unscheduled visits, performance of study assessments should be done only as clinically indicated. Results of any assessments or reports of adverse events must be documented and corresponding data must be reported on the study case report forms. The occurrence of any unscheduled visits and the reason for the visit should be recorded.

6.9 Revision Surgeries

As necessary, a study participant may receive replacement of the Altius System Components at the expense of the Sponsor until End-of-Trial Declaration.

7 Study Termination

7.1 Termination of Subject Participation

It will be explained to the subject that they may retain the inactive Altius System or have it explanted. If the subject requests to have the Altius System explanted, the subject shall be evaluated by the surgeon during explant and safety reporting will be required as defined in §16.3 Investigator Reporting Requirements. A post-surgery evaluation visit will be scheduled 2 weeks after the explant surgery to perform a postoperative evaluation. A long-term follow-up visit will be scheduled 6 months post explant. During both study visits, AEs will be reported and the subject will undergo a sensorimotor assessment.

7.1.1 *Withdrawal from the Study*

All study participants and legal representatives have the right to withdraw their consent to participation in this study at any time during the study. Whenever possible, the site's staff should obtain written documentation of the reason for withdrawal from the participant or legal representative that wishes to withdraw consent for further study participation. If the site's staff is unable to obtain written documentation, all information regarding the participant's withdrawal must be recorded in the participant's clinical record. In addition, the appropriate CRFs must be completed.

Upon withdrawal of consent, follow early termination procedures as defined in §7.1 Termination of Subject Participation

7.1.2 *Lost to Follow-Up*

Every attempt must be made to have all participants complete the study visit schedule. If a participant does not return for study visits, the study site must make every effort to obtain compliance. A subject will be considered "*lost to follow-up*" and terminated from the trial when all of the following criteria are met:

- Documentation of three (3) unsuccessful attempts on three different dates over a period of at least one (1) month by the Investigator or designee to contact the subject or next of kin.
- Unsuccessful response after sending a written letter from the site with delivery confirmation (e.g. Certified USPS, FedEx, and UPS).
- Failure to complete two (2) consecutive visits without due cause.

At a minimum, the effort must include three (3) attempts to contact the study subject via phone call, and if contact via phone is not successful, then a letter from the site must be sent to the participant's or participant's legal representative's last known place of residence. Both phone and letter contact efforts must be documented in both the participant's medical records and on the study CRFs. If both phone and letter contact are unsuccessful and the subject has missed two consecutive study visits, the patient will be considered Lost to Follow-up.

7.2 End-of-Trial

The End-of-Trial will occur following either (1) FDA commercial approval of the Altius System for Post Amputation Pain or (2) a determination to halt pursuit of FDA approval.

7.2.1 *End-of-Trial with Commercial Approval*

Following FDA approval for the commercial distribution of the Altius System, study subjects will have the choice to retain the commercially approved device. The study site will have 30 calendar days from the date of End-of-Trial Declaration to contact the subjects and discuss their wish to retain the Altius System and the subject's decision will be documented.

If a subject chooses not to retain the Altius System, the subject will have 30 days, from the date of their documented decision, to have the Altius System deactivated or explanted with the costs of explant covered as a study related procedure. If device is explanted, a post-surgery evaluation visit will be scheduled with the surgeon two (2) weeks after the explant surgery to perform a postoperative evaluation. A long-term follow-up visit will be scheduled 6 months post explant. During both study visits, AEs will be reported, the subject will complete a BPI, SF-12, P-GIC, and undergo a sensorimotor assessment.

Following End-of-Trial the Altius System will be monitored per the Medical Device Reporting (MDR) requirements published in the final rule dated December 11, 1995, and the device may also be required to continue in a post-market surveillance study as frequently required by FDA's PMA approval.

7.2.2 *End-of-Trial Without Commercial Approval*

The determination to halt pursuit of FDA approval may occur for various reasons including the discovery of unexpected, significant or unacceptable risk to the study subjects enrolled.

If commercial approval of the Altius System has not been granted and it has been determined to halt pursuit of FDA approval, the study site will have 30 calendar days from the date of End-of-Trial Declaration to contact the subject.

Subjects will be required to discontinue using the Altius System and will be required to return all investigational components of the Altius System, including the Patient Controller and Charging System. Technical support and replacement of external device components will no longer be provided if the pursuit of FDA approval is halted.

It will be explained to the subject that they may retain the inactive Altius System or have it explanted. If the subject asks to have the Altius System explanted, the subject shall be evaluated by the surgeon during explant, and safety reporting will be required as defined in §16.3 Investigator Reporting Requirements. A post-surgery evaluation visit will be scheduled with the surgeon 2 weeks after the explant surgery to perform a postoperative evaluation. A long-term follow-up visit will be scheduled 6 months post explant. During both study visit, AEs will be reported, the subject will complete a BPI, SF-12, P-GIC, and undergo a sensorimotor assessment.

7.2.3 *End-of-Trial Declaration*

Written End-of-Trial Declaration shall be provided to all clinical sites within 30 days of the End-of-Trial.

8 Blinding Methods

8.1 General Considerations

Knowledge about treatment allocation and its related expectations could influence the outcomes in randomized clinical studies. Blinding aims to eliminate or minimize this confounding influence and the importance of blinding has been repeatedly emphasized by regulatory and advisory agencies for clinical studies such as FDA and CONSORT group.

Subjects and the investigators, or designees, performing study assessments shall be blinded to the subjects' randomized group assignment from the time of randomization to study completion.

8.2 Subject Blinding

Subjects are blinded to the treatment settings throughout the duration of the study. From the time of Implant through the Month-3 visit, the subject will activate treatment as-needed, but remain blinded to which treatment is being delivered ($\mathbf{T}_t$ or $\mathbf{C}_t$). Subjects will remain blinded throughout the study until the last implanted study participant completes their Month-12 study visit.

8.3 Investigator Blinding

An additional complexity in carrying out a double-blinded parallel arm study with neurostimulation is blinding the investigator to the randomization assignment because the investigator is responsible for the device parameter settings and could impose bias. For this reason the investigator will have access to the randomization assignment, if necessary, but will remain blinded to the treatment parameters. Only after a subject completes the Month-3 visit (primary endpoint), the investigator or designee may have access to the subjects' future treatment settings.

8.4 Sponsor Blinding

The Sponsor will remain blinded to the subjects' group assignment throughout the duration of the study with the exception of the Field Clinical Specialist (FCS). While under the supervision of the investigator, the FCS will operate the device and supporting components to provide Test treatment ($\mathbf{T}_t$) or Control treatment ($\mathbf{C}_t$) as specified in the protocol.

The contracted study statistician and data management team will include unblinded team members to conduct data review and analysis. A blinding plan will be established to ensure role appropriate access to data. Sponsor and contracted study team members will be trained to the study blinding process. In addition, the DMC statistical analysis team will be unblinded for the conduct of interim analysis.

8.5 Blinding Script

It is important that both subjects receiving Test treatment ($\mathbf{T}_t$) and Control treatment ($\mathbf{C}_t$) have a nearly identical experience during device Programming. For this reason, training materials will be provided to all investigators and sites with an explanation for the rationale behind needing to maintain equal expectation of efficacy. In addition, a script will be read to the subject prior to device activation such that the treatment is described in the same way to both subjects receiving Test treatment ($\mathbf{T}_t$) and Control treatment ($\mathbf{C}_t$).

8.6 Blinding Assessment

A 3-tiered auxiliary questionnaire will be administered to investigate the effectiveness of blinding. The study subjects will state their belief regarding their group assignment.

The questionnaire will be administered at the conclusion of the Randomized Testing phase. In addition, since a subject may become aware of their group assignment by virtue of observing the effects of treatment (or lack thereof), the questionnaire will also be administered shortly after commencement of the Randomized Testing phase and intermittently throughout the study. Successive assessment of the subjects blinding will allow for characterization of therapeutic unblinding by means of multivariate analysis with time.

8.7 Breaking the Blind

The site and subject blind will be broken once the last implanted study participant completes their Month-12 visit. Prior to this, the only permissible reason for unblinding will be to protect

the safety or welfare of the subject as determined by the investigator. In the event of unblinding, details will be captured on a CRF. The Sponsor blind will be broken once the last implanted study participant completes their Month-3 visit.

9 Safety Endpoints

Adverse Event rates will be monitored for the entire duration of the study by an independent Data Monitoring Committee (DMC) comprised of medical and statistical expert reviewers.

9.1 Primary Safety Endpoint

The primary safety endpoint will be the incidence of all serious adverse events, including Serious Adverse Events (SAEs), Serious Adverse Device Effects (SADEs), and Unanticipated (Serious) Adverse Device Effects (UADEs), from the time of injection through three (3) months post-implant. The primary safety endpoint will be determined at the conclusion of the Randomized Testing phase of the study, after all active participants complete the Month-3 visit.

The incidence of all serious adverse events will be further categorized according to whether the event is related to the procedure, device, treatment, or "other" (for example, disease progression, medication related). The rates for the "other" category will be compared to the rates seen in Conventional Medical Management (CMM) of Amputation Pain to better understand which AEs can be ascribed to treatment or device effects.

Table 6. Primary Safety Endpoint SAE Categorization

Event Categories
• Procedure related, occurring intra-operatively or within 14 days post-operatively.
• Device (hardware) related
• Treatment related, resolved after treatment is stopped.
• Other, for example, disease progression or medication-related.

