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CLINICAL TRIAL REPORT

Primary 3-Month Outcomes of a Double-Blind Randomized Prospective Study (The QUEST Study) Assessing Effectiveness and Safety of Novel High-Frequency Electric Nerve Block System for Treatment of Post-Amputation Pain

Leonardo Kapural[1], Jim Melton[2], Billy Kim[3], Priyesh Mehta[4], Abindra Sigdel[5], Alexander Bautista[6], Erika A Petersen[7], Konstantin V Slavin[8,9], John Eidt[10], Jiang Wu[11], Said Elshihabi[12], Jason Matthew Schwalb[13], H Edward Garrett Jr[14], Elias Veizi[15], Giancarlo Barolat[16], Ravi R Rajani[17], Peter C Rhee[18], Maged Guirguis[19], Nagy Mekhail[20]

[1]Carolinas Pain Institute and Center for Clinical Research, Winston-Salem, NC, USA; [2]Department of Vascular Surgery, Cardiovascular Health Clinic, Oklahoma City, OK, USA; [3]Department of Vascular Surgery, The Surgical Clinic, Nashville, TN, USA; [4]Department of Pain Medicine, Meta Medical Research Institute, Dayton, OH, USA; [5]Department of Surgery, University of Louisville, Louisville, KY, USA; [6]Department of Anesthesiology and Perioperative Medicine, University of Louisville, Louisville, KY, USA; [7]Department of Neurosurgery, University of Arkansas, Little Rock, AR, USA; [8]Department of Neurosurgery, University of Illinois at Chicago, Chicago, IL, USA; [9]Department of Neurology, Jesse Brown VA Medical Center, Chicago, IL, USA; [10]Department of Vascular Surgery, Baylor Scott and White Heart and Vascular Hospital Dallas, Dallas, TX, USA; [11]Department of Anesthesiology & Pain Medicine, University of Washington Medical Center, Seattle, WA, USA; [12]Department of Neurosurgery, Legacy Brain & Spine Surgical Center, Atlanta, GA, USA; [13]Department of Neurosurgery, Henry Ford Medical Group, Detroit, MI, USA; [14]Department of Vascular Surgery, University of Tennessee-Memphis, Memphis, TN, USA; [15]Department of Pain Medicine, VA Northeast OH Healthcare System, Cleveland, OH, USA; [16]Department of Neurosurgery, Barolat Neuroscience, Presbyterian/St Luke's Medical Center, Denver, CO, USA; [17]Department of Vascular Surgery, Emory University and Grady Memorial Hospital, Atlanta, GA, USA; [18]Department of Orthopedic Surgery, Mayo Clinic, Rochester, MN, USA; [19]Department of Interventional Pain Management, Ochsner Health System, New Orleans, LA, USA; [20]Department of Pain Management, Cleveland Clinic, Cleveland, OH, USA

Correspondence: Leonardo Kapural, Carolinas Pain Institute and Center for Clinical Research, 145 Kimel Park Dr #330, Winston-Salem, NC, 27103, USA, Email lkapuralmd@gmail.com

Purpose: This multicenter, randomized, double-blinded, active sham-controlled pivotal study was designed to assess the efficacy and safety of high-frequency nerve block treatment for chronic post-amputation and phantom limb pain.

Patients and Methods: QUEST enrolled 180 unilateral lower-limb amputees with severe post-amputation pain, 170 of whom were implanted with the Altius device, were randomized 1:1 to active-sham or treatment groups and reached the primary endpoint. Responders were those subjects who received ≥50% pain relief 30 min after treatment in ≥50% of their self-initiated treatment sessions within the 3-month randomized period. Differences between the active treatment and sham control groups as well as numerous secondary outcomes were determined.

