SUMMARY OF SAFETY & EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Stimulator, Peripheral Nerve, Totally Implanted for Post-Amputation Pain

Trade Name: Altius® Direct Electrical Nerve Stimulation System

Device Product Code: SAZ

Applicant's Name and Address: Neuros Medical, Inc.
26800 Aliso Viejo Parkway, Suite 250
Aliso Viejo, CA 92656

Premarket Approval Application (PMA) Number: P230020

Date of Notice of Approval to the Applicant: 8/26/2024

Breakthrough Device: Granted breakthrough device status (formerly known as the Expedited Access Pathway, or EAP) on April 30, 2021.

II. INDICATIONS FOR USE

The Altius® Direct Electrical Nerve Stimulation System is indicated as an aid in the management of chronic intractable phantom and residual lower limb post-amputation pain in adult amputees.

III. CONTRAINDICTATIONS

The Altius System is contraindicated in the following:

- Unable to operate the system.
- Unsuitable for Neuros Altius implant surgery

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Altius System instructions for use.

V. DEVICE DESCRIPTION

The Altius System is an implantable neuromodulation device intended to use a high frequency alternating current (HFAC) to manage chronic intractable post-amputation pain (PAP). **Figure 1** illustrates implantation of the Altius System in the body. The Altius implantable pulse generator (IPG) is implanted in the abdomen (left image) and designed to generate a HFAC electrical stimulus (5-10kHz) that is conveyed to the nerve by a stimulating lead to an implanted cuff electrode wrapped around the target nerve(s) in the amputated leg proximal to the tip of the severed nerve (right image). The total therapy duration is 30 minutes. Patients can use the Altius System to treat pain episodes as needed (PRN).

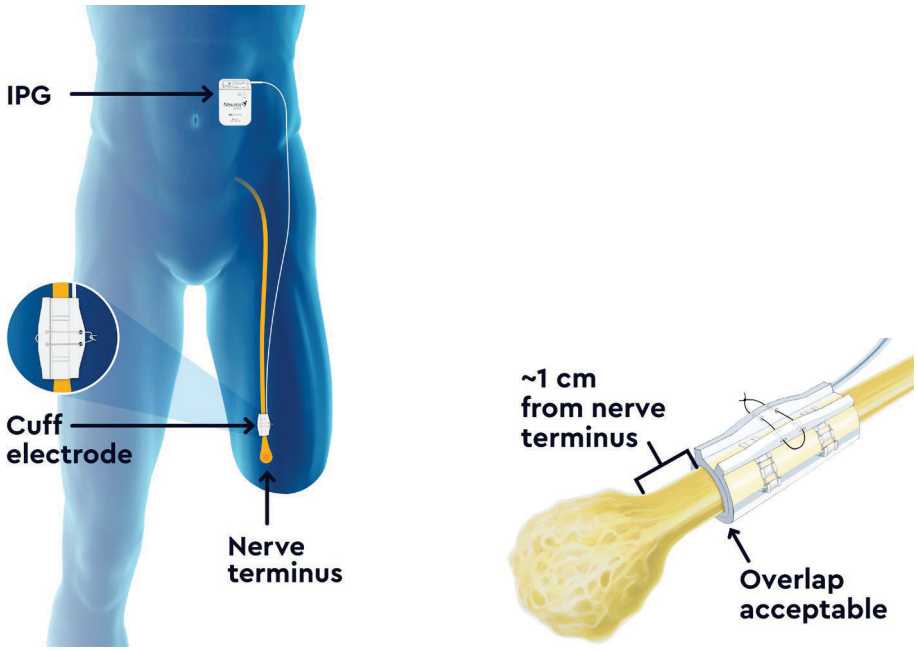

Figure 1: Altius System Principles of Operation (Left: System Implantation; Right: Cuff Electrode on Nerve

The Altius System is comprised of implanted and external components. Panel A of **Figure 2** displays all system components and panel B displays the permanently implanted components.

A **B**

Figure 2: Altius System Components

A. Implanted Components

The following components of the Altius System are implanted:

- **Implantable Pulse Generator (IPG):** Implanted, rechargeable device (**Figure 2B**) that generates HFAC electrical stimulus. The device has two independent programmable channels (A and B) with standard IS-1 electrode connector ports to

deliver voltage-controlled stimulus. Implanted typically in the abdomen (**Figure 1**, Left). Approximate dimensions of the IPG are 68.5 mm height, 47.0 mm width, and 11.0 mm thickness. If only one electrode is used, a silicone **Port Plug** (not shown) is used to plug the connector hole in the IPG. The IPG stimulation output parameters are listed in **Table 1**, and the primary materials of the IPG are listed in **Table 2**.

- **Nerve Cuff Electrode:** Implanted device (**Figure 2B**) that is wrapped around target peripheral nerve proximal to the terminus with an attached lead that tunnels to the IPG (**Figure 1**, Right). Delivers HFAC stimulus to the nerve. Cuff Electrodes are available in the following sizes (minimum diameter): 4-, 6-, and 9-mm. Cuff Electrode size selection is made by the implanting surgeon based on the diameter of the target nerve. The specifications and materials of the Cuff Electrode are listed in **Table 3** and **Table 4**, respectively.

Table 1: Altius Stimulation Output Parameters

Characteristic	Fixed Parameter
Waveform	Sinusoidal
Current/Voltage Regulated	Voltage Regulated
Therapy Delivery Mode	Continuous
Max Current	20 mA
Total Therapy Duration	30 minutes
Lock Out Duration	30 minutes
Characteristic	**Programmable Parameter**
Frequency	5 kHz, 10 kHz
Max Voltage	0 - 16V
Ramp Duration	0 - 15 mins

Table 2: Altius IPG Materials with Direct Tissue Contact

Component	Material
IPG Case	Titanium
IPG Header	Epoxy Resin, Silicone Adhesive
Septum Seals	Silicone Rubber
Port Plug	Silicone Rubber

Table 3: Altius Cuff Electrode Specifications

Parameter	Specification		
	Small	**Medium**	**Large**
Cuff size (minimum diameter)	4 mm	6 mm	9 mm
Self-sizing diameter range / target nerve diameter	4 to 6 mm	6 to 9 mm	9 to 13 mm
Cuff width	15 mm	20 mm	28 mm
Number of Electrode Bands	2		
Electrode Band spacing	5 mm	7 mm	11 mm
Connector	Standard Bipolar IS-1 Connector	Connector	Standard Bipolar IS-1 Connector
Lead Body (Cable) length	100 cm		

Table 4: Altius Cuff Electrode Materials with Direct Tissue Contact

Component	Material
Cuff	Silicone Rubber
Electrode Band	90/10 Platinum/Iridium
Lead Body	Silicone Rubber
IS-1	Stainless Steel, Silicone Rubber

B. External Components

The following components of the Altius System are external to the patient:

- **Battery Charger:** External device that wirelessly recharges the battery contained within the Altius IPG.
- **Patient Controller:** External device that allows patient to start an Altius therapy session (pain treatment) using programmed therapy parameters.
- **Clinician Programmer Wand:** External device used by physician or clinical user to set HFAC stimulus parameters for the Altius IPG.
- **Clinician Programmer Application:** Software that provides a graphical user interface for individual programming the Altius IPG.
- **Torque Wrench:** Tool for surgeon use to tighten IPG connections prior to IPG implantation; sterile item, packaged with IPG but not implanted in patient.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are alternatives for the treatment of chronic PAP, although none are curative. Pharmacological treatments are commonly used to treat PAP as a first and second line of treatment. Although many drug treatments are available, none are specifically indicated for treatment of PAP, and limitations include inconsistent pain relief, intolerable and concerning adverse effects, and insufficient improvement in daily function. First-tier therapy options provided typically include non-steroidal anti-inflammatory (NSAID) drugs, membrane stabilizers and regional nerve blocks, which may provide short-term pain relief. Second- tier pharmacologic options typically include the addition of opioids and gabapentinoids.

Several neurostimulation devices have received FDA marketing authorization for treatment of chronic intractable pain in the trunk and limbs, e.g., spinal cord stimulation (SCS) devices and peripheral nerve stimulation (PNS) devices. The effectiveness of these treatment options for chronic PAP is unclear when compared to other neuropathic pain states, and data supporting their use for treating PAP is limited.

A final option for treating PAP is surgical ablation of a neuroma at the severed end of the nerve(s), should one be present. The long-term outcomes of peripheral nerve surgery are mixed, and studies have found that patients only experience a short duration of pain relief, with recurrence of the neuromas.

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

VII. MARKETING HISTORY

The Altius System is not yet approved or registered for marketing in any country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of potential adverse effects (e.g., complications) associated with the use of the Altius System. The adverse effects include: (1) those associated with any surgical procedure and (2) those specifically associated with having an implanted Altius System. In addition to the risks listed below, there is the risk that the Altius therapy may not be effective in relieving PAP. Additional intervention may be required to correct some of the adverse effects.

