Altius® System Direct Electrical Nerve Stimulation System
Clinical Summary

Caution: Federal (US) law restricts this device to sale by or on the order of a physician

LB-0201 Rev C

ALTIUS SYSTEM CLINICAL SUMMARY

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Please read the complete documentation provided before you use the device.

Although FDA has determined that the probable benefits outweigh the probable risks, there remains some uncertainty regarding the manufacturer's human factors engineering (HFE) and usability engineering (UE) analysis and validation testing. As a condition of approval, FDA is requiring the manufacturer to provide an HFE/UE analysis and validation testing and recommending that this analysis and testing is designed using the FDA's 2016 guidance document "Applying Human Factors and Usability Engineering to Medical Devices"
(https://www.fda.gov/media/80481/download).

This manual can also be found at: www.neurosmedical.com

The Altius® System is protected by several U.S. Patents.
For an up-to date list of relevant patents and patent applications, visit our patents page:
https://www.neurosmedical.com/patents

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Information available for the Altius System:

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The information for prescribers manual and patient manual provide information about indications, contraindications, warnings, precautions, adverse events, sterilization, patient selection, individualization of treatment, and component disposal.

Product manuals, including the patient guide, the programming guide, and implant manual, provide device descriptions, package contents, device specifications, battery longevity and instructions for use.

For information that supports the clinical use of the Altius System, this document includes a clinical summary.

ALTIUS SYSTEM CLINICAL SUMMARY

1. 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.

2. SUMMARY OF PRIMARY CLINICAL STUDY

Neuros Medical Inc. performed a pivotal clinical study, the QUEST Study, to establish reasonable assurance of safety and effectiveness of post-amputation pain relief in lower limb adult amputees in the U.S. under IDE #G130203. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

2.1. Study Design

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.

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).

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.

- 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

2.1.1. 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.

2.1.2. 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 1** below. Adverse events were collected at every visit beginning at the baseline visit.

TABLE 1: QUEST SCHEDULE OF ASSESSMENTS

PARAMETER q	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.

2.1.3. Critical 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

Intended for Labeling Claims

The study's secondary effectiveness endpoints intended to be tested for labeling claims were as follows (in hierarchical order for statistical testing):

- 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

Not Intended for Labeling Claims

The study's secondary effectiveness endpoints not intended to be tested for labeling claims were as follows:

- 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.