9.2 Additional Safety Parameters

The incidence of all safety events including non-serious adverse event (AE), non-serious adverse device effects (ADE), serious adverse events (SAE), serious adverse device effects (SADE), and unanticipated adverse device effects (UADE), from time of injection through the Month-12 visit, will be determined.

The incidence of all adverse events will be further categorized as:

- Serious or non-serious; (AE/ADE vs. SAE/SADE/UADE)
- Procedure-related or device-related, (subcategorizing within ADE/SADE/UADE)
- Treatment related – reversible or permanent
- Unanticipated adverse device effects. (UADE)

Events will be considered to be permanent if the adverse event does not resolve despite medical management, changes in device programming, or stopping treatment**.**

In addition, a summary of all AEs and SAEs occurring post informed consent through initiation of implant procedure will be presented. This assessment will be reported for both the Enrolled-not-Implanted and the Enrolled-and-Implanted populations.

10 Effectiveness Endpoints

10.1 Primary Effectiveness

10.1.1 *Study Hypothesis*

The hypothesis for this study is that the responder rate is significantly higher in the Test ($\mathbf{T}_t$) group than the responder rate in the Control ($\mathbf{C}_t$) group during the Randomized Testing phase of the study.

$$H_O: P_T = P_C \text{ vs. } H_A: P_T \neq P_C,$$

where P is the proportion of responders (responder rate) and H_o will be rejected in favor of H_A when $p \leq 0.05$ with a two sided-significance level.

In general, a responder is defined as any subject who attained significant pain reduction at the end of more than half of the treatment sessions during the parallel Randomized Testing phase of the study. Specifically, a responder must attain ≥ 50% pain reduction in ≥ 50% of the treatment sessions during the Randomized Testing phase of the study.

10.1.2 *Responder Criterion*

The percent change of pain intensity quantified by NRS has been widely used to define a positive response in a wide range of clinical studies of devices as well as drugs. The cutoff point in percent change for a positive response is usually 50% reduction in pain intensity for device studies, such as spinal cord stimulator for low back pain and occipital nerve stimulation for migraine headache (Kumar et al 2007, North 2011, and Saper 2011). This 50% reduction threshold is also defined as the benchmark for defining a “substantial improvement” in IMMPACT recommendations on interpreting the clinical importance of treatment outcomes in chronic pain clinical studies (Dworkin et al 2008).

Examples for using the 50% cutoff point are: a change of pain intensity from 7 to 3 after a treatment session represents a 4/7 = 57% ≥ 50% pain reduction, a successful session; while a change from 7 to 5 represents a 2/7 = 29% < 50% reduction, a failed session. Further examples for responder determination are: during these 8 weeks, subject X had 40 successful sessions out

of a total of 56 treatment sessions, i.e., a proportion of success of 40/56 = 71% ≥ 50%, thus a responder; subject Y had 13 successful sessions out of a total of 28 treatment sessions, i.e., a proportion of success of 13/28 = 46% < 50%, thus a non-responder.

The responder analysis will exclude any treatment session for which duration of treatment is less than the intended complete duration (<30min (Treatment) or <8min (Control)), or in which baseline pain score is <4. A supportive analysis will be conducted that includes sessions of a duration shorter than the intended complete duration.

10.1.3 *Study Success Criterion*

Study success will be determined by a superiority test on the difference between responder rates in the Control and Test groups at Month-3. The Cochran-Mantel-Haenszel test (analogous to Pearson chi-square test but stratifying by clinical site) will be used on the data sets prepared based on a modified intention-to-treat, i.e., all randomized subjects who receive study treatment ($\mathbf{T}_t$ or $\mathbf{C}_t$) will be counted in each group. A study success will be determined if the responder rate is significantly higher in the Test group than the Control group at Month-3 with an overall significance level of 0.05.

10.1.4 *Secondary Analyses*

A per protocol analysis and covariate adjusted analysis of the primary efficacy endpoint will be conducted as supportive and informational analyses. Further detail on these supportive analyses will be included in the final study SAP.

10.2 Secondary Efficacy Endpoints

In order to control type I error, secondary endpoints intended for labeling claim will be tested in a hierarchical, gatekeeping manner in the order specified below, and only after the primary study endpoint success has been achieved. A hierarchical closed test procedure will be used to account for multiple testing with the goal of controlling the "maximum overall Type I error rate," which is the maximum probability that has been prespecified that one or more null hypotheses are rejected incorrectly.

The following five secondary efficacy endpoints are intended for label claim and will be tested in the order specified below. Each successful test will prompt the next subsequent test. If at any point an endpoint analysis is not significant, no further endpoints will be tested.

10.2.1 *Change in Opioid Pain Medication Use (MED) at Month-3*

Opioid pain medication use will be assessed using morphine equivalent dose (MED) from both rescue (p.r.n.) and routine opioid pain medications. The average daily morphine equivalent dose (MED/day) will be calculated for each subject across two weeks at Baseline and preceding Month-3. The mean change from baseline in average MED/day will be compared between Test group and Control groups using a t-test with a significance level of $p \leq 0.05$.

The hypothesis for this endpoint is that average change in Opioid Pain Medication use from Baseline to Month-3 is significantly greater in the Test ($\mathbf{T}_t$) group than in the Control ($\mathbf{C}_t$) group.

$$H_O: D_T = D_C \text{ vs. } H_A: D_T \neq D_C,$$

where D is the change from baseline in average MED/day and H_o will be rejected in favor of H_A when $p \leq 0.05$ with a two sided-significance level.

10.2.2 *Pain Interference to Activities of Daily Living (ADL) at Month-3*

Pain interference to the activities of daily living (ADL) due to limb pain will be assessed using the interference scale of the Brief Pain Inventory (BPI-Interference). The mean change in BPI-Interference summary score from Baseline to Month-3 will be compared between Test and Control group using a t-test with a significance level of $p \leq 0.05$.

The hypothesis for this endpoint is that mean change in BPI interference summary score from Baseline to Month-3 is significantly greater in the Test ($\mathbf{T}_t$) group than in the Control ($\mathbf{C}_t$) group.

$$H_O: D_T = D_C \text{ vs. } H_A: D_T \neq D_C,$$

where D is the change from baseline in BPI-Interference summary score and H_o will be rejected in favor of H_A when $p \leq 0.05$ with a two sided-significance level.

10.2.3 *12-Item Short Form Health Survey (SF-12) PCS at Month-3*

Health-related quality of life (HR-QOL) will be assessed using SF-12 physical component summary (PCS). The mean change in the SF-12 PCS from Baseline to Month-3 will be compared between Test and Control group using a t-test with a significance level of $p \leq 0.05$.

The hypothesis for this endpoint is that mean change in the SF-12 PCS from Baseline to Month-3 is significantly greater in the Test ($\mathbf{T}_t$) group than in the Control ($\mathbf{C}_t$) group.

$$H_O: D_T = D_C \text{ vs. } H_A: D_T \neq D_C,$$

where D is the change from baseline in the SF-12 PCS and H_o will be rejected in favor of H_A when $p \leq 0.05$ with a two sided-significance level.

10.2.4 *12-Item Short Form Health Survey (SF-12) MCS at Month-3*

Health-related quality of life (HR-QOL) will be assessed using SF-12 mental component summary (MCS). The mean change in the SF-12 MCS from Baseline to Month-3 will be compared between Test and Control group using a t-test with a significance level of $p \leq 0.05$.

The hypothesis for this endpoint is that mean change in the SF-12 MCS from Baseline to Month-3 is significantly greater in the Test ($\mathbf{T}_t$) group than in the Control ($\mathbf{C}_t$) group.

$$H_O: D_T = D_C \text{ vs. } H_A: D_T \neq D_C,$$

where D is the change from baseline in the SF-12 MCS and H_o will be rejected in favor of H_A when $p \leq 0.05$ with a two sided-significance level.

10.2.5 *EuroQual-5D (EQ-5D) at Month-3*

Health-related quality of life (HR-QOL) will be assessed using EQ-5D. The mean change in the EQ-5D summary index from Baseline to Month-3 will be compared between Test and Control group using a t-test with a significance level of $p \leq 0.05$.

The hypothesis for this endpoint is that mean change in the EQ-5D summary index from Baseline to Month-3 is significantly greater in the Test ($\mathbf{T}_t$) group than in the Control ($\mathbf{C}_t$) group.

$$H_O: D_T = D_C \text{ vs. } H_A: D_T \neq D_C,$$

where D is the change from baseline in the EQ-5D summary index and H_o will be rejected in favor of H_A when $p \leq 0.05$ with a two sided-significance level.

The following additional secondary efficacy endpoints are prespecified but are not intended for label claim:

10.2.6 *Responder in Control Subjects at Month-6*

The Responder Rate (defined as any subject who ≥ 50% pain reduction in ≥ 50% of the treatment sessions) will be presented by for Control Subjects at Month-6 (following crossover and 3 months of treatment) and compared to the responder rate for Control Subjects at Month-3.