- Risks associated with any surgical procedure: bleeding; hematoma; swelling; bruising; scarring; 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 intravenous 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; sensitivity to one or more of the materials of the Altius System IPG leading to removal of device.
- Risks associated with the use of the Altius System: electrode or lead migration; IPG migration; allergic response or tissue reaction to the implanted material(s); hematoma or seroma at the implant site; skin erosion at the implant site; persistent pain at the IPG or electrode sites; nerve damage; premature battery depletion, or failure of system components leading to loss of therapy; loss of pain relief over time; and uncomfortable

stimulation or ineffective pain control caused by failure of the system components or battery, changes in electrode position, loose electrical connections, electrode/lead insulation breaches or fractures. The risks of the Altius System are similar to those associated with any active implantable medical device, such as other implantable devices for pain relief.

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

IX. SUMMARY OF PRECINICAL STUDIES

A. Bench Performance Testing

1. Implantable Pulse Generator

   Bench testing (**Table 5**) was performed in accordance with design verification test protocols that were developed to verify that the Altius IPG meets product specifications.

Table 5: Summary of Key Testing – Altius IPG

Test	Test Purpose	Acceptance Criteria	Result
Volume	Verify the IPG is the appropriate size for implantation.	Volume < 45 cm^3.	Pass
Insulation	Verify sufficient insulation provided by septum seals.	Impedance > 50 kΩ per ISO 5841- 3.	Pass
Lead Retention Force	Verify nerve cuff lead retention with the set screws engaged.	Retention force ≥ 15 N when the set screws are tightened with the supplied torque wrench.	Pass
Lead Insertion and Withdrawal Forces	Verify IPG and Lead meet interface requirements for insertion and withdrawal.	Lead insertion and withdrawal force ≤ 14 N.	Pass
Environmental - Pressure	Verify the IPG can withstand pressure changes that may be encountered during distribution or use.	IPG functions after exposure to pressure conditions of 70 kPa to 150 kPa per ISO 14708-1 Section 25.1.	Pass
Environmental - Temperature	Verify the IPG can withstand temperatures that may be encountered during distribution.	IPG functions after exposure to temperature conditions of -30°C to 60°C per ASTM D4332.	Pass
Environmental - Mechanical	Verify the IPG can withstand mechanical stresses that may be encountered during distribution.	IPG functions after exposure to distribution testing per ASTM D4169.	Pass
Particulate Matter	Verify the cleanliness of the implanted device.	Particulate testing meets the requirement of ISO 14708-1:2014 Clause 14.2 using light obscuration method with ≤6,000 particles ≥10µm and ≤600 particles ≥25µm.	Pass
Communication Range	Verify communication distances between the IPG and system components.	Demonstrate communication distances: Programmer Wand up to 3.5cm Patient Controller up to 5cm Battery Charger up to 2.5cm	Pass
Measurement of Output (Stimulation)	Verify that the stimulation output for each channel meets programmed or expected values.	Stimulation outputs including amplitude, frequency, ramp-up, and lock-out duration are within specifications.	Pass
Battery Longevity	Verify that the lithium-ion battery can operate over a 10-year typical use lifespan.	Battery charging cycle bench testing demonstrates 10-year life (with typical setting and usage).	Pass
Charging	Verify IPG battery charge completion criteria.	Charge session, charge timeout, and voltage max conditions are within specifications. Battery is protected by a fuse.	Pass
Short Circuit /Open Circuit	Verify short circuit and open circuit protection.	The IPG can withstand continuous short circuit and open circuit of its outputs without permanent damage.	Pass

2. Nerve Cuff Electrode

Bench testing (Table 6) was performed in accordance with design verification test protocols that were developed to verify that the Altius Cuff Electrode meets product specifications.

Table 6: Summary of Key Testing – Altius Cuff Electrode

Test	Test Purpose	Acceptance Criteria	Result
Dimensional Requirements	Verify dimensional requirements are met for features such as cuff sizing, electrode band spacing, cuff thickness, IS-1 connector dimensions, and lead body (cable) length.	Meets dimensional specifications.	Pass
Environmental - Pressure	Verify the device can withstand pressure changes that may be encountered during distribution or use.	Device functions after exposure to pressure conditions of 70 kPa to 150 kPa per ISO 14708-1 Section 25.1.	Pass
Simulated Handling	Verify the device can withstand expected use conditions.	Device functions after simulated handling exposure.	Pass
IS-1 Connector Insertion/Withdrawal Force	Verify force requirements are met to insert/withdraw the IS-1 Connector.	Insertion and withdrawal force ≤14N per ISO 5841-3.	Pass
Lead Resistance	Verify lead resistance per electrode band.	Resistance ≤ 25Ω.	Pass
Cuff Impedance	Verify that the cuff impedance meets specifications.	Cuff impedance within specific ranges.	Pass
IS-1 Impedance	Verify the IS-1 connector impedance meets specifications.	Impedance > 50kΩ before and after 10-day soak in saline solution.	Pass
Conductor Insulation Integrity	Verify the conductor insulation maintains integrity in physiological conditions.	Leakage current ≤ 2mA after 10-day soak in saline solution.	Pass
Tensile	Verify the cuff (subassembly) can withstand a specified pull force.	Force ≥ 3.5N.	Pass
Lead Body Structural Integrity	Verify the lead body maintains integrity after elongation.	≤ 5% permanent elongation and ≤25Ω resistance after 10-day soak in saline solution and 20% elongation for 1 minute.	Pass
Lead Body Flex	Verify the lead body maintains continuity after flex cycling.	≤ 25Ω resistance after 10 million cycles of +90° to -20° flex angle.	Pass
Crush/Distal Fatigue	Verify the cuff and lead maintain continuity after fatigue cycling.	≤ 25Ω resistance after 10 million cycles of 30% cuff deformation and 10% lead stretch.	Pass
IS-1 Connector Flex	Verify the IS-1 connector maintains continuity after flex cycling.	≤ 25Ω resistance after 164,000 cycles of ±45° flex angle.	Pass
Corrosion	Verify corrosion resistance of the cuff in simulated use conditions.	≤ 25Ω resistance with no visual signs of corrosion at electrodes.	Pass
Particulate Matter	Verify the cleanliness of the implanted device.	Particulate testing meets the requirement of ISO 14708-1:2014 Clause 14.2 using light obscuration method with ≤6,000 particles ≥10µm and ≤600 particles ≥25µm.	Pass

3. External Components

Bench testing was performed in accordance with design verification test protocols that were developed to verify that the external components of the Altius System meet product specifications. Testing included the following:

- Functional testing of device features.
- Functional testing after environmental conditioning and shipping simulation (Battery Charger, Patient Controller, and Programmer Wand). Environmental conditioning per ASTM D4332. Shipping simulation per ASTM D4169 (Cycle 13 and 14, Assurance

Level I).

- Firmware/software testing (discussed below).
- Electrical safety testing per IEC 60601-1 (discussed below).

4. Software

   The software associated with the Altius System was developed and tested in accordance with the FDA guidance document entitled, "Guidance for the Content of Pre-market Submission for Software Contained in Medical Devices" (May 11, 2005), and with IEC 62304, and all requirements were met.

5. Electrical Safety and Electromagnetic Compatibility

   Electrical safety testing and evaluation of the Altius System was performed in accordance with the applicable clauses of the following standards:

   - IEC 60601-1, Medical electrical equipment - Part 1: General requirements for basic safety and essential performance
   - ISO 14708-1, Implants for surgery – Active implantable medical devices. Part 1, General requirements for safety, marking and for information to be provided by the manufacturer.
   - ISO 14708-3, Implants for surgery – Active implantable medical devices. Part 3, Implantable neurostimulators

   All electrical safety tests and evaluations were successfully completed, and all acceptance criteria were met for compliance with IEC 60601-1 and the applicable clauses of the standards listed above. The Altius System was also tested for compatibility with external defibrillation and diagnostic ultrasound exposure. The Altius System has not been evaluated for MRI compatibility.

   Electromagnetic compatibility (EMC) testing was performed in accordance with the applicable clauses of the following standards.

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

   All tests EMC tests for emissions and immunity were successfully completed, and all acceptance criteria were met for compliance with IEC 60601-1-2 and the standards listed above. Altius System IFUs include required EMC information.

6. System Testing

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

7. Biocompatibility

   Biocompatibility testing was performed for all patient-contacting components of the Altius System in accordance with ISO 10993-1 Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process, on the finished sterilized devices. The IPG and port plug are implants in permanent contact (> 30 days) with tissue/bone (e.g., muscle). The cuff electrode is an implant in permanent contact (> 30 days) with neural tissue (e.g., sciatic nerve) and non-neural tissue/bone (e.g., muscle). None of the implanted components are intended to directly or indirectly contact cerebrospinal fluid or blood. Altius System components with intact skin contact include the battery charger paddle, programmer wand and patient controller. All biocompatibility studies were conducted in compliance with Good Laboratory Practices (GLP), 21 CFR Part 58. All pre- specified test acceptance criteria were met, and all tests passed.

8. Sterility, Packaging and Shelf Life

   The Altius System components that are provided sterile, including the IPG, port plug and cuff electrode, are terminally sterilized using a 100% ethylene oxide (EO) sterilization process to provide a minimum sterility assurance level (SAL) of 10^{-6}. Validation of the sterilization process is in compliance with ANSI/AAMI/ISO 11135, Sterilization of health care products – Ethylene oxide – Requirements for the development, validation and routine control of a sterilization process for medical devices. Sterilant residuals conform to the maximum allowable limits of EO and ethylene chlorohydrin (ECH) residuals specified in ISO 10993-7, Biological Evaluation of Medical Devices – Part 7: Ethylene Oxide Sterilization Residuals. The product bacterial endotoxin limits are based on FDA's Guidance for Industry - Pyrogen and Endotoxins Testing: Questions and Answers (June 2012) and are verified using Limulus Amebocyte Lysate (LAL) testing.