2.2. 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

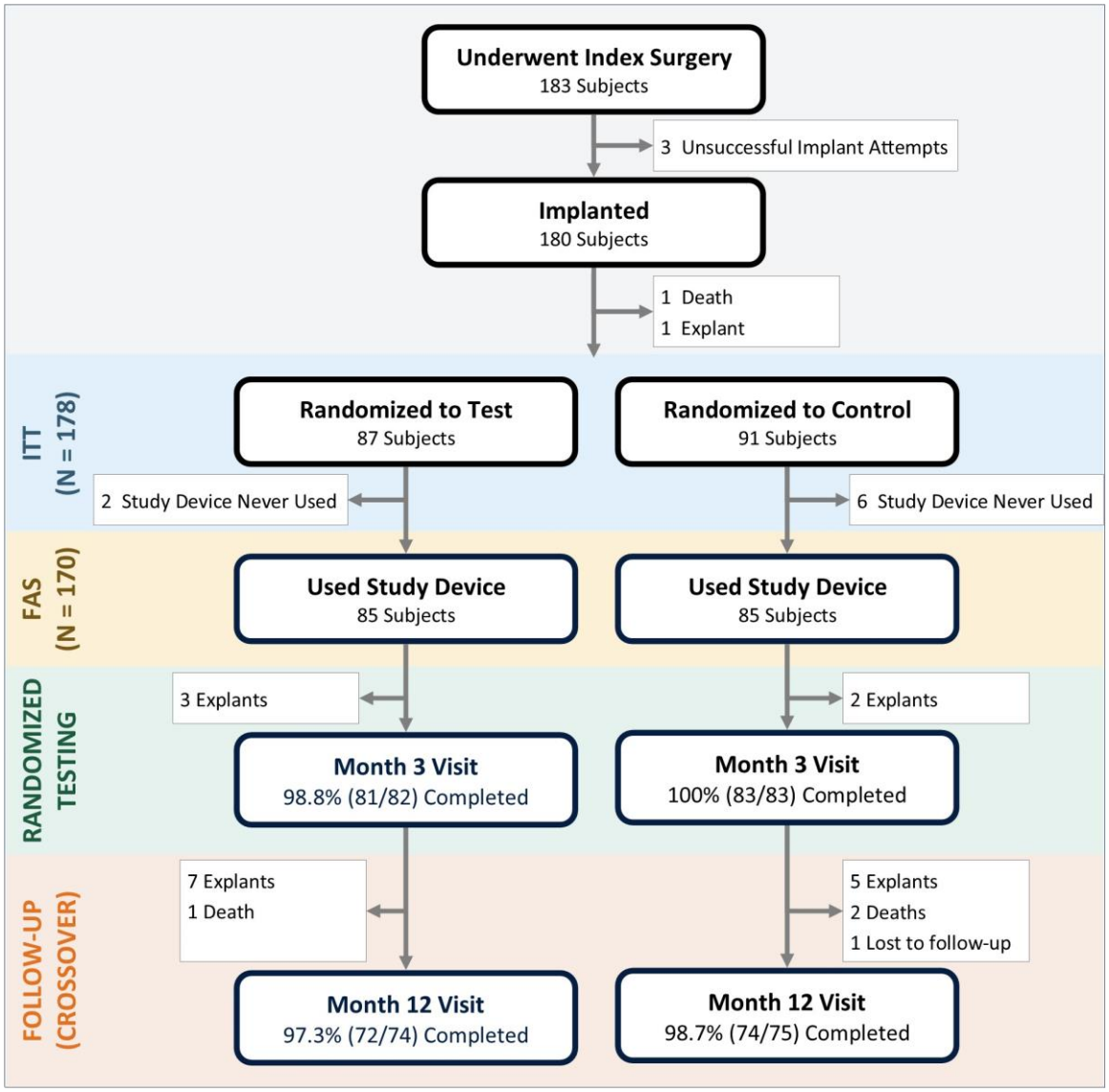

FIGURE 1: SUBJECT DISPOSITION BY VISIT THROUGH MONTH 12

2.3. Study Population Demographics and Baseline Parameters

Table 2 summarizes the key demographic, medical history and baseline parameters for the FAS population. The two treatment arms were well balanced across all baseline factors.

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TABLE 2: 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/m²)	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)	
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

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	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]**
Average daily limb pain (categories)				
No Pain (0)	0.0% (0/85)	0.0% (0/85)	0.0% (0/170)	0.419
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)	
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)	0.873
Persistent; It Builds and Remains for Most of the Day	63.1% (53/84)	64.7% (55/85)	63.9% (108/169)	
Limb pain type				
Stump Only	6.0% (5/84)	3.6% (3/84)	4.8% (8/168)	0.833
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)	
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)	0.152
>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)	
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)	0.117
Past, resolved	1.2% (1/85)	6.0% (5/84)	3.6% (6/169)	
No prior history	98.8% (84/85)	94.0% (79/84)	96.4% (163/169)	
Anxiety				
Current condition	41.2% (35/85)	50.6% (43/85)	45.9% (78/170)	0.409
Past, resolved	1.2% (1/85)	2.4% (2/85)	1.8% (3/170)	
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)	

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	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]**
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)	0.915
Past, resolved	3.5% (3/85)	3.6% (3/84)	3.6% (6/169)	
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.				

2.4. Safety & Effectiveness Results

2.4.1. 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 3**), 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 4**), 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 4,** 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 3: 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 4: 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)		

ALTIUS SYSTEM CLINICAL SUMMARY

	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)**
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 5**). 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 5: 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, 04-Jan-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 low at 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.

2.4.2. 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.

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 effectiveness.

In the Test arm, 24.7% (21/85) of subjects were responders, compared to 7.1% (6/85) of Control subjects (**Table 6**). 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.

TABLE 6: 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 2,** 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.