10.2.7 *Pain Relief after 2 Hours*

Sustained pain relief after treatment will be assessed using pain intensities reported 2 hours after each treatment session. Specifically, pain intensity will be reported immediately preceding a treatment session and again after 30 minutes and 2 hours (120 minutes). Percent change of pain intensity will be determined by the difference of pain intensity from before treatment to pain intensity after 30 minutes and after 2 hours. The average percent change of pain intensity after 2 hours will be compared to the average percent change of pain intensity after 30 minutes with a significance level of $p \leq 0.05$. In addition, the average percent change from baseline (to 30 minutes and to 2 hours) in the Test group will be compared to the average percent change from baseline (to 30 minutes and to 2 hours) in the Control group.

10.2.8 *Pain Days per Week*

The number of pain days will be assessed using the intensity scale of the Brief Pain Inventory (BPI-Intensity). A pain day will be defined as a day for which the worst daily pain was moderate-to-severe (NRS ≥ 4). The number of pain days per week will be averaged across two weeks at Baseline, Month-3, Month-6 and Month-12. The average number of pain days per week will be compared at Month-3, Month-6 and Month-12 to Baseline with a significance level of $p \leq 0.05$. In addition, the change in average number of pain days from baseline to Month-3 in the Test group will be compared to the change in average number of pain days from baseline to Month-3 in the Control group.

10.2.9 *Opioid Pain Medication Use (MED) at Follow-up*

Opioid pain medication use will be assessed using morphine equivalent dose (MED) from both rescue (p.r.n.) and routine medications. The average daily morphine equivalent dose (MED/day) will be averaged across two weeks at Baseline, Month-3 Month-6 and Month-12. The average MED/day will be compared at Month-3, Month-6 and Month-12 to Baseline with a significance level of $p \leq 0.05$.

10.2.10 *Nonopioid Pain Medication Use*

Nonopioid pain medication use will be assessed using dose in milligrams for both rescue (p.r.n.) and routine nonopioid medications. The average daily dose in milligrams of nonopioid medications will be averaged across two weeks at Baseline, Month-3, Month-6 and Month-12. The average dose in milligrams of nonopioid medications will be compared at Month-3, Month-6 and Month-12 to Baseline with a significance level of $p \leq 0.05$. In addition, the change in average dose in milligrams of nonopioid medications from baseline to Month-3 in the Test group will be compared to the change in average dose in milligrams of nonopioid medications from baseline to Month-3 in the Control group.

10.2.11 *Pain Interference to Activities of Daily Living (ADL) at Follow-up*

Pain interference to the activities of daily living (ADL) due to limb pain will be assessed using the interference scale of the Brief Pain Inventory (BPI-Interference). The BPI-Interference summary score will be compared at Month-3, Month-6 and Month-12 to Baseline with a significance level of $p \leq 0.05$.

10.2.12 *EuroQual-5D (EQ-5D)*

Health-related quality of life (HR-QOL) will be assessed using EQ-5D. The EQ-5D summary index, will be compared at Month-3, Month-6 and Month-12 to Baseline with a significance level of $p \leq 0.05$.

10.2.13 *12-Item Short Form Health Survey (SF-12)*

Health-related quality of life (HR-QOL) will be assessed using the SF-12. Both the SF-12 physical component summary (PCS) and mental component summary (MCS) will be compared at Month-3, Month-6 and Month-12 to Baseline with a significance level of $p \leq 0.05$.

10.2.14 *Patient Global Impression of Change (PGIC)*

Patient global impression of change (PGIC) will be assessed using surveys conducted during office visits at Month-3, Month-6 and Month-12. The percentage of subjects reporting “Much Improved” or “Very Much Improved” at Month-3, Month-6 and Month-12 will be reported. The percentage of subjects reporting “Much Improved” or “Very Much Improved” at Month-3 will be compared between treatment groups (Test vs. Control) with a significance level of $p \leq 0.05$.

10.2.15 *Session Success Rate*

A successful session will be assessed using the NRS reported at the beginning and end of each session. A session that results in ≥ 50% pain reduction will be considered a successful session. The proportion of successful sessions will be averaged across subjects and compared between treatment groups (Test vs. Control) at Month-3 with a significance level of $p \leq 0.05$.

10.2.16 *Composite Responder Rate*

For the Composite Responder Rate endpoint, a responder is defined as any subject who attains ≥ 50% pain reduction in ≥ 50% of the treatment sessions during the Randomized Testing phase of the study (Primary Endpoint Responder) AND has an absence of increase in medication usage, defined as either 1) a decrease from Baseline in either average daily morphine equivalent dose OR average daily non-opioid pain medication use OR 2) no change in pain medication usage over

the period of two weeks prior to follow-up assessment as compared to Baseline. A Composite Responder must have no addition of new opioid or new non-opioid medications over those defined in the baseline medication contract.

The proportion of Composite Responders at Month-3 will be compared between treatment groups (Test vs. Control) with a significance level of $p \leq 0.05$.

10.3 Additional Study Outcomes

10.3.1 *Technical Success Rate*

Technical success is defined as implantation and activation of the study device. The percentage of subjects and devices in which technical success is achieved will be summarized across all attempts with a proportion and 95% confidence intervals.

10.3.2 *Prosthetic Use*

Prosthetic use will be assessed using the daily self-reported number of hours of prosthetic leg use. The hours of prosthetic use per week will be averaged across two weeks at Baseline, Month-3, Month-6 and Month-12. The average hours of prosthetic use per week will be compared at Month-3, Month-6 and Month-12 to Baseline with a significance level of $p \leq 0.05$. In addition, the change in number of hours of prosthetic use per week from Baseline to Month-3 in the Test group will be compared to change in number of hours of prosthetic use per week from Baseline to Month-3 in the Control group.

11 Statistical Considerations

11.1 Analysis Sets

Safety endpoints will be evaluated for all subjects enrolled in the study who undergo surgery. The primary analysis of the primary efficacy endpoint will be analyzed on a modified intention-to-treat basis (mITT). In addition, a per-protocol and ITT analysis will be conducted. Secondary efficacy endpoints will be evaluated utilizing the modified ITT, the ITT and the per-protocol basis.

11.1.1 *Safety Analysis Set*

In the safety analysis, all subjects who undergo surgery will be included.

11.1.2 *Intention-to-Treat (ITT) Analysis Set*

The Intention-to-Treat (ITT) Analysis Set includes all subjects who were randomized. This analysis estimates the causal effect of being assigned to the intervention vs control. Subjects who were enrolled-not-implanted, or enrolled-and-implanted but were terminated from the study prior to randomization will not be included in the ITT analysis. Subjects who were enrolled-and-implanted but never used the device to deliver treatment will be included with missing data imputed per the procedures described in Section 11.2. This analysis set will be utilized for a supportive analysis of both the primary and key secondary study endpoints.

11.1.3 *Modified Intention-to-Treat (mITT) Analysis Set*

The Primary analysis for the primary efficacy endpoint will be analyzed on a modified intention-to-treat basis (mITT). This analysis estimates the causal effect of being assigned to the intervention vs control and undergoing the assigned treatment. In the mITT analysis, all subjects who were randomized and had documented treatment use will be included in the analysis. Subjects who were enrolled-not-implanted, or enrolled-and-implanted but were terminated from the study prior to randomization, or enrolled-and-implanted but never used the device to deliver treatment will not be included in the mITT analysis. Secondary study endpoints will be analyzed in the mITT analysis population.

11.1.4 *Per-Protocol Analysis Set*

The Per-Protocol Analysis set will be restricted to study participants who fulfil the protocol in the terms of the eligibility, treatment, and outcome assessment. This analysis attempts to estimate the treatment effect when complying with the protocol, but is typically subject to selection bias and thus leads to a biased treatment effect estimate. Subjects will be excluded from this Per-Protocol Analysis Set for reasons including: programmed to a treatment opposite their group assignment, missing study required visits, use of non-contract pain medications, and device noncompliance including inadequate occurrences of device use (duration of sessions, number of sessions). If necessary, inclusion of a subject or session in the Per-Protocol analysis dataset may be assessed by the independent physician adjudicator (IPA) in a blinded manner.

A Per-Protocol Analysis will be provided as supplemental in addition to the primary mITT analysis.

11.1.5 *Enrolled-Not-Implanted Population*

Enrolled subjects in whom the device is not implanted will be summarized separately, including reason for screen failure and any adverse events occurring in this population.

11.2 Missing Data

All reasonable efforts will be made to obtain complete data for all subjects; however, missing observations will occur due to loss to follow-up, withdrawal, or non-adherence with required assessments. Reasons for missing visits will be captured in data collection forms as a protocol deviation or as a subject exit and study termination (see §7 Study Termination).

Reasons for missing data related to the device use are required to adequately conduct analyses that account for missingness. During general follow-up visits, subjects will be asked about device use and device use interruption during that visit internal, and reasons for lack of device use or interruption if applicable.

The best indicator of a subject's overall response to treatment, Test ($\mathbf{T}_t$) or Control ($\mathbf{C}_t$), will be the subject's available responses to treatment. As such, subjects who are randomized into the Test ($\mathbf{T}_t$) or Control ($\mathbf{C}_t$) group to receive treatment but who terminate prior to their Month-3 Visit (primary endpoint) will be determined to be a responder or non-responder based on their available data prior to termination.