   Packaging and shelf- life validation tests were completed in compliance with ISO 11607-1, Packaging for Terminally Sterilized Medical Devices. Part 1: Requirements for materials, sterile barrier systems and packaging systems.

   Shelf-life for the Altius IPG and port plug have been established as five years from the date of manufacturing.

   Shelf-life for the Altius cuff electrode has been established as three years from the date of manufacturing.

9. Human Factor Study

   TBD (the current HF testing is inadequate. The sponsor will conduct a nonclinical HF Post-Approval Study or PAS)

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed the "High-FreQUEncy Nerve Block for PoST-Amputation Pain: QUEST" Investigational Device Exemption (IDE) Trial (a pivotal clinical study, IDE number: G130203), to establish reasonable assurance of safety and effectiveness of the Altius® Direct Electrical Nerve Stimulation System as an aid in the management of chronic intractable phantom and residual lower limb post-amputation pain in adult amputees. A summary of the clinical study is presented below.

A. Study Design

The study was a multi-center, prospective, randomized, double-blinded, active-sham-controlled trial comparing the Altius System (programmed to therapeutic stimulation level, Test) to an active sham (Altius System programmed to deliver low-level sub-therapeutic stimulation, Control). Specifically, subjects in the Test arm received high-frequency electrical stimulation (frequency: 5 kHz or 10 kHz) for a treatment session of 30 minutes. The voltage was gradually increased to a level that produced a strong but tolerable transient sensation for the subject. This voltage value was used for Test treatment. Subjects in the Control arm received low-frequency electrical stimulation (frequency: 0.1 Hz) for a treatment session of 8 minutes. The voltage was gradually increased to a level that reliably produced a perceivable sensation. This voltage value was used for the Control treatment.

Subjects were treated between 09 October 2014 and 13 September 2021. The last subject completed the Month 3 primary endpoint follow-up on 22 December 2021 and the Month 12 secondary endpoint follow- up on 8 November 2022. The database for this PMA reflected data collected through 4 January 2023, which was the complete dataset through Month 12, and included 180 subjects in the Full Analysis Set (FAS). There were 34 investigational sites, all located in the U.S.

Subjects and study staff (e.g., investigators, study coordinators, evaluators) were blinded as to their treatment assignment. A total of 180 subjects met all enrollment criteria, were implanted with the Altius System and were randomized at the time of programming in a 1:1 ratio to the Test and Control groups.

The study incorporated the following features to minimize bias:

- Randomized, controlled study design.
    - Randomization post-implant
    - Active sham control
- Blinding/Masking
    - Study subjects
    - Investigators and site personnel performing subject assessments
    - Sponsor
    - Data Monitoring Committee
    - Independent Physician Adjudicator
    - Study Monitors
- Maintained equipoise
    - Balanced interactions with both treatment groups
    - Setting of neutral expectations (e.g., script for programming)
- Outcome data collected, through use of an eDiary, prior to and independent of site interaction with the subject and prior to programming changes.
- Rigorous screening process including saline (placebo) and lidocaine test injections prior to implantation.
- Independent trial oversight
    - Data Monitoring Committee (DMC)

- Independent Physician Adjudicator (IPA)
- Independent statisticians

- Frequent monitoring and site audits
- Comprehensive training, including a requirement for up-to-date Good Clinical Practice (GCP) training for all site personnel
- Minimization of financial conflict of interest

1. **Inclusion/Exclusion Criteria**

   Enrollment in the QUEST study was limited to patients who met 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 (based on numerical rating scale [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.

Patients were not permitted to enroll in the QUEST study if they met 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.

2. **Visit and Follow-Up Schedule**

All subjects were consented during the baseline visit. Subjects were then assessed as to whether they fulfilled all eligibility criteria, including eDiary eligibility criteria and injection evaluation criteria.

Subjects who failed one or more of the eligibility criteria at these pre-operative steps were considered screen failures. Subjects who withdrew consent or were withdrawn by the investigator prior to implant surgery were exited from the study and were not counted towards the 180-subject sample size.

At baseline, subjects had a physical exam, pregnancy test for women of child-bearing potential, medical history, baseline pain assessment and baseline quality of life (QoL) questionnaires. Subjects who passed the initial eligibility assessment were issued an eDiary device for recording pain intensity and medication and prosthetic use, if applicable. A baseline eDiary was collected for at least 14 calendar days with 2 or fewer days of missing data, including the severity, frequency, and duration of pain, medication consumption, and prosthetic use. Subjects whose eDiary confirmed frequent and recurring pain episodes of ≥ 5 (NRS) per week proceeded to the Injection Visit. At the injection visit, to assess the effect of placebo, 1 ml of saline was first injected as close to the nerve terminus as possible. An allowable, non-therapeutic, response to saline was defined as a reduction <30% on NRS at 15 minutes after administration. If the subject successfully passed the saline injection, 15 ml 2% lidocaine was then injected. A positive response to lidocaine was defined as a reduction ≥50% on NRS at 20 minutes after lidocaine administration, relative to the pain intensity prior to saline injection. Subjects who demonstrated a therapeutic response to saline or who did not respond to lidocaine were documented as screen failures.

Subjects who met all enrollment criteria, as judged by the investigator, including eDiary and injection criteria, proceeded to Altius System implant surgery. At 14 days post-surgery, after confirming contact between the programming system and the Altius IPG, subjects were randomized to one of the two treatment arms, and stimulation was programmed according to the subject's blinded treatment group assignment. Subjects then used the Altius System to treat pain episodes as needed (PRN), recording their pain level using NRS prior to Altius treatment and at 30-minutes and two-hours post-treatment. Subjects returned for follow-up visits, including QoL measures and pain medication use, at 21 days, 1 month, 42 days, 56 days, 3 months (primary endpoint), 105 days, 6 months, 9 months and 12 months (secondary endpoint). Subjects originally randomized to sham-control crossed over to active Altius treatment at Month 3. With their agreement, subjects are followed on an annual basis until End-of-Trial declaration.

The key timepoints for each assessment are shown in **Table 7** below. Adverse events were collected at every visit beginning at the baseline visit.

Table 7: QUEST Schedule of Assessments

PARAMETER	VISIT	Screening	Injection[1]	Implant	Day 14[2]	Day 21	Month 1	Day 42	Day 56	Month 3	Day 105[3]	Month 6	Month 9	Month 12	LTFU[4]	Revision[5]	Explant[6]
	POD Start	<0	<0	0	11	18	25	35	49	77	98	169	260	335	-30	NA	NA
	POD End				17	24	31	49	63	105	112	213	294	395	+30		
Informed consent		X															
Demographics		X															
Medical History		X															
Urine Dipstick[7]		X															
DASS		X															
BPI		X					X			X		X		X			
SF-12		X					X			X		X		X			
EQ-5D		X					X			X		X		X			
HbA1c[8]			X														
Sensorimotor Evaluation			X		X					X				X		X	X
Injection Evaluation			X														
Procedure Details				X													
Blinding Questionnaire					X		X			X		X					
PGIC										X		X		X			
NRS (eDiary)		X	X	X	X	X	X	X	X	X	X	X	X	X			
Pain Medications		X	X	X	X	X	X	X	X	X	X	X	X	X			
AE Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Programming					X	O	[9]	[9]	[9]	X	X	O	O	O	O	O	

DASS: Depression Anxiety Stress Scales; POD: Post-operative day; LTFU: Long-term follow-up; X: Required; O: As needed

[1] Injection evaluation scheduled after the subject passed two-week eDiary assessment.

[2] Randomization performed after device has been successfully activated. If Day 14 visit (randomization) was postponed due to inability to verify system integrity or delayed wound healing, subsequent visit windows would be adjusted accordingly.

[3] Day 105 visit for programming adjustment not required.

[4] During LTFU, subjects followed annually (every 365 days).

[5] Following revision, subject required to complete post-op follow-up visit 14 ±7 days after surgery

[6] Following explant, subject required to complete post-op follow-up visits 14 ±7 days and 183 ±30 days after surgery.

[7] Urine dipstick pregnancy test only required for subjects with child-bearing potential.

[8] HbA1c required for diabetic subjects prior to performing injection evaluation. A blood sample within 3 months of injection could be used.

[9] Programming adjustments during the Randomized testing phase were only made if necessary.

3. **Clinical Endpoints**

Primary Effectiveness Endpoint

The primary effectiveness endpoint was the responder rate of subjects in each arm, active Altius treatment (Test) vs. sham-control treatment (Control), during the Randomized Testing phase of the study (Month 1 to Month 3). A responder was defined as a subject who demonstrates ≥50% reduction in NRS pain score from pre-treatment to 30-minutes post-treatment for ≥50% of all pain episodes in which the treatment was used. Study success was determined by a superiority test on the difference between responder rates in the Test and Control groups at Month 3.