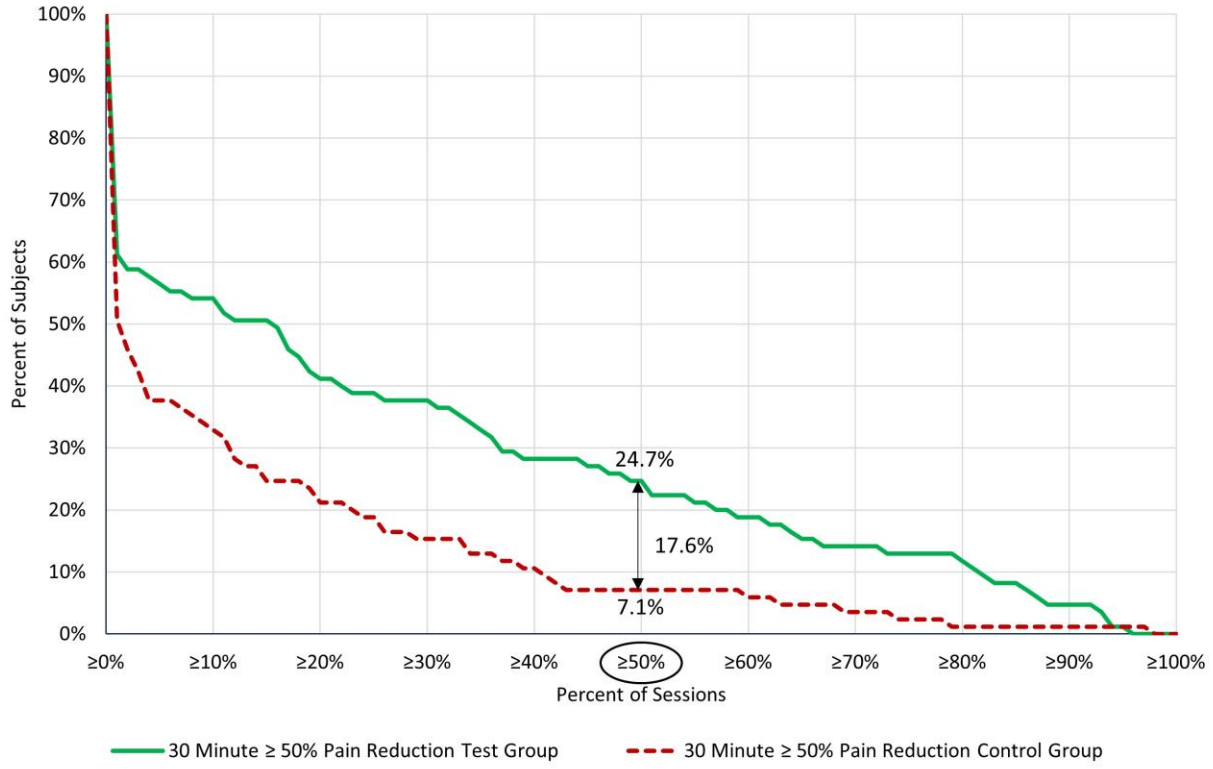

FIGURE 2: CUMULATIVE RESPONDER DISTRIBUTION AT 30 MINUTES AS A FUNCTION OF % SESSIONS, FAS POPULATION

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 7**)**.** 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 Contol subjects; this difference was highly statistically significant ($p<0.001$), confirming that Altius treatment is durable for at least two hours after device use.

TABLE 7: RESPONDER RATE AT TWO HOURS – 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 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

Five secondary effectiveness endpoints were designated as being intended for labeling claims. All 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 intended for labeling were prioritized and 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 8** with the outcome of the remaining three secondary effectiveness endpoints in the last three rows. **Active Altius subjects (Test) demonstrated significant reduction in opioid use and significant improvement in pain interference to ADL compared to sham-control.** Details of the first two successful endpoints are provided below.