Sensitivity analysis will be performed to evaluate the potential impact of analyzing available data from subjects who terminate prior to the primary endpoint. The following scenarios will be implemented to explore the impact on the primary efficacy outcome:

Assume random dropouts. Sensitivity analysis will remove all subjects from the modified ITT data set who did not reach the primary endpoint. In this way the primary efficacy endpoint would be analyzed using only subjects who completed the primary endpoint. To further explore the effect of random dropouts, sensitivity analysis will consider subjects within the modified ITT data set who did not reach the primary endpoint as "responder" or "non-responder" in the same proportion as subjects who did completed the primary endpoint. For example, if 54% of the subjects in the Test group who completed the primary endpoint are responders, of the subjects in the Test group who did not reach the primary endpoint, 54% would be assigned a value of "responder" and 46% the value "non-responder". However, assuming that dropouts are random and not related to a subject's unobserved outcomes may not be a valid assumption.

Assume informative dropouts. Sensitivity analysis will consider all subjects within the modified ITT data set who did not reach the primary endpoint as non-responders. It is plausible that subjects withdraw due to a lack of efficacy from this "as needed" treatment and it would be appropriate to consider these subjects non-responders. Thus it will be assumed that Test treatment ($\mathbf{T}_t$) or Control treatment ($\mathbf{C}_t$) had no effect and a subject who did not reach the primary endpoint would be assigned a value of "non-responder", independent of group assignment.

Sensitivity analysis will be performed to evaluate the potential impact of a modified intent-to-treat data set. The following scenario will be implemented to explore the impact on the primary efficacy outcome:

Assume Intent-to-treat. Sensitivity analysis will include all subjects who were implanted, but not included in the modified ITT, as non-responders. Subjects who were enrolled-and-implanted but were terminated from the study prior to randomization, or enrolled-and-implanted but never used the device to deliver treatment, will be included in the analysis as non-responders. A data set including all subjects who received an implant will represent an ITT analysis.

Further sensitivity analyses such as multiple imputation and tipping point analyses may be considered and will be described in the Statistical Analysis Plan (SAP).

For the primary analysis, missing observations for a particular treatment session will be considered a failure for that session. Treatment sessions that are interrupted with rescue (p.r.n.) pain medications will utilize the assessment of pain at the time of the interruption when available.

11.3 Additional Analysis

11.3.1 *Subgroup Analysis*

Exploratory data analysis will be performed and results reported based on the following subgroups. The following subgroups were not included in the enrollment stratification and are not expected to have adequate power to be considered as endpoints.

- Amputation level (AKA, BKA)
- Pain Type (phantom, stump, both)
- Etiology (dysvascular, trauma, other)
- Prosthetic (user, non-user)
- Age (less than 55, greater than 55)
- Sex (male, female)
- Race (White, black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Number of Treatment sessions during randomized phase
- Timing of administration of treatment
- Treatment Session Duration (for session-based analysis: 0 min,-<30 min, 30 min)
- Proportion of Pain episodes in which treatment is initiated during randomized phase
- Timing of Pain episodes in which treatment is initiated (month 1 vs month 2 post randomization)
- Pain score at initiation of treatment (for session-based analysis)
- Rescue Medication (day of/prior to treatment, during treatment)
- Use of Non-Contract Medication (yes, no)
- Lidocaine injection concentration (1%, 2%)

11.3.2 *Covariate Analysis*

A multivariable logistic regression will be conducted as supportive and informational analyses to assess treatment difference on the primary endpoint adjusting for covariates. Given this is a randomized study, treatments should theoretically be balanced between treatments; thus, adjustment for covariates has the potential to increase precision in the treatment effect estimate. Further detail on this analysis will be included in the final study SAP. The covariates are listed below.

- Amputation location (AKA, BKA)
- Pain Type (phantom, stump, both)
- Etiology (dysvascular, trauma, other)
- Prosthetic (user, non-user)
- Baseline Pain Intensity (moderate, severe)
- Baseline Pain Duration (episodic, persistent)
- Baseline Pain Duration in months
- Baseline Average Number of Pain Episodes/Week (4-6, 7-9, 10 or more)
- Baseline Opioid Pain Medication (MED, morphine equivalent dose)

- Baseline Non-Opioid Pain Medication use (avg daily dose in mg)
- Treatment Amplitude (voltage, current),
- Sensory Threshold Amplitude (voltage, current),
- Injection Response (percent change in pain intensity)
- Age (less than 55, greater than 55)
- Gender (male, female)
- Race (White, black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)

11.3.3 *Complier-Average Causal Effect (CACE) Analysis.*

The CACE estimates the causal effect for compliers, under certain assumptions – for example, assuming that the proportion of "always compliers" is the same in the control group as (unobserved) as it is in the treatment group (observed). This analysis uses the entire mITT dataset. In its basic form, the CACE treatment effect = mITT / Pc, where Pc is the proportion of compliers in the treatment group and mITT is the treatment effect under modified intent-to-treat as described above.

11.3.4 *Frequency and Timing of Treatment Analysis*

Using the mITT population, multivariable logistic regressions will be conducted as supportive and informational analyses to examine the effect of the number of treatments, and the timing of their administration on the primary endpoint adjusting for the number of treatment sessions. The first logistic model will include an interaction term for the number of treatment sessions by treatment group. The second logistic model will include an interaction term for the number of treatment sessions in the first month by treatment group. The third logistic model will include an interaction term for the number of treatment sessions in the first two months by treatment group.

11.3.5 *Justification of Pooling Across Sites*

Data analysis will be performed on data pooled across clinical sites within the context of the Cochran-Mantel-Haenszel test. To assess the differences across clinical sites chi-square test for homogeneity of 2x2 tables will be utilized (Zar, 1996).

11.3.6 *Justification of Pooling Across Subjects*

Post amputation limb pain is routinely classified as either residual limb pain (also referred to as "stump pain") or phantom-limb pain. Residual limb pain is often due to underlying disease process, surgical trauma, wound healing complications, tissue loading, local scarring, bone abnormality, causalgia, and neuroma. Phantom limb pain is multi-faceted involving deafferentation, pain memory, and cortical reorganization. It is likely a variable combination of the above etiologies is concurrent in any single individual (Nikolajsen et al. 1996).

Subgroup analysis will be performed as described in §11.3.1 Subgroup Analysis to assess subject poolability.

11.3.7 *Changes to Planned Analyses*

The Sponsor shall obtain approval of a supplemental application under 812.30(a), and IRB approval when appropriate (56.110, 56.111) for any changes to the statistical plan that effect validity of data or scientific soundness.

11.4 Interim Analyses

The interim analyses will occur after the targeted number of subjects have reached their Month-3 primary endpoint. The points of interim data analysis will be: n=20 (12.3%), n=40 (24.7%), and n=80 (49.4%). Recommendations to the Data Monitoring Committee (DMC) at each interim analysis will proceed according to pre-specified decision rules for assessing futility. The interim analysis recommendations will result in one of the following two scenarios for the study:

(1) Enrollment continues uninterrupted and reaches the planned maximum.
(2) Enrollment is stopped and the study is terminated due to futility.

The group sequential design will utilize a beta spending function to distribute the probability of type II error (β = 0.10) throughout the study. A beta-spending function was used to maintain the beta-spent from the first interim look already completed, while maintaining futility significance levels for the upcoming futility analyses that are approximately similar to the futility significance levels in the original protocol. The function uses the following cumulative beta-spent at each look: 0.006, 0.00615, 0.0102, 0.1, providing some chance for identifying futility early in the study. In this manner, study futility will be assessed at all interim analyses.

For each analysis point, the P-value boundaries to accept H_0 (claim futility) are provided in **Table 7**. The probabilities of crossing a boundary are listed within the column labeled "Boundary Crossing Probabilities".

Table 7. Interim Analysis Boundaries

Information Fraction	Accrual	Cumulative β Spent	One-sided P-value Boundaries to accept H_O futility	Boundary Crossing Probabilities Under H_O
0.123	20	0.006	≥ 0.91440	0.086
0.247	40	0.00615	≥ 0.96312	0.101
0.494	80	0.0102	≥ 0.62107	0.401
1.000	162	0.1	≥ 0.025	0.975

Information to be provided to the DMC will include treatment effect estimates and their confidence intervals (blinding the group assignment), whether a futility boundary has been crossed, the conditional power of crossing by the end of the study if none have yet been crossed, and safety assessments. The DMC will make the recommendation on whether to continue or stop the study after each look. The planned statistical boundaries are "non-binding", meaning that the DMC is not required to stop the study if a boundary is crossed - all available information about the study will be used to make the recommendation. The DMC might also decide to stop for low conditional power even though a boundary was not crossed.

11.5 Sample Size

The sample size calculation was performed using PASS 15. The formula uses a normal approximation multiplied by an inflation factor dependent on the beta spending function to account for interim analysis (§11.4 Interim Analyses). With an estimated attrition rate up to 10%, to account for subjects who received implantation but do not proceed to randomization due to various reasons such as significant change in pain intensity or frequency, the sample size equals 180 subjects. The inputs necessary to estimate sample size are summarized in the following table:

Table 8. Sample Size Calculation Inputs

Sample Size Inputs	Values
Probability of a type I error	α=0.05
Probability of a type II error	β=0.1
Power, 1-β	1-β = 0.9
Test	Two-tailed
Expected responder rate to Test treatment (**T_t**)	P_T = 0.50
Expected responder rate to Control treatment (**C_t**)	P_C = 0.25
Interim significance tests	3
Variance for standard error	Unpooled
Interim analysis boundaries	Non-binding
Percent attrition from implant to randomization	0.10
Inflation Factor	1.09
Sample Size	N=180

The values of proportion-of-success for the Test and Control treatment groups are estimated based on the preliminary findings from our Pilot study and relevant clinical literature. These values are also consistent with the outcomes from similar studies using implantable neuromodulation devices for pain or other symptom relief, in which a relative reduction of 50% in the responder rate is desired or required considering the invasiveness and costs. The resulting expected 25% absolute difference between Test and Control groups is generally considered as a clinically meaningful difference for interventions involving implantable devices (Kumar et al 2007, North 2011, and Saper 2011).