Primary Safety Endpoint

The primary safety endpoint was the incidence of all Serious Adverse Events (SAEs), including Serious Adverse Device Events (SADEs), and Unanticipated (Serious) Adverse Device Events (UADE), from the time of injection through Month 3. The primary safety endpoint was determined at the conclusion of the Randomized Testing phase of the study, after all active participants completed the Month 3 Visit.

The study was intended to show that the SAE rate for the active Altius treatment group is non-inferior to that of the sham-control group and that therapeutic electrical stimulation does not increase SAEs compared to non-therapeutic stimulation.

Secondary Effectiveness Endpoints

Note that none of these secondary effectiveness endpoints was found adequately supported to be included for labeling.

- Change from baseline in Opioid Pain Medication Use (Morphine Equivalent Dose (MED)) at Month 3
- Change from baseline in Brief Pain Inventory (BPI) at Month 3
- Change from baseline in Short Form Health Survey (SF-12) Physical Component Summary (PCS) at Month 3
- Change from baseline in Short Form Health Survey (SF-12) Mental Component Summary (MCS) at Month 3
- Change from baseline in EuroQol (EQ-5D) at Month 3
- Primary effectiveness beyond Month 3 through Month 12
- Pain Relief after 2 Hours
- Pain Days per Week
- Change from baseline in Non-Opioid Analgesic Pain Medication Use through Month 12
- Change from baseline in Opioid Pain Medication Use (Morphine Equivalent Dose (MED)) through Month 12
- Change from baseline in Brief Pain Inventory (BPI) through Month 12
- Change from baseline in EuroQol (EQ-5D) through Month 12
- Change from baseline in Short Form Health Survey (SF-12) Physical Component

Summary (PCS) through Month 12

- Change from baseline in Short Form Health Survey (SF-12) Mental Component Summary (PCS) through Month 12
- Change from baseline in Patient Global Impression of Change (PGIC)
- Session Success Rate
- Composite Responder Rate (Reduction in pain AND absence of increase in medication usage)

Secondary Safety Endpoints

The secondary safety endpoint was the incidence of all adverse events including non-serious adverse events, non-serious adverse device effects, SAEs, SADEs, and UADE, from time of injection through the Month 12 visit.

B. Accountability of PMA Cohort

At the time of the database lock for this PMA report, 183 subjects underwent surgery to implant the Altius System (Safety population). Three subjects were anesthetized for index surgery, but the Altius device was not implanted, in two cases because the target nerve could not be located and in one case because there was insufficient sciatic nerve to support implant of the cuff electrode. Therefore, 180 subjects were implanted with the Altius System. Two subjects were implanted with the Altius device but were not randomized; one died from pulmonary embolism on POD 5, and the other had the device explanted prior to activation because of axonal discontinuity at the target nerve. Thus, 178 subjects were randomized, 87 to active Altius treatment (Test) and 91 to sham-control (Control) (ITT population). Eight of those 178 subjects (two Test and six Control) never used the Altius device, so 170 subjects (85 Test and 85 Control) completed the randomized testing phase and were evaluable for the primary effectiveness endpoint at Month 3 (FAS population). The Month 12 visit was completed by 146 of 149 eligible subjects. Refer to **Figure 3**.

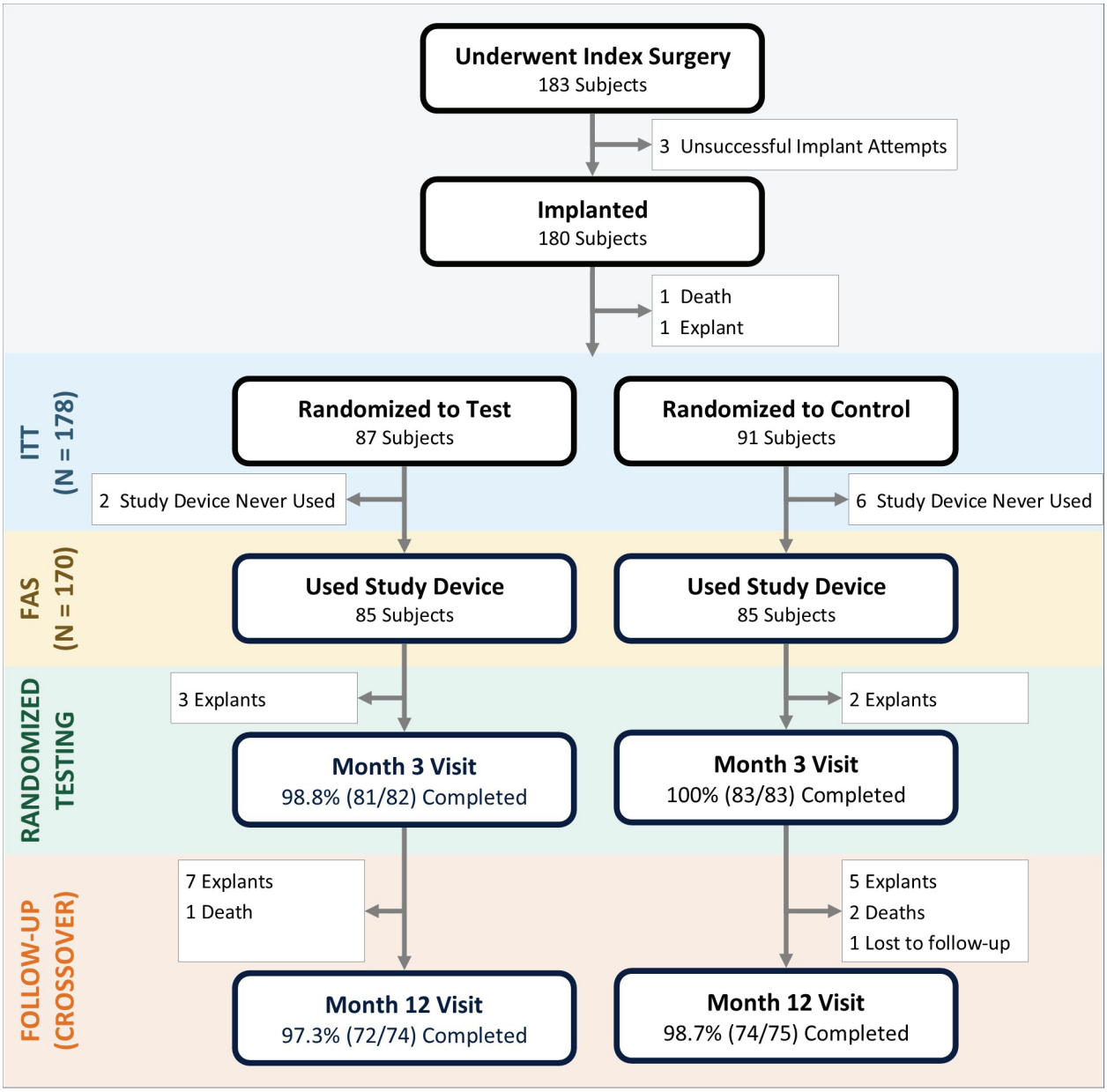

Figure 3: Subject Disposition by Visit through Month 12

C. Study Population Demographics and Baseline Parameters

Table 8 summarizes the key demographic, medical history and baseline parameters for the FAS population. The two treatment arms were well balanced across all baseline factors.

Table 8: Key Demographics, Medical History and Baseline Parameters (FAS)

	Test **N = 85** Mean ± SD (Min, Max) or n (%)	**Control** **N = 85** Mean ± SD (Min, Max) or n (%)	**Total FAS** **N = 170** Mean ± SD (Min, Max) or n (%)	**p-value [1]**
Age (years)	58.1 ± 12.21 (26, 84)	57.9 ± 12.57 (22, 87)	58.0 ± 12.35 (22, 87)	0.916
Sex				
Male	60.0% (51/85)	60.0% (51/85)	60.0% (102/170)	>0.999
Female	40.0% (34/85)	40.0% (34/85)	40.0% (68/170)	
Race				
American Indian or Alaska Native	2.4% (2/85)	1.2% (1/85)	1.8% (3/170)	0.899
Asian	0.0% (0/85)	0.0% (0/85)	0.0% (0/170)	
Black or African American	14.1% (12/85)	11.8% (10/85)	12.9% (22/170)	
Native Hawaiian or Other Pacific Islander	1.2% (1/85)	0.0% (0/85)	0.6% (1/170)	
White	77.6% (66/85)	83.5% (71/85)	80.6% (137/170)	
Other	0.0% (0/85)	0.0% (0/85)	0.0% (0/170)	
Multiple	2.4% (2/85)	1.2% (1/85)	1.8% (3/170)	
Unknown	2.4% (2/85)	2.4% (2/85)	2.4% (4/170)	
Ethnicity – Hispanic or Latino	1.2% (1/85)	0.0% (0/85)	0.6% (1/170)	>0.999
BMI (kg/m^2)	30.5 ± 7.75 (16, 50)	28.8 ± 5.73 (15, 45)	29.7 ± 6.85 (15, 50)	0.098
Level of Amputation				
Above knee (AKA)	44.7% (38/85)	41.2% (35/85)	42.9% (73/170)	0.757
Below knee (BKA)	55.3% (47/85)	58.8% (50/85)	57.1% (97/170)	
Cause of Amputation				
Dysvascular	42.4% (36/85)	41.2% (35/85)	41.8% (71/170)	0.839
Trauma	43.5% (37/85)	41.2% (35/85)	42.4% (72/170)	
Other	14.1% (12/85)	17.6% (15/85)	15.9% (27/170)	
Time From Amputation to Baseline Visit (Months)	93.2 ± 107.46 (12.0, 615.0)	72.6 ± 71.17 (12.0, 373.0)	82.9 ± 91.45 (12.0, 615.0)	0.142
Worst daily limb pain (0-10)	9.1 ± 0.98 (85) (6.0, 10.0)	9.1 ± 1.05 (85) (6.0, 10.0)	9.1 ± 1.01 (170) (6.0, 10.0)	>0.999
Worst daily limb pain (categories)				
No Pain (0)	0.0% (0/85)	0.0% (0/85)	0.0% (0/170)	0.663
Mild (1-3)	0.0% (0/85)	0.0% (0/85)	0.0% (0/170)	
Moderate (4-6)	2.4% (2/85)	2.4% (2/85)	2.4% (4/170)	