TABLE 8: SUMMARY OF SECONDARY EFFECTIVENESS ENDPOINTS FOR LABELING

Endpoint	Outcome T_t vs. C_t (P-Value)	Statistical Success
Change from baseline in opioid pain medication at Month 3, FAS	-5.3 ± 13.76 vs. -1.3 ± 6.80 (**0.012**)	**Yes** Criteria for labeling claim met
Change from baseline in pain interference to ADL at Month 3, FAS	-2.3 ± 2.60 vs. -1.3 ± 2.40 (**0.010**)	**Yes** Criteria for labeling claim met
Change from baseline in SF-12 PCS at Month 3, FAS	4.1 ± 9.05 vs. 4.3 ± 7.19 (0.571)	No
Change from baseline in SF-12 MCS at Month 3, FAS	2.3 ± 8.71 vs. -2.1 ± 12.11 (**0.004**)	**Yes** Criteria for labeling claim not met
Change from baseline in EuroQoL-5D at Month 3, FAS	0.043 ± 0.163 vs. 0.035 ± 0.183 (0.395)	No

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. Two subjects, one in each treatment arm, had extreme decreases in opioid pain medication use, with a change from baseline in average daily MED ≥6 standard deviations from the mean, and extenuating circumstances regarding opiate use and were excluded from the analysis. Test subjects had a mean change from baseline of -5.3±13.76 MED compared to -1.3±6.80 in the Control arm (**Table 9:)** a statistically significant difference (p=0.012). Among subjects who reported opioid use at baseline and any utilization (even if zero) at Month 3, there was a 55.1% decrease from baseline to Month 3 in the Test arm and a 42.2% decrease in the Control arm. See also **Figure 3.**

TABLE 9: SECONDARY EFFECTIVENESS ENDPOINT FOR LABELING CLAIM – 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

	2 Weeks at Baseline		2 Weeks Before Month 3		
	Test N=84	**Control N=84**	**Test N=76**	**Control N=78**	**p-value [3]**
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.

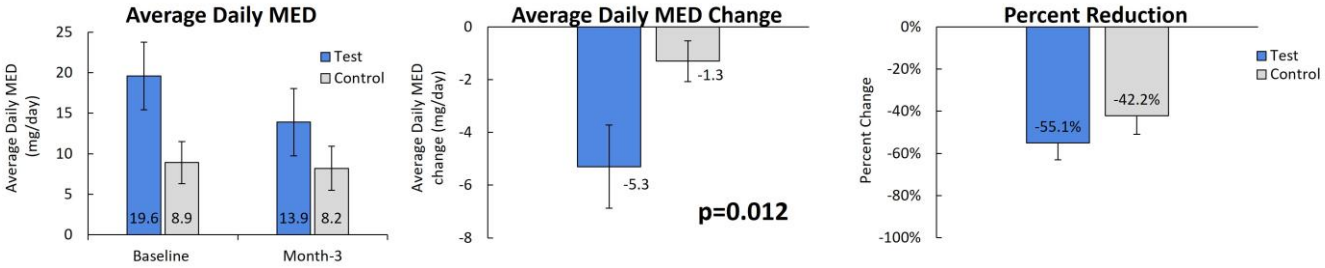

FIGURE 3: AVERAGE DAILY MED AT BASELINE AND MONTH 3 (LEFT), CHANGE FROM BASELINE IN IN DAILY MED AT MONTH 3 (MIDDLE) AND % REDUCTION FROM BASELINE TO MONTH 3 (RIGHT) BY TREATMENT ARM – EXCLUDING OUTLIERS, FAS POPULATION

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 10**), was -2.3±2.60 in the Test arm and -1.3±2.40 in the Control arm, indicating a reduction in pain interference to ADL in both study arms, a statistically significant difference in favor of Test (p=0.010), and a clinically meaningful improvement in pain (38% improvement in pain interference to ADL for Test subjects vs. 22% for Control subjects).

TABLE 10: SECONDARY EFFECTIVENESS ENDPOINT FOR LABELING CLAIM – 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.