11.6 Number of Subjects per Investigational Site

The Sponsor will monitor enrollment to ensure a single institution does not enroll and implant more than approximately 20% of the overall study population.

11.7 Blinding Analysis

A 3-tiered auxiliary questionnaire will be administered for evaluating blinding (or masking). The study subjects will state their belief regarding their group assignment.

Subject unblinding shall be evaluated based on the expected frequencies of the subject's responses to the questionnaire. The expected frequencies shall be derived from the questionnaire's 3x2 frequency table where columns denote the actual treatment provided to the subject and rows denote the subject's belief regarding treatment. The frequency table is summarized in **Table 9**.

Table 9. 3x2 frequency table for 3-tiered blinding questionnaire.

Believed Treatment (i.e. guessed)	**Actual Treatment**	
	Test (**T**$_t$)	Control (**C**$_t$)
Test (**T**$_t$)	$n_{T\|T}$	$n_{C\|T}$
Control (**C**$_t$)	$n_{T\|C}$	$n_{C\|C}$
Don't Know (**dk**)	$n_{T\|dk}$	$n_{C\|dk}$

The questionnaire will be administered at the conclusion of the Randomized Testing phase. In addition, since a subject may become aware of their group assignment by virtue of observing the effects of treatment (or lack thereof), the questionnaire will also be administered shortly after commencement of the Randomized Testing phase and intermittently throughout the study. Successive assessment of the subjects' blinding will allow for characterization of therapeutic unblinding by means of multivariate analysis with time.

Several indices will be used to investigate the quality of the blind. The James Blinding Index (BI) will be used to assess the blinding of the study overall. The James BI is a modification of Cohen's kappa (κ), a commonly used method to assess observed agreement (i.e. between Believed and Actual Treatment) verses agreement expected by chance. The James BI is designed specifically for the situation of blinding assessment, where correct guesses are least supportive of blinding and therefore assigned a weight of 0, incorrect guesses are moderately supportive of unblinding and therefore assigned a weight of 0.5, and "Don't Know" responses are in fact most supportive of blinding and therefore assigned a weight of 1. The James BI can attain values in the interval [0, 1] with higher values denoting increasing levels of blinding. Therefore, $BI = 1$ indicates perfect blinding and $BI = 0$ an unblinded study.

The above frequency table can also be used to calculate the other most prominent blinding index, the Bang BI, which addresses several critiques of the James BI. In contrast to the James BI, the Bang BI gives less weight to "Don't Know" responses and more to decisive responses. It is also treatment-arm specific, so it can detect different levels of blinding for patients randomized to Test (**T**$_t$) and Control (**C**$_t$) treatment groups. Finally, it is sensitive to "reverse unblinding" in which patients consistently guess the incorrect treatment assignment.

11.8 Statistical Analysis Plan

A Statistical Analysis Plan (SAP) detailing the full specification of all analyses to be conducted will be generated prior to release of unblinded data for analysis.

12 Data Management

12.1 Data Collection, Processing, and Review

The Investigator or designee at each site will perform data collection based on source-documented hospital chart reviews. Electronic Case Report Forms (eCRFs) will be used to collect study data. All appropriate sections of the eCRFs must be completed. The clinical study site will be monitored periodically by a Sponsor study monitor or delegate for protocol adherence, accuracy of CRFs, and compliance to applicable regulations (see §17 Monitoring).

eCRFs that are incomplete or have incorrect information will be identified and deficiencies queried to the investigator or designee at the sites.

The Sponsor will employ a relational database designed for 21 CFR Part 11 compliance. Authorized personnel with access to the Electronic Data Capture (EDC) system will use an electronic username and password method to enter, review and correct data. Data review will be utilized to test for logical and consistency errors. Periodic analysis of each data field (across cases) will be performed in order to examine the expected distributions of data, and to identify outliers for possible data mistakes.

Source document worksheets may be provided by the Sponsor. Source document worksheets and eCRFs will be reviewed by the Sponsor or designee for omitted data, gross data inconsistencies, and timeliness of reporting. Any deficiencies will be queried and the sites will revise all errant eCRFs. The cycle of data edits will be ongoing until all the data are clean.

If further data entry or source documentation errors are discovered during a routine monitoring visit, the needed corrections will be identified at that time and the eCRF corrected and resubmitted by the study site.

All exported datasets for analyses will undergo a final data cleaning procedure using programmed logical routines unique to each exported dataset.

Incremental computer data back-up is performed multiple times daily, while a full database back up is performed nightly.

12.2 eDiaries

The primary study endpoint is a patient-reported outcome measure of the Numerical Rating Scale (NRS) for pain. The data will be collected by means of an electronic diary (eDiary). Data from the eDiary will be uploaded, via a 2G (minimum) connection, to a 21 CFR Part 11 compliant database. Subjects will also have the option to use a wireless (WiFi) connection should they live in an area with poor cellular connection. Data completion will be reviewed by the Sponsor or designee and any incompliance due to data omission will be reported to the site or call center. The site or call center will contact the patient by phone to request data entry to resolve the omission. Data entry that exceeds the reporting time limit of recollection will not be permissible for entry into the eDiary. For subjects that demonstrate routine non-compliances, corrective actions will be implemented to mitigate future data omissions. eDiary non-compliance by the subject will not

be reported as a protocol deviation, but will be aggregated and presented at time of final study analysis.

12.3 Generator Log

A subject's use of their Generator is recorded in a device log stored on the implanted Generator. The device log can save at least 300 past line items, and the line items include both treatment sessions and charging events. The device log will be downloaded from the subject Generator no less than once every 3 months to ensure no overwriting of data. This assumes a maximum-use scenario for which the patient is generating three-line items per day, for example initiating treatment twice daily and charging daily.

12.4 Data Retention

The investigator will perform the record keeping and reporting obligations described in this Protocol and as required by all applicable Laws. The clinical site shall maintain and store the Study Data and Source Records in a secure manner and protect the Study Records from unauthorized use, access, duplication, disclosure, loss or damage.

Records will be retained for a minimum period of two (2) years after the date the site receives written End-of-Trial Declaration, or such longer period as required by applicable Law. After the required retention period, the clinical site will provide the Sponsor with thirty (30) days written notice before destroying any Study Records.

13 Risk-Benefit Analysis

The risk-benefit ratio is within reason for foreseeable risks. However, risk analysis cannot guarantee prediction of all side effects that may be experienced. Observation and follow-up of all subjects is required as outlined in the protocol.

13.1 Anticipated Benefits

While no direct benefit of participation in the study can be guaranteed, in the proposed patient population, it is possible that treatment with the Altius System may reduce the subject's symptoms of post-amputation pain. Presently, this is an underserved patient population wherein commercially available pain treatments provide only limited effectiveness and the potential benefit from the Altius System, if realized, offers a significant advance in the treatment of patients with post-amputation pain.

13.2 Contraindications

The contraindications of the Altius System are specified in the Labeling contained in the Investigator Guide. These contraindications include: Active Implantable Devices, Magnetic Resonance Imaging, and Diathermy.

Patients who require an implanted cardiac pacemaker or other active implantable devices should not be implanted with the Altius System. Patients implanted with the Altius System, or any of its components, should not be subjected to Magnetic Resonance Imaging (MRI). If an MRI is needed

for any reason, the Altius System must be explanted prior to the diagnostic MRI. Diathermy should not be used on patients with the Altius System, or any of its components, either as a treatment for a medical condition or as part of a surgical procedure.

13.3 Anticipated Adverse Events

Based on review of similar clinical procedures and devices plus experience from previous studies using the Altius System or components, there are several risks that can be anticipated.

The following are anticipated risks with injection screening:

- At the injection site there may be warm skin, itching, small red spots, numbness, pain, bruising, bleeding, swelling,
- Some people may have mild dizziness, flushing, nausea, or vomiting after the injection,
- There is a small possibility of an allergic reaction such as hives, difficulty breathing, and swelling of your face, lips, tongue, or throat,
- An unintended injection into the bloodstream may cause cardiotoxicity, central nervous system toxicity, respiratory arrest, or cardiac arrest.

The following are anticipated procedural or surgical risks related to this study:

- General surgical risks, for example: bleeding, hematoma, swelling, bruising, scarring, and infection
- Injury to nerve, blood vessels, abdominal wall, and other tissue near the implanted components
- Unsuccessful implant requiring additional surgery
- Pain at location of implanted components, which may be temporary or persistent
- Anesthetic risks, for example: pain at the IV site, mouth and throat, coughing, hoarseness, lung infection, nausea and vomiting, high/low blood pressure, muscle aches, drug reactions, prolonged procedure, blood clots, paralysis, blindness, limb damage, respiratory arrest, cardiac arrest, unexplained brain damage, stroke, heart attack and death.