	Test N = 85 Mean ± SD (Min, Max) or n (%)	Control N = 85 Mean ± SD (Min, Max) or n (%)	Total FAS N = 170 Mean ± SD (Min, Max) or n (%)	p-value [1]
Severe (7-9)	57.6% (49/85)	50.6% (43/85)	54.1% (92/170)	
Worst Possible Pain (10)	40.0% (34/85)	47.1% (40/85)	43.5% (74/170)	
Average daily limb pain (0-10)	6.1 ± 1.45 (2.7, 10.0)	5.9 ± 1.47 (3.1, 10.0)	6.0 ± 1.46 (2.7, 10.0)	0.224
Average daily limb pain (categories)				
No Pain (0)	0.0% (0/85)	0.0% (0/85)	0.0% (0/170)	
Mild (1-3)	3.5% (3/85)	7.1% (6/85)	5.3% (9/170)	
Moderate (4-6)	62.4% (53/85)	64.7% (55/85)	63.5% (108/170)	
Severe (7-9)	32.9% (28/85)	24.7% (21/85)	28.8% (49/170)	0.419
Worst Possible Pain (10)	1.2% (1/85)	3.5% (3/85)	2.4% (4/170)	
Pain duration type				
Episodic or Breakthrough Pain	36.9% (31/84)	35.3% (30/85)	36.1% (61/169)	
Persistent; It Builds and Remains for Most of the Day	63.1% (53/84)	64.7% (55/85)	63.9% (108/169)	0.873
Limb pain type				
Stump Only	6.0% (5/84)	3.6% (3/84)	4.8% (8/168)	
Phantom Only	9.5% (8/84)	7.1% (6/84)	8.3% (14/168)	
Stump is Much Worse	10.7% (9/84)	15.5% (13/84)	13.1% (22/168)	
Phantom is Much Worse	27.4% (23/84)	27.4% (23/84)	27.4% (46/168)	0.833
Both Stump and Phantom Pain are Bad	46.4% (39/84)	46.4% (39/84)	46.4% (78/168)	
Hours Per Day of Prosthetic Leg Use				
0	11.9% (10/84)	15.3% (13/85)	13.6% (23/169)	
>0 to 4	13.1% (11/84)	14.1% (12/85)	13.6% (23/169)	
>4 to 8	27.4% (23/84)	11.8% (10/85)	19.5% (33/169)	
>8 to 12	19.0% (16/84)	20.0% (17/85)	19.5% (33/169)	
>12 to 16	16.7% (14/84)	28.2% (24/85)	22.5% (38/169)	
>16 to 20	4.8% (4/84)	5.9% (5/85)	5.3% (9/169)	
>20 to < 24	0.0% (0/84)	0.0% (0/85)	0.0% (0/169)	0.152
All Day	0.0% (0/84)	1.2% (1/85)	0.6% (1/169)	
N/A - no prosthetic leg	7.1% (6/84)	3.5% (3/85)	5.3% (9/169)	
Alcohol Abuse				
Current condition	0.0% (0/85)	0.0% (0/84)	0.0% (0/169)	
Past, resolved	1.2% (1/85)	6.0% (5/84)	3.6% (6/169)	0.117
No prior history	98.8% (84/85)	94.0% (79/84)	96.4% (163/169)	
Anxiety				
	Test N = 85 Mean ± SD (Min, Max) or n (%)	Control N = 85 Mean ± SD (Min, Max) or n (%)	Total FAS N = 170 Mean ± SD (Min, Max) or n (%)	p-value [1]

Current condition	41.2% (35/85)	50.6% (43/85)	45.9% (78/170)	0.409
No prior history	57.6% (49/85)	47.1% (40/85)	52.4% (89/170)	
Depression				
Current condition	44.7% (38/85)	53.6% (45/84)	49.1% (83/169)	0.311
Past, resolved	4.7% (4/85)	7.1% (6/84)	5.9% (10/169)	
No prior history	50.6% (43/85)	39.3% (33/84)	45.0% (76/169)	
Diabetes				
Current condition	40.0% (34/85)	28.6% (24/84)	34.3% (58/169)	0.237
Past, resolved	1.2% (1/85)	1.2% (1/84)	1.2% (2/169)	
No prior history	58.8% (50/85)	70.2% (59/84)	64.5% (109/169)	
Peripheral Neuropathy				
Current condition	29.4% (25/85)	27.4% (23/84)	28.4% (48/169)	0.799
Past, resolved	1.2% (1/85)	0.0% (0/84)	0.6% (1/169)	
No prior history	69.4% (59/85)	72.6% (61/84)	71.0% (120/169)	
Peripheral Vascular Disease				
Current condition	27.1% (23/85)	29.8% (25/84)	28.4% (48/169)	
Past, resolved	3.5% (3/85)	3.6% (3/84)	3.6% (6/169)	0.915
No prior history	69.4% (59/85)	66.7% (56/84)	68.0% (115/169)	
Taking Any Rescue Medication at Baseline	36.5% (31/85)	37.6% (32/85)	37.1% (63/170)	
Taking Rescue Opioid and Opioid/Nonopioid Combination at Baseline	32.9% (28/85)	20.0% (17/85)	26.5% (45/170)	
Taking Rescue Anticonvulsant at Baseline	2.4% (2/85)	7.1% (6/85)	4.7% (8/170)	
Taking Any Routine Medication at Baseline	63.5% (54/85)	49.4% (42/85)	56.5% (96/170)	
Taking Routine Opioid and Opioid/Nonopioid Combination at Baseline	28.2% (24/85)	20.0% (17/85)	24.1% (41/170)	
Taking Routine Anticonvulsant at Baseline	50.6% (43/85)	47.1% (40/85)	48.8% (83/170)	
[1] Statistical comparison between treatment groups for categorical variables performed using two-sided Fisher's exact test and for continuous variables two-sided two sample t-test. Significance for both evaluated at the 0.05 level.				

D. Safety & Effectiveness Results

1. Safety Results

Primary Safety Endpoint – All SAEs through Month 3

The primary safety endpoint was the incidence of all serious adverse events (SAEs), including serious adverse device-related events (SADEs) and unanticipated adverse device effects (UADEs), from the time of injection through the conclusion of the blinded Randomized Testing phase at Month 3. The primary safety analysis was based on the Safety population of subject who underwent surgery (N=183) and was repeated in the ITT population of subjects who were implanted and randomized (N=178).

Among the 183 Safety subjects (**Table 9**), 8 SAEs that were device-related (SADE) occurred in 8 subjects (4.4%), and 20 procedure-related SAEs occurred in 15 subjects (8.2%). The overall SAE rate was 26.2% (48/183) in the Safety population.

In the ITT population (**Table 10**), N=178 subjects (87 Test, 91 Control), 3 device-related SAEs occurred in 3 Test subjects (3.4%) and 5 occurred in 5 Control subjects (5.5%). Procedure-related SAEs occurred in 8 Test subjects (9.2%) and 7 Control subjects (7.7%). The overall SAE rate was 28.7% in the Test arm and 24.2% in the Control arm in the ITT population. There was no difference between the two treatment arms with respect to device-related, procedure-related and overall SAEs, based on 95% confidence intervals (CI). These results indicate that a therapeutic level of nerve stimulation (Test) did not cause more SAEs than a sub-therapeutic dose (Control). There were no UADEs.

As summarized in **Table 10**, the most common device-related SAEs were infections and wound-related complications related to the IPG and/or cuff electrode implant sites. After an initial spike in infection/wound-related events during the early part of the QUEST study and the implementation of infection control measures, the rate of such events declined to ≤5% among the last 159 implanted subjects.