Secondary Effectiveness Analyses Not Intended for Labeling

A number of additional secondary effectiveness analyses were performed but were not intended for labeling claims, as summarized below:

- The responder rate in crossed-over Control subjects at Month 6, 22.1%, was similar to the Month 3 Test responder rate, 24.7%, and indicates that control subjects had a numerically and clinically meaningful improvement in pain after Altius stimulation was increased to therapeutic levels at cross-over.
- Test subjects experienced significant additional pain relief from 30 minutes to two hours post-stimulation at all follow-up timepoints, Months 3, 6 and 12, reflecting durability of the Altius treatment effect, as did Control subjects at Months 6 and 12.
- Subjects in both treatment arms began the study reporting pain almost 7 days per week. By Month 12, both treatment arms demonstrated a reduction of approximately 3.5 pain days per week, a 50%+ reduction in pain days compared to baseline.
- There was a consistent, statistically significant and clinically meaningful decline in daily opioid pain medication use in the Test arm from Baseline to Month 12. By Month 12, the cohort of subjects taking opioids at baseline reduced its daily opioid utilization by over 60% from baseline.

- Overall non-opioid pain medication use declined from baseline to Month 3 in both treatment arms and continued with small further declines at Months 6 and 12.
- Pain interference to ADL showed a statistically significant decrease compared to baseline in both treatment arms at all follow-up timepoints, including in post-cross-over control subjects.
- There was a significant quality of life improvement for subjects in both treatment arms over the course of the study, as demonstrated by improvement variously in EQ-5D, SF-12 PCS, and SF-12 MCS.
- Based on PGIC, subjects in both treatment arms reported improvement at Months 6 and 12.
- Technical success, implantation and activation of the study device, was achieved in 97.3% of subjects.

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 11**:).

TABLE 11: RESPONDER RATE AT 30 MINUTES – 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.

Summary

In conclusion, the QUEST pivotal study met its primary safety and effectiveness endpoints and two of the secondary effectiveness endpoints for labeling. This study demonstrates that the Altius System is safe and effective for its intended purpose and has a favorable benefit/risk profile. The Altius System represents an important step forward in the treatment of post-amputation pain for a patient population, lower limb adult amputees, who are currently under-treated and in dire need of effective, non-addictive pain relief and the significant quality of life improvements that accrue from reducing or eliminating pain from their lives. Furthermore, the Altius System has the potential to address pain in a significant portion of the U.S. population that might otherwise use opiates and develop opioid addiction.

Pediatric Extrapolation

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

3. Conclusions Drawn from Preclinical and Clinical Studies

3.1. 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.

Comparison between the Test and Control groups on three secondary effectiveness endpoints for labeling demonstrate the following clinical benefits of the Altius System:

- Greater reduction in opioid pain medication use at Month 3 by mean MED
- Greater reduction (improvement) in pain interference to ADL at Month 3 by mean BPI
- Greater improvement in quality of life at Month 3 as measured by SF-12 MCS

Additional multiple secondary effectiveness endpoints demonstrate the following clinical benefits in both Test and post-cross-over Control subjects:

- Continuing improvement in pain from baseline to Month 6 and Month 12 in both Test and Control
- Improvement in pain relief in both groups from 30 minutes to two hours post-Altius therapy at all timepoint
- Significant reduction in pain days per week in both groups at all timepoints, culminating at Month 12 in a reduction of approximately 3.5 pain days per week, >50% reduction in pain days compared to baseline
- Consistent significant decline in daily opioid and non-opioid pain medication use in both groups through Month 12
- Significant quality of life improvement in both treatment arms over the course of the study, as demonstrated by improvement variously in EQ-5D, SF-12 PCS, and SF-12 MCS

The benefits observed during the blinded study phase continued to increase through one year. Across all pre-specified primary and secondary endpoints, the 12-month data demonstrated that patients have reduced pain, reduce opioid medication consumption, and improved quality of life. 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. All of these factors are crucial in evaluating the effectiveness of the Altius therapy.

3.2. 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 Cord 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.

3.3. Patient Perspectives

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

3.4. 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, as well as by improved pain interference to ADL and quality of life and significant reduction in opioid pain medication use. 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, reduced pain days per week, improved pain interference to ADL, improved quality of life, and reduced opioid and non-opioid pain medication use. 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.

3.5. Overall Conclusions

The data in this application constitute valid scientific evidence within the meaning of 21 CFR 860.7, as the QUEST Study was well-controlled and well-design pivotal trial that 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 claims of post-amputation pain relief (pain reduction), reduced opioid medication use and improved quality of life.

4. References

ALTIUS SYSTEM CLINICAL SUMMARY

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