The following are anticipated risks for having the device throughout the study and long-term:

- Undesirable response to electrical treatment, for example: pain, discomfort, undesirable sensation (incl. numbness, and tingling), and stimulation of surrounding tissue (incl. nerves and muscle)
- Heating pain or tissue injury during battery charging
- Falling or other unintentional response due to sudden change in treatment
- Infection, cellulitis, abscess, fever, and sepsis
- Immune or inflammatory response to any of the implanted materials or components, for example: rejection, skin irritation, rash or redness, allergic reaction, dermatitis, inflammation, granuloma, and itching,
- Skin breakdown, for example: poor healing, wound reopening, pressure sores, and erosion at location of implanted components

- Stiffness and decreased range of motion
- Pain, for example: pain near implanted components, phantom sensation or pain, and neuroma pain
- Malfunction of device which may result in loss of treatment, for example: dislodgement, breakage (incl. fragments), loose connections, electrical shunt, short or open circuits
- Nerve injury and neuropathy (numbness, pain and tingling) including compression injury
- Interference with prosthesis
- Radiation exposure if diagnostic x-rays are needed
- Effects as a result of MRI or diathermy.

13.4 Risks Associated with the Study Device

There are known risks associated with the use of neuromodulation devices for the treatment of pain. These risks include those related to the surgery, use of the device, and the presence of implanted components. Subjects in this study will be implanted with the Altius System, and risks associated with the surgery and the implantable devices are part of this study.

Most side effects related to the use of the device can be treated by programming adjustments.

13.5 Risks Associated with Study Participation

The investigational portion of this study involves assessments, and questionnaires commonly obtained during the standard of care of a patient with post-amputation pain (e.g. pain scores and BPI). Inherently, by participating in the study, more data are collected and may be viewed by others outside of the doctor's office, thus risking confidentiality. While this risk is possible, every effort will be made to ensure the confidentiality of all subjects.

13.6 Minimization of Risks

Selection of investigators with extensive experience implanting neurostimulation systems is one important protection against risks during this study. Study eligibility criteria have been developed to include individuals with the highest chance of benefit, and to exclude those who are at higher risk for experiencing an anticipated adverse event. At any time during the study, in the event of a serious adverse event that may be related to the implant procedure, device or treatment, an unblinded investigator will have access to treatment status and will be available to provide that information to appropriate medical personnel in the event of medical emergencies.

During follow-up, patients will be cared for by professionals with expertise in pain management and that have extensive experience with caring for individuals with post-amputation pain. Ongoing monitoring of the Altius System will be performed by the investigator in consultation with the study surgeon that performed the implant procedure. During long-term follow-up, medical care will be provided in the most appropriate setting for the patient.

At a minimum, an Independent Physician Adjudicator (IPA) will review and adjudicate all deaths, all procedure related SAEs, any SAEs associated with the target limb or abdominal implant site, and any treatment or device related SAEs.

A DMC will review aggregate safety data on a regularly scheduled basis as identified in the DMC Charter. The IPA and/or the DMC will alert the study Sponsor if any safety concerns arise during the conduct of the study.

The investigators and Sponsor conducting this study have been trained specifically in standard clinical research practices and ethics and in the protection of research subjects and their personal information.

13.7 Conclusion

The intended use of High Frequency Nerve Block in the proposed study is expected to have a similar risk profile as that reported for SCS applications. The risk for significant injury or death due to Altius System implantation and High Frequency Nerve Block of peripheral nerves is low and is balanced by the potential for benefit. Furthermore, procedures to minimize the potential risks to individuals that participate in this study have been incorporated into the study design and protocol. However, it is recognized that risks have yet to be fully quantified in the amputee patient population under study and unanticipated adverse device effects may occur.

The level of risk associated with the proposed intended use of High Frequency Nerve Block with the Altius System in this study is acceptable. At the same time, the potential for benefit is great, especially given that the patients that will be enrolled in the study have received limited effectiveness from commercially available pain treatments.

14 Informed Consent

Informed Consent must be obtained for all patients who are potential study subjects. Each potential subject will be given an explanation of the study, educated on the possible risks and benefits to participating, and be asked to provide written consent. Each participant must sign an IRB-approved Informed Consent document before any study-specific tests or procedures are performed.

The potential study subject shall be fully informed of all aspects of their participation in the study so as to be able to exercise free power of choice without undue inducement or any element of force, fraud, deceit, duress, or other form of constraint or coercion.

Authorization of release of protected health information, as required by Health Insurance Portability and Accountability Act (HIPAA), will be included in accordance with HIPAA compliance practices at the clinical site as either part of study Informed Consent document or as a separately signed document.

15 Compliance

15.1 Statement of Compliance

This study is to be conducted according to US standards of Good Clinical Practice (GCP) regulations and guidance issued by the Food and Drug Administration (FDA) which are included in the following parts of the FDA Code of Federal Regulations (CFR):

- 21 CFR Part 50: Protection of Human Subjects,
- 21 CFR Part 54: Financial Disclosure,
- 21 CFR Part 56: Institutional Review Boards,
- 21 CFR Part 812: Investigational Device Exemption

Copies of these materials may be provided to the investigator by the Sponsor.

The purpose of these regulations is to define the standards and principles for the proper conduct of clinical studies. The ethical standards defined within GCP are intended to ensure that human subjects are provided with an adequate understanding of the possible risks of their participation in the study, and that they have a free choice to participate or not; the study is conducted with diligence and in conformance with the protocol in such a way as to ensure the integrity of the findings; and the potential benefits of the research justify the risks.

15.2 Device and Equipment Accountability

Devices for this study will be supplied to the clinical site from the Sponsor's inventory and will contain the investigational use caution statement on the package labelling. Information on each device used in the study will be documented, and device accountability for each device used will be maintained. Only approved investigators in this study will receive devices, and devices will be implanted only in patients enrolled in the study.

15.3 Investigator Responsibilities

The investigator of an investigational site is responsible for ensuring that the study is conducted according to the signed investigator agreement, the study protocol, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care.

The Principal Investigator's responsibilities include:

- Prior to beginning the study, sign the Clinical Trial Agreement (CTA) and the protocol investigator signature page, documenting agreement to conduct the study in adherence to the protocol. Sub-Investigators are required to sign the Sub-Investigator Agreement.
- Provide reasonable medical care to subjects participating in the clinical study in the case of adverse events, as described in the Informed Consent. Inform subjects when medical care is needed for conditions unrelated to the study.
- Assure IRB review and provide Sponsor with written IRB approval of the protocol and Informed Consent document.

- Maintain adequate and accurate source documents on each subject participating in the study.
- Ensure accuracy, completeness, legibility and timeliness of the data recorded in the source worksheets, eCRFs and all required reports, including eDiary completion and resolution of incompliance.
- Personally conduct and supervise the investigation and ensure appropriate delegations. Be available to subjects during conduct of study.

15.3.1 *Institutional Review Board*

The investigator must submit the study protocol to the governing Institutional Review Board (IRB) and obtain written approval from the IRB before obtaining study data. The investigator is also responsible for fulfilling any conditions of approval imposed by the IRB.

15.3.2 *Informed Consent*

The investigator (or designee) must explain to each potential subject or the potential subject's legal representative the nature of the study, its purpose, procedures, expected duration, alternative therapy available and the benefits and risks involved in study participation. Each potential subject or the potential subject's legal representative will be given the opportunity to ask questions and will be informed of the patient's right to withdraw from the study at any time without prejudice. After this explanation and before entering the study, the potential subject or the potential subject's legal representative will voluntarily sign an informed consent statement in the presence of a witness if there is agreement to participate.

15.3.3 *Investigator Records*

The investigator is responsible for maintaining the following records for a period of two years from End-of-Trial Declaration (§7.2.3 End-of-Trial).The Principal Investigator must maintain adequate records on all aspects of the study, including the following:

- All study-related correspondence with the IRB, another investigator, Sponsor, study monitor, and regulatory agencies, including required reports.
- Records of each subject's case history, including information reported on all study-required Case Report Forms (CRFs), evidence of informed consent, all relevant observations of adverse events, the results of diagnostic testing, and the date of each study treatment.
- Copies of the approved study protocol and any amendments and documentation of any deviations from the protocol including documented dates and reasons for each deviation.

15.3.4 *Investigator Reports*

The investigator is responsible for the following reports:

- Unanticipated adverse device effects (UADEs) (to be reported to the Sponsor within 24 hours of becoming aware of the event and the IRB per policy as soon as possible but no later than ten working days after the UADE is known to the investigator),

- Withdrawal of IRB approval (to be reported to the Sponsor within five working days after the withdrawal of IRB approval is known to the investigator),
- Progress reports (provided to the Sponsor and IRB at regular intervals (as requested by the governing IRB) but no less than yearly),
- Major deviations (those that impact the safety, well-being of the study subject or others or impact the overall study integrity) from the protocol (to be reported to the Sponsor and IRB as soon as possible but no later than five working days after the deviation is known to the investigator. Except in an emergency, prior approval from the Sponsor is required)
- A final report (to be provided to the Sponsor and IRB within three months after termination or completion of the investigation).
- Other study-related reports (upon request by a reviewing IRB, study IPA or DMC or FDA).