Table 9: Primary Safety Endpoint - All SAEs From Injection to Month 3, Safety Population

	Implanted		Not Implanted		Safety Population	
	Number of Events	Number of Subjects with Event N = 180	Number of Events	Number of Subjects with Event N = 3	Number of Events	Number of Subjects with Event N = 183
All Serious Adverse Events	65	26.7% (48/180)	0	0.0% (0/3)	65	26.2% (48/183)
Serious Device Related AEs [5][6]	8	4.4% (8/180)	0	0.0% (0/3)	8	4.4% (8/183)
Serious Procedure Related AEs [5]	20	8.3% (15/180)	0	0.0% (0/3)	20	8.2% (15/183)
UADEs	0	0.0% (0/180)	0	0.0% (0/3)	0	0.0% (0/183)

Table 10: Primary Safety Endpoint - All SAEs and Device-Related SAEs by Type, From Injection to Month 3, ITT Population

	Test			Control			
	Number of Events	**Number of Subjects with Event N = 87**	**95% CI [3]**	**Number of Events**	**Number of Subjects with Event N = 91**	**95% CI [3]**	**Difference Test - Control (95% CI)**
All Serious Adverse Events	33	28.7% (25/87)	19.54, 39.43	31	24.2% (22/91)	15.81, 34.28	4.56% (-8.32%, 17.34%)
Serious Device Related AEs	3	3.4% (3/87)	0.72, 9.75	5	5.5% (5/91)	1.81, 12.36	-2.05% (-9.15%, 4.90%)
Serious Procedure Related AEs	11	9.2% (8/87)	4.05, 17.32	9	7.7% (7/91)	3.15, 15.21	1.50% (-7.09%, 10.33%)
UADEs	0	0.0% (0/87)	N/A	0	0.0% (0/91)	N/A	N/A
Serious Device Related AEs by Event Type (MedDRA coded)							
Gastrointestinal disorders	0	0.0% (0/87)		1	1.1% (1/91)		
Abdominal pain	0	0.0% (0/87)		1	1.1% (1/91)		
General disorders and administration site conditions	2	2.3% (2/87)		1	1.1% (1/91)		
Discomfort	1	1.1% (1/87)		0	0.0% (0/91)		
Medical device discomfort	1	1.1% (1/87)		0	0.0% (0/91)		
Medical device site pain	0	0.0% (0/87)		1	1.1% (1/91)		
Infections and infestations	0	0.0% (0/87)		2	2.2% (2/91)		
Postoperative wound infection	0	0.0% (0/87)		2	2.2% (2/91)		
Injury, poisoning and procedural complications	0	0.0% (0/87)		1	1.1% (1/91)		
Wound dehiscence	0	0.0% (0/87)		1	1.1% (1/91)		
Product issues	1	1.1% (1/87)		0	0.0% (0/91)		
Device extrusion	1	1.1% (1/87)		0	0.0% (0/91)		

Secondary Safety Endpoint – All SAEs from Month 3 to Month 12

The incidence of all SAEs, including SADEs and UADEs, from Month 3 to Month 12 was analyzed in the ITT population (**Table 11)**. The Month-3-to-12 SADE rate was 3.4% in the Test arm and 5.5% in the Control arm. There was no difference between the two treatment arms with respect to SADEs from Month 3 to Month 12, based on 95% CI.

Table 11: Additional Safety Parameters – All SAEs From Month 3 to Month 12, ITT Population

	Test			Control			
	Number of Events	**Number of Subjects with Event N = 87**	**95% CI [3]**	**Number of Events**	**Number of Subjects with Event N = 91**	**95% CI [3]**	**Difference (95% CI) [4]**
All Serious Adverse Events	29	24.1% (21/87)	15.60, 34.50	35	24.2% (22/91)	15.81, 34.28	-0.04% (-12.49%, 12.51%)
Serious Device Related AEs [5][6]	3	3.4% (3/87)	0.72, 9.75	5	5.5% (5/91)	1.81, 12.36	-2.05% (-9.15%, 4.90%)
Serious Procedure Related AEs [5]	2	2.3% (2/87)	0.28, 8.06	1	1.1% (1/91)	0.03, 5.97	1.20% (-3.94%, 6.97%)
Serious Explant or Revision of Study Device Related AEs [5]	0	0.0% (0/87)	0.00, 4.15	0	0.0% (0/91)	0.00, 3.97	N/A

Deaths

As of the data cut-off date, January 4, 2023, 13 subjects were reported to have died during the QUEST study. Nine of the 13 died more than a year after Altius System implantation. Ten deaths (3 respiratory failure/arrest, 2 cancer, 2 cardiac disorder/failure, 1 hepatic cirrhosis,1 suicide, 1 COVID-19 infection) were determined to be not related to the Altius device or the implantation surgery, and 3 deaths (1 pulmonary embolism, 1 cerebrovascular accident, 1 unknown cause) were adjudicated as unknown. There were no deaths attributed to the Altius System or the associated surgery.

Revisions & Explants

In the FAS population, 17 subjects (10 Test, 7 Control) had the Altius IPG and/or cuff electrode(s) explanted within 12 months of index surgery. Four explants were the result of subject request (1 related to insufficient pain relief in control subject; 1 due to need for MRI; 2 no reason specified); 5 due to implant site infection or wound dehiscence; 6 due to device-related complication (e.g., discomfort, device extrusion, wound dehiscence); 1 due to IS-1 connector failure; and 1 due to unrelated surgery.

In the same population and timeframe, 21 subjects (11 Test, 10 Control) had one or more revisions of the Altius IPG and/or cuff electrode(s). The primary reason for revision was IS-1 connector failure (N=10 subjects); medical device site pain or discomfort (5); infection at the implant site (4); cuff sizing correction (1); and cosmetic reason (1).

For both explants and revisions, the need for intervention was independent of treatment group assignment. Corrective actions were taken during the study to address infection/wound complication events and the IS- 1 connector issue. While the revision/explant rate seen in the QUEST study is acceptable and consistent with similar AIMDs, this rate is expected to be lower in commercial use as a result of the mitigations.

Safety Conclusions

The overall rate of safety events associated with the Altius System summarized below.

- The occurrence of overall SAEs, SADEs and procedure-related SAEs was similar between the Test and Control groups, indicating no adverse effect from active HFAC stimulation.
- There were no UADEs and no deaths attributable to the Altius System.
- The rate of SADEs was 4.4%.
- All SADEs were resolved during the study.

The rate of overall SAEs is attributed to the medical complexity of this post-amputation population, which is prone to co-morbidities and poor overall health.

2. Effectiveness Results

Analysis Populations

The primary effectiveness analysis and all secondary analyses, whether intended for labeling or not, were performed on the FAS population (N=170; 85 Test, 85 Control) and key endpoints were confirmed in the Per-Protocol (PP) population (N=156; 76 Test, 80 Control). Because Control subjects crossed over to Test (active Altius therapy) at Month 3, some Month 3-12 analyses were also performed in the combined Test + Control FAS cohort.

Primary Effectiveness Analysis

The study's primary effectiveness endpoint was the responder rate of subjects in each arm, Test vs. Control, during the Randomized Testing phase of the study (Month 1 through Month 3). Study success was determined by a superiority test on the difference between responder rates in the Control and Test groups at Month 3, using logistic regression. The logistic regression model controlled for amputation etiology, amputation location, pain type, baseline pain intensity and baseline pain duration.

In the Test arm, 24.7% (21/85) of subjects were responders, compared to 7.1% (6/85) of Control subjects (**Table 12)**. The absolute difference between the treatment arms was 17.6% (95% CI: 7.0%, 28.3%) and was highly statistically significant using a one-sided significance level (alpha) of 0.025 (p=0.002). Subjects undergoing active Altius treatment were >3 times more likely to experience significant pain relief than subjects who were randomized to the sham-control arm. As such, the QUEST study met its pre-specified primary endpoint, demonstrating superior pain relief with the active Altius treatment compared to control, and the study is deemed a success with respect to primary effectiveness endpoint.

Table 12: Primary Effectiveness Analysis – Responder Rate at 30 Minutes – through 3 Months, FAS Population

	Test Group N = 85	Control Group N = 85	Difference Test - Ctrl (95% CI)	One-sided p-value [1]
Primary Performance Endpoint - Responders [2] [3] [4]	24.7% (21/85)	7.1% (6/85)	17.6% (7.0%, 28.3%)	0.002
95% CI	(15.5%, 33.9%)	(1.6%, 12.5%)		

[1] The responder rate was compared between treatment groups using logistic regression controlling for the following covariates: Etiology (dysvascular, trauma, other), Amputation Location (AKA, BKA), Pain Type (phantom, stump, both), Baseline Pain Intensity (5-6, 7-10) defined as the average of the end-of-day worst pain scores from the subject's e-diary compliant eligibility window, and Baseline Pain Duration (episodic, persistent). Significance is evaluated using a one-sided test with alpha level 0.025.

[2] A responder was defined as any subject who attained ≥50% pain reduction at the 30-minute follow-up assessment in ≥50% of the treatment sessions during the Randomized Testing phase of the study.

[3] Missing pain score at 30 minutes for a particular completed treatment session was considered a failure for that session. Treatment sessions that were interrupted with rescue (p.r.n.) pain medications utilize the assessment of pain at the time of rescue medication, missing observations were considered a failure for that session.

[4] Subjects who were randomized to receive treatment but who terminated prior to their scheduled Month 3 Visit (Day 91 + 14 days post- implantation) were determined to be a responder or non-responder based on their available data prior to termination.

The primary effectiveness results were demonstrated to be robust, with the same outcome in favor of active Altius treatment found in three sensitivity analyses, a multiple imputation analysis and a tipping point (ITT Population) analysis. The primary results were also confirmed in the PP population.

The Cumulative Distribution Function (CDF) is a method of evaluating patient responses over a full range of response levels, utilizing the same data as the primary endpoint. Rather than relying on one cut-point for evaluation, the CDF provides a more accurate reflection of the full nature of the data. This analysis, presented in **Figure 4**, shows a consistent advantage of Test over Control in treatment effect at all proportions of sessions from just above 0% to almost 100%. The Altius treatment effect is robust, with a similar treatment effect across a wide range of session effect. In addition, the significant treatment effect is preserved through that effective range.

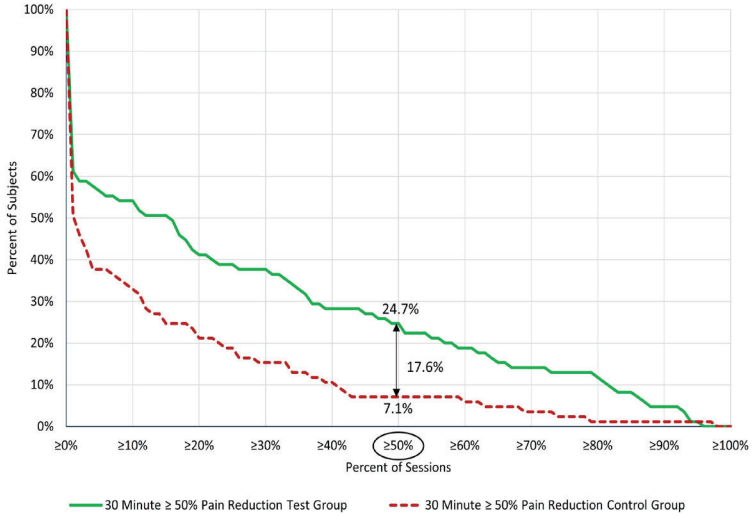

Figure 4: Cumulative Responder Distribution at 30 Minutes as a Function of % Sessions, FAS Population

Secondary Analyses of the Primary Effectiveness Endpoint

To evaluate durability of Altius treatment effect past 30 minutes, the responder rate, using the same criteria of ≥50% pain reduction in ≥50% sessions, was calculated for pain scores recorded at two hours post-treatment (**Table 13).** The treatment effect of Test vs. Control was 25.8% (95% CI: 11.5%, 40.2%), with 48.1% of Test subjects responding to treatment vs. 22.2% of Control subjects.

Table 13: Primary Effectiveness Analysis – Responder Rate at Two Hours – through 3 Months, FAS Population

	Test Group **N = 85**	**Control Group** **N = 85**	**Difference** **Test - Ctrl (95% CI)**	**-sided p-value [1]**
Primary Performance Endpoint at 120 Minutes - Responders [2] [3] [4]	48.1% (37/77)	22.2% (18/81)	25.8% (11.5%, 40.2%)	<0.001
95% CI	(36.9%, 59.2%)	(13.2%, 31.3%)		

[1] The responder rate was compared between treatment groups using logistic regression controlling for the following covariates: Etiology (dysvascular, trauma, other), Amputation Location (AKA, BKA), Pain Type (phantom, stump, both), Baseline Pain Intensity (5-6, 7-10) defined as the average of the end-of-day worst pain scores from the subject's e-diary compliant eligibility window, and Baseline Pain Duration (episodic, persistent). Significance is evaluated using a one-sided test with alpha level 0.025.

[2] A responder was defined as any subject who attained ≥50% pain reduction at the 120-minute follow-up assessment in ≥50% of the treatment sessions during the Randomized Testing phase of the study.

[3] Missing pain score at 120 minutes for a particular completed treatment session was excluded from the analysis. Treatment sessions that were interrupted with rescue (p.r.n.) pain medications utilize the assessment of pain at the time of rescue medication, missing observations were considered a failure for that session.

[4] Subjects who were randomized to receive treatment but who terminated prior to their scheduled Month 3 Visit (Day 91 + 14 days post- implantation) were determined to be a responder or non-responder based on their available data prior to termination.

Secondary Effectiveness Analyses Intended for Labeling

All secondary effectiveness endpoints were analyzed based on the FAS population, and no imputation for missing data was used; analyses were conducted based on available data. The secondary endpoints tested in a hierarchical gatekeeping manner, at a one-sided 0.025 significance level, to control the maximum overall Type I error rate. The secondary effectiveness endpoints for labeling are summarized in **Table 14.**

Table 14: Summary of Secondary Effectiveness Endpoints

Endpoint	Outcome Tt vs. Ct (P-Value)
Change from baseline in opioid pain medication at Month 3, FAS	-5.3 ± 13.76 vs. -1.3 ± 6.80 (0.012)
Change from baseline in pain interference to ADL at Month 3, FAS	-2.3 ± 2.60 vs. -1.3 ± 2.40 (0.010)
Change from baseline in SF-12 PCS at Month 3, FAS	4.1 ± 9.05 vs. 4.3 ± 7.19 (0.571)
Change from baseline in SF-12 MCS at Month 3, FAS	2.3 ± 8.71 vs. -2.1 ± 12.11 (0.004)
Change from baseline in EuroQoL-5D at Month 3, FAS	0.043 ± 0.163 vs. 0.035 ± 0.183 (0.395)

Change from Baseline in Opioid Pain Medication Use at Month 3

Opioid pain medication use was assessed using morphine equivalent dose (MED) for both rescue and routine opioid pain medications. The average daily MED (MED/day) was calculated for each subject across two weeks at baseline and the two weeks preceding Month 3. Based on the FAS Population, subjects who received the Test treatment (Tt) had a mean change from baseline of -6.9±19.64 MED compared to -3.6±21.33 MED in subjects who received the Control treatment (Ct), a statistically non-significant difference (p=0.157). After removing two outliers, one in each arm, the re-run results showed subjects in the test arm had a mean change from baseline of -5.3±13.76 MED compared to -1.3±6.80 MED in subjects in the control arm, a statistically significant difference (p=0.012, **Table 15**). Additionally, as patient self-reported MED are often inaccurate, uncertainty about the presumed benefit of the Altius® system in reducing opioid usage is high. As such, opioid reduction not included in the IFU or the labeling.

Table 15: Secondary Effectiveness Endpoint – Change from Baseline in Opioid Pain Medication Use at Month 3 – Excluding Outliers, FAS Population [1]

	2 Weeks at Baseline		2 Weeks Before Month 3		
	Test N=84	**Control N=84**	**Test N=76**	**Control N=78**	**p-value [3]**
Average Daily MED [2]					
Mean ± SD (N)	19.6 ± 38.25 (84)	8.9 ± 23.98 (84)	13.9 ± 36.33 (76)	8.2 ± 24.14 (78)	
Median (Min, Max)	0.0 (0.0, 228.6)	0.0 (0.0, 165.4)	0.0 (0.0, 245.7)	0.0 (0.0, 163.0)	
Mean Change from Baseline ± SD					
Mean ± SD (N)			-5.3 ± 13.76 (76)	-1.3 ± 6.80 (78)	0.012
Median (Min, Max)			0.0 (-60.0, 22.5)	0.0 (-18.8, 37.1)	
Mean % Change from Baseline ± SD					
Mean ± SD (N)			-55.1 ± 46.18 (34)	-42.2 ± 41.79 (23)	
Median (Min, Max)			-68.0 (-100.0, 36.4)	-33.3 (-100.0, 24.7)	

[1] Includes FAS population excluding subjects with a decrease of 6 or more standard deviations from the mean without a minimum requirement for days reported within the Month 3 Visit Window. One (1) Test Group subject (05-021) and one (1) Control Group subject (27-031) were categorized as outliers. There were 6 subjects who did not have a Month 3 Visit and as a result could not be counted at the Month 3 timepoint. An additional 8 subjects had a Month 3 Visit but did not report their medication use at any time during the 2 week window and were not included in the Month 3 timepoint.

[2] Average daily morphine equivalent dose (MED), both rescue (p.r.n.) and routine opioid pain medications, calculated for each subject across two weeks at Baseline and preceding Month 3.

[3] One-sided p-value reported for the comparison between Test and Control groups on the mean change from baseline in per-subject average MED/day using an ANOVA model. Significance evaluated at the 0.025 level, if and only if the primary effectiveness endpoint is achieved.

Change from Baseline in Pain Interference to ADL at Month 3

Pain interference to activities of daily living (ADL), a measure of pain related QoL, was calculated using the mean of the seven items from the BPI Interference scale, which include General Activity, Mood, Walking Ability, Normal Work, Relationships with Other People, Sleep, and Enjoyment of Life. Each item was scored on a scale of 0 - 10, by intervals of one, where 0 indicates 'Does not interfere' and 10 indicates 'Completely Interferes'. The mean change in pain interference to ADL from baseline to Month 3, including all FAS subjects (Table 16), was -2.3±2.60 in the Test arm and -1.3±2.40 in the Control arm.