15.3.5 *Delegation of Responsibility*

The investigator should ensure that any individual to whom a task is delegated is qualified by education and experience to perform the delegated task, and has been provided adequate training and supervision. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

15.3.6 *Investigational Site Inspection*

If a regulatory agency selects the investigational site for an audit, the investigator will immediately notify the Sponsor. The Sponsor will assist the investigator to prepare for the audit. The investigator will permit study-related monitoring, audits, and inspections by the local IRB, the Sponsor, and government regulatory bodies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.).

Participation as an investigator in this study implies acceptance of potential inspection by local IRB, the Sponsor, and government regulatory authorities.

15.3.7 *Deviations*

The investigator and study staff must avoid all protocol deviations. The investigator should not implement any deviation from, or changes to, the protocol without agreement by the Sponsor and prior review and documented favorable opinion from the IRB, except where necessary to eliminate an immediate hazard(s) to study participant.

When a deviation occurs in an emergency situation, such as when a departure from the protocol is required to protect the life or physical well-being of a participant, the Sponsor and the reviewing IRB must be notified as soon as possible, but in no event later than 5 days after the emergency occurred (21 CFR 812.150(a)(4)).

Except in an emergency situation as described above, FDA device regulations require prior approval by the Sponsor for changes in or deviations from the investigational plan. If these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB prior approval also is required (21 CFR 812.150(a) (4)).

All site specific deviations will be reviewed and, if necessary, site corrective actions will be implemented to mitigate future deviations. eDiary non-compliance will not be reported as a protocol deviation, but will be aggregated and presented at time of final study analysis.

15.4 Sponsor Responsibilities

The study Sponsor is responsible for the following:

- ensuring the investigational sites obtain IRB approval prior to initiating the study,
- obtaining a signed investigator agreement,
- ensuring patient informed consent is obtained,
- providing investigators with the information they need to properly conduct the study,
- ensuring that the study is conducted according to the protocol,
- ensuring that the investigational treatment is made available only to qualified investigators participating in the study,
- ensuring no changes that effect the rights, safety, and welfare of the subjects are made to the study protocol without prior IRB approval,
- ensuring that regulatory agencies and all participating investigators are properly informed of significant new information regarding adverse effects or risks associated with the device being studied.

15.4.1 *Sponsor Records*

The Sponsor shall maintain accurate, complete, and current records relating to the study. These records include:

- a copy of this protocol that has been signed and dated by the investigator,
- a copy of the written IRB approval of the protocol,
- a copy of the written IRB approval of the informed consent,
- signed investigator agreements,
- correspondence with investigators, IRB, and FDA,
- records of investigational device shipment and disposition,
- adverse device effects (whether anticipated or unanticipated) and complaints.

15.4.2 *Sponsor Reports*

The Sponsor must prepare and submit the following reports:

- unanticipated adverse device effects to FDA, reviewing IRBs, and participating investigators within 10 working days after the Sponsor receives notice of the event;
- final report to IRBs, and investigators within three months of completion or termination of the study.

15.4.3 *Sponsor Inspections*

The Sponsor is required to permit FDA to enter and inspect any establishment where investigational devices are held and where records and results from use of the devices are kept.

FDA may also inspect and copy all records relating to an investigation including, in certain circumstances, records which identify subjects.

15.4.4 *Role of Sponsor Representative*

A representative from the Sponsor can provide technical support at the request of the investigator, surgical staff, or other healthcare provider during device implant or revisions, testing required by the protocol, and study visits. Technical support may include training, and answering questions to the healthcare staff concerning the study device.

While under the supervision of the investigator, the Sponsor personnel may operate the Device or supporting components to assist with programming the device or conduction of a test specified in the protocol, and interact with the subject.

In this study, a representative of the Sponsor may:

- provide technical expertise on the Altius System and Programmer Application software
- be present at follow up visits to assist with the collection of study information stored in the Programmer Application
- have some direct contact with the subject; and
- be aware of the Altius System programming settings.
- enter technical data on study forms.

In this study a representative of the Sponsor shall not:

- practice medicine,
- discuss a subject's condition or treatment with the subject without the approval and presence of the investigator.

16 Safety Reporting

The occurrence of adverse events will be assessed at all study visits and at any unscheduled visits.

16.1 Definitions and Classification

The following definitions are from Good Clinical Practice (ISO 14155:2011) and FDA Code of Federal Regulations for Medical Devices (21 CFR 812.3(s)).

16.1.1 *Adverse Event (AE)*

An AE is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.

AE includes events related to the investigational device or the comparator. This includes events related to the procedures involved (any procedure in the clinical investigation plan). For users or other persons this is restricted to events related to the investigational medical device.

AE does not include conditions pre-existing to the subject's enrollment. Pre-existing conditions will not be reported as AEs, including hospitalization, unless the condition has an increased occurrence or intensity.

16.1.2 *Serious Adverse Event (SAE)*

An SAE is any AE that:

a. led to a death,
b. led to a serious deterioration in health that either:
    (1) resulted in a life-threatening illness or injury,
    (2) resulted in a permanent impairment of a body structure or a body function,
    (3) required in-patient hospitalization or prolongation of existing hospitalization,
    (4) resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
c. led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

SAE does not include in-patient hospitalization for a planned study procedure. Planned study-related in-patient hospitalization is not an SAE.

SAE includes device deficiencies that might have led to a serious adverse event if (a) suitable action had not been taken or (b) intervention had not been made or (c) if circumstances had been less fortunate. These are handled under the SAE reporting system. A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a serious adverse event.

16.1.3 *Device Deficiency*

A Device Deficiency is any inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling.

16.1.4 *Adverse Device Effect (ADE)*

An ADE is an AE related to the use of an investigational medical device.

ADE includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. This includes any event that is a result of a use error or intentional misuse.

16.1.5 *Serious Adverse Device Effect (SADE)*

An SADE is an ADE that has resulted in any of the consequences characteristic of a serious adverse event.

16.1.6 *Unanticipated (Serious) Adverse Device Effect (UADE)*

A UADE is a SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Per 812.3(s) this includes any SAE caused by, or associated with, a device, if that SAE was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

16.2 Relationship to Study Device(s)

An AE should be evaluated to determine its relationship to the study device. The investigator should employ techniques to evaluate the relatedness. These techniques may include evaluating the AE when the device is both on and off.

At a minimum, the Independent Physician Adjudicator (IPA) will review and adjudicate all deaths, all procedure related SAEs, any SAEs associated with the target limb or abdominal implant site, and any treatment or device related SAEs. The IPA will categorize the event based on seriousness, procedure-relatedness, Altius system-relatedness, and treatment-relatedness, and whether or not the event constitutes a UADE. All AE adjudications will be documented in a case report form. Review of individual cases by the IPA shall not relieve the Sponsor of the regulatory responsibilities, regarding evaluation of these events and reporting as required to FDA.

The DMC will be informed in a timely manner of any cases for which unblinding of treatment at the clinical site or by the investigator is thought to be necessary to provide an appropriate intervention, so that the DMC can assess the potential impact of such actions on the overall study blind.

16.3 Investigator Reporting Requirements

In the event of a UADE the investigational site will inform the Sponsor within 24 hours of knowledge of the event. A UADE must also be reported to the reviewing IRB per reporting requirements but in no event later than 10 working days after the investigator first learns of the effect.

An SAE should be reported to the Sponsor within two (2) business days of the investigational site's knowledge of the event. An SAE must also be reported to the reviewing IRB per the IRB reporting requirement.

Each AE will be assessed and documented by the investigator at all study visits on the AE eCRF. An event suspected to be an AE (serious and non-serious) must be recorded and reported to the Sponsor. Each AE should be reported as soon as possible after the investigational site's knowledge of the event. The investigational site will provide source documentation as requested by the IRB to facilitate review.

In the event of death, when available, a copy of the death certificate and a copy of the autopsy report should be obtained. In the event that no source documents are available documenting the cause of death, the investigator will write a memo describing what is known about the

verification and circumstances of the participant's death. Any source documents relied upon to make a determination of death classification and cause of death must also be filed with the participant's study documents.

Table 10. Investigator Adverse Event and Deficiency Reporting

Event	What Documents	When to Communicate to Sponsor	Until when
SAE	AE CRF Form Source Documentation	• Within 2 business days of becoming aware of the event. • De-identified source documentation should be provided, as available, including updates.	SAE reporting and updates are required until End-of-Trial declaration.
Device Deficiency	Device Deficiency CRF	• Within 1 business day of becoming aware of the event.	Device Deficiency reporting is required until End-of-Trial declaration.
ADE	AE Form	• No later than 10 business days of first becoming aware of event.	ADE reporting is required until End-of-Trial declaration
SADE	AE Form Source Documentation	• Within 2 business days of becoming aware of the event. • De-identified source documentation should be provided as available including updates.	SADE reporting and updates are required until End-of-Trial declaration.
UADE	AE Form Source Documentation	• Within 24 hours of becoming aware of the event. • De-identified source documentation should be provided, as available, including updates.	UADE reporting and updates are required until End-of-Trial declaration.

16.4 Altius Device Deficiencies

A device deficiency occurs in any case when the device does not perform its intended function. All device deficiencies must be documented on the device deficiency CRF. If a device deficiency results in an adverse event (AE) for the study participant, this adverse event must be reported. Device deficiencies will not be collected as AEs. Any adverse event that results from a Device Deficiency will be reported as an AE, except for recurrence of underlying post-amputation pain being treated by the device.

Device deficiencies include:

- Electrode dislodgement, which should be confirmed and documented. Imaging, clinical assessment, direct observation and/or high impedance values may be used to assist in evaluation of suspected electrode dislodgement. Electrode lead breakage, which should be confirmed and documented. Imaging, clinical assessment, direct observation and/or high impedance values may be used to assist in evaluation of suspected lead breakage.
- Other device-malfunction resulting in loss of therapy or therapeutic effect.
- Other device-malfunction resulting in undesirable response to electrical treatment such as pain other than amputation pain being treated, discomfort, and undesirable sensation and stimulation of surrounding tissue.

16.5 Reporting to Regulatory Authorities / IRBs / Investigators

An investigator shall submit to the reviewing IRB a report of any UADE occurring during an investigation as per policy, but in no event later than 10 working days after the investigator first learns of the effect. UADEs must be reported to the Sponsor within 24 hours of becoming aware of the event in accordance with **Table 10** above.

The Sponsor shall immediately conduct an evaluation of any reported UADE. If it is determined that an UADE presents an unreasonable risk to subjects the Sponsor shall terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur not later than 5 working days after the Sponsor makes this determination and not later than 15 working days after the Sponsor first received notice of the effect.

The Sponsor shall report the results of a UADE evaluation to FDA and to all reviewing IRB's and participating investigators within 10 working days after the Sponsor first receives notice of the effect.

17 Monitoring

17.1 Monitoring Responsibilities

The Sponsor or designee will be responsible for monitoring the study. Appropriately trained Sponsor personnel or representatives will conduct on-site and centralized monitoring. Monitors will ensure accuracy of data, timeliness of data submissions, adequate enrollment, investigational device accountability, compliance with applicable laws and regulations, compliance with the protocol, compliance with the signed investigator agreement, and compliance with IRB conditions and guidelines. Any non-compliance with these items will be discussed with the investigator who will be responsible for ensuring that the non-compliance is adequately addressed with relevant corrective and preventative actions.

Frequency of monitoring will be based upon enrollment, study duration, compliance, and any suspected inconsistency in data that requires investigation.

17.2 Monitoring Reports

After each monitoring visit, the monitor will compile and send to the investigator a letter summarizing the monitoring visit. The report will include the date of the monitoring visit, the name of the monitor, the names of other individuals present for the monitoring visit, items reviewed during the visit, findings, and any required follow-up. The investigator will be responsible for ensuring that any follow-up actions needed to resolve issues are completed in an accurate and timely manner.

17.3 Final Monitoring Visit

A final monitoring visit will be conducted at the close of the study site. The purpose of the final visit is to collect all outstanding study data documents, ensure that the investigator's files are accurate and complete, review record retention requirements, and ensure that all applicable requirements are met for the study.

18 Committees

18.1 Independent Physician Adjudicator (IPA)

An Independent Physician Adjudicator (IPA) will be contracted for adjudication of events. The IPA will have expertise in relevant medical specialties (pain specialist and/or surgeon) and will not be an investigator in the study.

At a minimum, the role of the IPA will be to review and adjudicate all deaths, all procedure related SAEs, any SAEs associated with the target limb or abdominal implant site, and any treatment or device related SAEs as identified in the IPA charter. The IPA will classify the adjudicated AEs for seriousness, procedure-relatedness, device-relatedness, and treatment-relatedness, and whether or not the event constitutes an unanticipated serious adverse device effect. All adverse event adjudications will be documented by the IPA. The IPA will be responsible for verbally and in writing communicating any safety, scientific concerns, or perceived problems with the study to the Sponsor as soon as possible.

18.2 Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) will be established. The DMC will consist of three professionals from relevant medical specialties that are not investigators in the study and a statistical expert. The medical specialties will include pain specialists and surgeons.

The role of the DMC will be to monitor and review aggregate adverse events and deaths. The DMC will be responsible for verbally and in writing communicating any safety, scientific concerns, or perceived problems with the study to the Sponsor as soon as possible. The DMC will be responsible for aggregate review of data at predefined points per the DMC charter and at the time of the prespecified interim analyses. Data will be prepared for the DMC by an independent set of statisticians following the pre-determined analysis plan defined in §11.4 Interim Analyses. The blinded DMC includes a blinded statistician. This statistician will present the data for all

interim analysis to the other members of the DMC in a blinded fashion, and himself remain blinded. The DMC will make the recommendation on whether to continue or stop the study after each interim analysis. The DMC will be responsible for verbally and in writing communicating any safety, scientific concerns, or perceived problems with the study to the Sponsor as soon as possible.

19 Publication Strategy

At the conclusion of study enrollment, an abstract reporting the enrollment and study status may be prepared and presented at a major professional society meeting. A primary, multi-site publication also will be prepared for print in a peer-reviewed scientific journal when all enrolled patients have reached their Month-3 visit, at the conclusion of the Randomized Testing phase.

Additional manuscripts may be submitted for publication as determined by the Sponsor and investigators, for example when all participants have reached other major follow-up milestones (such as at the conclusion of the Long-Term Follow-Up phase), or for presentation of secondary endpoint results. Manuscripts reporting the results of other analyses of secondary endpoints may be submitted for publication following publication of the study's primary manuscript.

The Sponsor or designee, along with the investigators, will be responsible for overseeing the development of study manuscripts, abstracts, and presentations.

Before publishing or presenting data, the investigator must submit copies of any and all proposed manuscripts to the Sponsor at least 30 days in advance of submitting such proposed manuscripts to a publisher or other third party.

20 Glossary of Abbreviations and Definitions

20.1 Abbreviations

AE	Adverse Event
ADE	Adverse Device Effect
AKA	Above Knee Amputation
BKA	Below Knee Amputation
BPI	Brief Pain Inventory
CFR	Code of Federal Regulations
CMM	Conventional Medical Management
CRF	Case Report Form
DASS	Depression Anxiety Stress Scales
DMC	Data (and safety) Monitoring Committee
EQ-5D	EuroQual-5D
FCS	Field Clinical Specialist
FDA	U.S. Food and Drug Administration
HbA1c	Glycated Hemoglobin
HFNB	High Frequency Nerve Block
HIPAA	Health Insurance Portability and Accountability Act
HR-QOL	Health-related quality of life
ICH	International Conference on Harmonization's Guideline for Good Clinical Practice
IDE	Investigational Device Exemption
IMM	Independent Medical Monitor
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IPA	Independent Physician Adjudicator
IPG	Implantable Generator
IRB	Investigational Review Board
MRI	Magnetic Resonance Imaging
NRS	Numerical Rating Scale
PCA	Patient controlled analgesia

P-GIC	Patient-Global Impression of Change
PI	Principal Investigator
PLP	Phantom Limb Pain
SF-12	12-Item Short Form Health Survey
SADE	Serious Adverse Device Effect
UADE	Unanticipated (Serious) Adverse Device Effect

20.2 Definitions

Altius System Charger	A system that provides high-frequency nerve block treatment.
Charging System	A portable device used to recharge the battery of the implanted Generator.
Chronic Pain Connector	The Charging System consists of a Charger with charging coil and Power Supply. The system is used for recharging the implanted Generator.
Connector Port Plug	Pain that has been persistent over six (6) months.
Connector Port	Proximal IS-1 end of a Cuff Electrode or Extension
Contacts	Insert for plugging an unused Connector Port.
Contraindications Cuff	IS-1 receptacle in header of Generator.
Cuff Electrode	Exposed platinum on the Cuff that deliver electrical treatment to the nerve.
	Conditions which must be avoided because risks to the patient outweigh benefit.
Extension	Distal end of Cuff Electrode which houses the Contacts and wraps around the nerve.
End-of-Trial Declaration	A device that conducts electrical signals from the Generator to the nerve. It consists of a distal Cuff, proximal Connector, and adjoining cable.
	The entire Extension assembly including the Receptacle, Connector, and adjoining cable.
Enrolled-and-implanted	A written Declaration to all sites specifying that the study has reached completion. End-of-Trial Declaration will occur either: (1) after commercial approval from the FDA or (2) when it has been determined that further pursuit of FDA approval will no longer occur.
	All subjects who signed an informed consent prior to study participation and received an Altius System implant.

Enrolled-not-implanted	Subjects enrolled because the patient had signed an informed consent document, but for which an Altius System had not been implanted.
Generator	An implantable waveform generator. The Neuros Altius Generator consists of electronic circuitry, rechargeable battery, titanium enclosure, and epoxy header.
Patient Controller	A battery powered hand-held controller used to start and stop treatment from the Generator.
Programmer Wand	A device that makes communication possible between the implantable Generator and the computer used by an investigator (or designee) or FCS to program the Generator.
Receptacle	Distal, 'female connector' of an Extension.
Subject Study Completion	A study participant will reach study completion after their Month-12 visit.
Setscrew	Stainless steel screw in Header of Generator.
Setscrew Septum Seal	Silicon rubber that seals setscrew.
Torque Wrench	Torch-limited hexagonal wrench for tightening the Setscrew.

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