Table 16: Secondary Effectiveness Endpoint – Change from Baseline in Pain Interference to ADL at Month 3, FAS Population

	Baseline		Month 3		
	Test N=85	**Control N=85**	**Test N=81**	**Control N=83**	**p-value [3]**
BPI-Interference Summary Score [1] [2]					
Mean ± SD (N)	6.1 ± 2.11 (85)	5.8 ± 1.94 (85)	3.7 ± 2.70 (81)	4.4 ± 2.50 (83)	
Median (Min, Max)	6.1 (1.4, 10.0)	6.0 (2.0, 10.0)	3.6 (0.0, 9.9)	4.4 (0.0, 9.4)	
Quartiles (1,3)	(4.9 ,7.7)	(4.4 ,7.1)	(1.4 ,5.7)	(2.0 ,6.1)	
Mean Change from Baseline ± SD					0.010
Mean ± SD (N)			-2.3 ± 2.60 (81)	-1.3 ± 2.40 (83)	
Median (Min, Max)			-1.9 (-9.0, 3.1)	-1.0 (-6.7, 4.1)	

[1] Calculated as the mean of 7 Brief Pain Inventory items: General Activity, Mood, Walking Ability, Normal Work, Relations with Other People, Sleep, Enjoyment of Life. Each item was scored on a scale of 0 - 10, by intervals of one, where 0 indicates 'Does not interfere' and 10 indicates 'Completely Interferes'.

[2] Subjects missing >0% but <50% of the responses to these 7 items at a given visit had missing responses imputed with the median of the remaining responses at that visit prior to calculating the 7-item average. Subjects missing more than 50% of the responses at a given visit were considered to have missing BPI-interference score at that visit.

[3] One-sided p-value reported for the comparison between Test and Control groups on the mean change from baseline in per-subject BPI- Interference Summary Score using ANOVA. Significance evaluated at the 0.025 level, if and only if the 1) primary effectiveness endpoint and 2) change from baseline in opioid pain medication at Month 3 are achieved.

Long Term Results

The responder rate was analyzed for the FAS population from Month 3 to Month 12. The Month 3-12 responder data in the crossed-over Control group reflects active Altius treatment in subjects who previously received active sham therapy. The purpose of this analysis was to assess both the durability of ongoing Altius treatment and the responder rate in Control subjects who crossed over to active treatment. In the FAS population comprising the Month 3-12 dataset (N=152), the responder rate was 30.1% (22/73) in the Test arm (12-months of active Altius treatment) and 15.2% (12/79) in the Control arm (9 months of active Altius treatment post Month-3) (**Table 17**).

Table 17: Primary Effectiveness Analysis – Month 3 through Month 12, FAS Population

	Test Group N = 73	Control Group N = 79	Difference Test - Ctrl (95% CI)	One-sided p-value [1]
Primary Performance Endpoint – Responders [2] [3] [4]	30.1% (22/73)	15.2% (12/79)	14.9% (1.8%, 28.1%)	0.206
95% CI	(19.6%, 40.7%)	(7.3%, 23.1%)		

[1] The responder rate was compared between treatment groups using logistic regression controlling for the following covariates: Etiology (dysvascular, trauma, other), Amputation Location (AKA, BKA), Pain Type (phantom, stump, both), Baseline Pain Intensity (5-6, 7-10) defined as the average of the end-of-day worst pain scores from the subject's e-diary compliant eligibility window, Baseline Pain Duration (episodic, persistent), and the Month 3 response outcome. Significance was evaluated using a one-sided test with alpha level 0.025.

[2] Subjects were considered a responder if they attained a significant pain reduction at the end of more than half of the treatment sessions subsequent to Month 3 through Month 12. Specifically, a responder must have attained ≥50% pain reduction in ≥50% of the treatment sessions during the Crossover phase of the study (Month 3 through Month 12).

[3] Missing pain score at 30 minutes for a particular completed treatment session was considered a failure for that session. Treatment sessions that were interrupted with rescue (p.r.n.) pain medications utilized the assessment of pain at the time of rescue medication, missing observations were considered a failure for that session.

[4] Subjects who were randomized to receive treatment but who terminated prior to their scheduled Month 12 Visit were determined to be a responder or non-responder based on their available data prior to termination.

Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 42 investigators who implanted the Altius System and/or treated and evaluated study subjects during the course of the study (e.g., pain specialists), none of whom were full-time or part-time employees of the Sponsor. Two clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The applicant has adequately disclosed the financial arrangement with the clinical investigator. The information provided does not raise any questions about the reliability of the data.

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Neurological Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECILINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Effectiveness for the Altius System was based on Level 1 evidence from the prospective multicenter randomized sham-controlled double-blind QUEST pivotal trial. One-hundred-eighty (180) subjects were implanted with the Altius System and randomized to active Altius stimulation therapy or sham-control (sub-therapeutic Altius stimulation); 170 subjects completed the Month 3 primary endpoint, 85 Test and 85 Control, and comprise the FAS population.

The QUEST study met its pre-specified primary effectiveness endpoint, demonstrating superior pain relief with the active Altius treatment (Test) compared to sham control, and the study was deemed a success with respect to effectiveness. The absolute difference between the treatment arms in terms of responder rate at Month 3 (i.e., treatment effect) was 17.6% in favor of active Altius treatment, and this difference was highly statistically significant. The benefits observed during the blinded study phase continued to increase through one year. In addition, improvements were observed between Month 3 and Month 12 on all primary and secondary effectiveness outcomes in the Control group following crossover to therapeutic treatment levels.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory data and published literature as well as data collected in the QUEST clinical study conducted to support PMA approval as described above. SAEs related to the device occurred in 4.4% of the 180 patients implanted and randomized, and all SADEs resolved. No deaths attributed to the device or procedure occurred in the study. There were no unanticipated adverse device effects (UADE).

Regarding total SAEs throughout the study, the rates were similar in both study groups (41.4% of Test subjects vs. 42.9% of Control subjects) and 42.1% combined, in a study population with a high degree of co-morbidity and medical complexity. Implant site infection and/or wound complications occurred in 20% of subjects, most early in the study prior to the implementation of infection control mitigations; the infection rate was ≤5%% in the last 159 subjects enrolled, which is consistent with that of Spinal Code Stimulation (SCS) devices.[1,2,3,4,5] Of all infection/wound complication events, 72% were minor and resolved without surgical intervention. Electrode cuff IS-1 connector failures occurred in 14.7% of FAS subjects; this issue was addressed with a design change and manufacturing improvements. Taking into account the infection mitigations and device deficiency resolution, the safety of the Altius System is similar to other approved implanted neuromodulation devices.

C. Benefit-Risk Conclusions

The probable benefits of the device are based on the data collected in the QUEST pivotal clinical study described above. Effectiveness was demonstrated by improvement in pain at Month 3 with success of the primary effectiveness endpoint. The benefits observed during the blinded Randomized Testing phase continued to increase through one year. Across all pre-specified endpoints, the 12-month data demonstrated that patients have reduced pain overall and reduced pain days per week. In addition, the device -related SAE rate was 4.4% for both Test and Control groups combined and the risk of the device is similar to those of other active implantable systems such as SCS devices, despite the medical complexity of this patient population. In conclusion, therefore, given the available information cited above, the data support that, for relief of chronic PAP, the probable benefits of the Altius System outweigh the probable risks.

1. Patient Perspectives

   This submission did not include specific information on patient perspectives for this device.

XIII. OVERALL CONCLUSIONS

The data in this application constitute valid scientific evidence within the meaning of 21 CFR 860.7, as the QUEST Study pivotal trial met its primary safety and effectiveness endpoints. These data support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The data support the intended use of the Altius® Direct Electrical Nerve Stimulation System as an aid in the management of chronic intractable phantom and residual lower limb post-amputation pain in adult amputees.

XIV. CDRH DECISION

CDRH issued an approval order on 8/26/2024.

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

[1] Lyons KE, Wilkinson SB, Overman J, Pahwa R. Surgical and hardware complications of subthalamic stimulation: a series of 160 procedures. Neurology. 2004 Aug 24;63(4)612-6. doi: 10.1212/01.wnl.0000134650.91974.1a.

[2] Vergani F, Landi A, Pirillo D, Cilia R, Antonini A, Sganzerla EP. Surgical, medical, and hardware adverse events in a series of 141 patients undergoing subthalamic deep brain stimulation for Parkinson disease. World Neurosurg. 2010 Apr;73(4):338-44. doi: 10.1016/j.wneu.2010.01.017.

[3] Hoelzer BC, Bendel MA, Deer TR, et al. Spinal cord stimulator implant infection rates and risk factors: a multicenter retrospective study. Neuromodulation. 2017 Aug;20(6):558-562. doi: 10.1111/ner.12609. Epub 2017 May 11.

[4] Falowski SM, Provenzano DA, Xia Y, Doth AH. Spinal cord stimulation infection rate and risk factors: results from a United States payer database. Neuromodulation. 2019 Feb;22(2):179-189. doi: 10.1111/ner.12843. Epub 2018 Aug 17.

[5] Bullard AJ, Hutchinson BC, Lee J, Chestek CA, Patil PG. Estimating risk for future intracranial, fully implanted, modular neuroprosthetic systems: a systematic review of hardware complications in clinical deep brain stimulation and experimental human intracortical arrays. Neuromodulation. 2020 Jun;23(4):411-426. doi: 10.1111/ner.13069. Epub 2019 Nov 20.