Results: At 30-min, (primary outcome), 24.7% of the treatment group were responders compared to 7.1% of the control group (p=0.002). At 120-minutes following treatment, responder rates were 46.8% in the Treatment group and 22.2% in the Control group (p=0.001). Improvement in Brief Pain Inventory interference score of 2.3 ± 0.29 was significantly greater in treatment group than the 1.3 ± 0.26-point change in the Control group (p = 0.01). Opioid usage, although not significantly different, trended towards a greater reduction in the treatment group than in the control group. The incidence of adverse events did not differ significantly between the treatment and control groups.

Conclusion: The primary outcomes of the study were met, and the majority of Treatment patients experienced a substantial improvement in PAP (regardless of meeting the study definition of a responder). The significant in PAP was associated with significantly improved QOL metrics, and a trend towards reduced opioid utilization compared to Control. These data indicate that Altius treatment represents a significant therapeutic advancement for lower-limb amputees suffering from chronic PAP.

Keywords: post-amputation pain, phantom limb pain, neuromodulation, peripheral nerve stimulation, high-frequency nerve block

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Introduction

There are currently 2.3 million lower limb amputees in the US, with approximately 185,000 new amputations occurring annually.[1] Its prevalence is expected to nearly double to 3.6 million by 2050, largely owing to the increasing prevalence of diabetes and peripheral arterial disease.[2] Most amputees experience chronic post-amputation pain (PAP), with up to 80% reporting phantom limb pain (PLP; pain in the non-existent limb) and up to 70% reporting residual limb pain (RLP; pain in the remaining portion of the amputated limb).[3,4] Amputations and chronic PAP have a significant socioeconomic impact on both amputees and the healthcare system. Over 50% of amputees remain non-ambulatory six months post-amputation,[5] and up to 42% remain out of work seven years post-amputation.[6] The lifetime direct cost of lower-extremity amputation was estimated to be $878,927 per amputee in 2019, translating to an overall cost to the healthcare system of over $51 billion USD.[7]

The mechanisms of PAP are complex and involve pathophysiological changes at the level of the damaged peripheral nerve, spinal cord, and sensory cortex.[8] Peripherally, the severed nerve begins to sprout new axons and upregulates the expression of voltage-gated sodium channels (VGSC) leading to increased spontaneous signals to the CNS.[9] Over time, this leads to a central sensitization of the CNS to peripheral stimuli, resulting in chronic PAP.[10] The complex mechanisms and clinical presentation of PAP make its treatment challenging. Injection of local anesthetics at the site of amputation is a primary therapy for acute PAP. Anesthetics such as lidocaine provide regional nerve blocks through the blockage of VGSCs at the damaged nerve end. Although anesthetics can provide immediate relief, their effects are short-lived, and toxicity is a concern with their prolonged utilization.[11,12] Opioids and anticonvulsants have been used as second-tier therapies to treat persistent PAP. Opioids have been effective in reducing PAP;[13,14] however, they are associated with severe, often intolerable side effects and an addiction rate of up to 50%.[15] Anticonvulsants, including gabapentin, have been used to treat neuropathic pain; however, their effectiveness in reducing PAP is not optimal.[16–18]

Surgical options are also available for patients with chronic PAP who remain refractory to first- and second-tier therapies. Surgical removal of a neuroma, when present, has shown promise for reducing chronic PAP.[19,20] This treatment is often temporary with a recurrence rate of approximately 50%.[21] More advanced surgical techniques, including targeted muscle reinnervation (TMR) and regenerative peripheral nerve interface (RPNI), have been developed to allow nerve regeneration into functional targets following amputation. These approaches have shown some benefits in reducing neuroma pain and PLP primarily when performed at the time of amputation; however, their use secondarily, late after amputation to treat pain, needs to be studied further.[20,22]

Electrical neuromodulation devices such as spinal cord stimulators (SCS) and peripheral nerve stimulators (PNS) modulate pain signals before they reach the cortex. While there is strong evidence of neuromodulation in the treatment of neuropathic pain, the results on PAP are mixed.[8,23] SCS using any available waveform has demonstrated limited benefits in PAP, and data on PLP are limited and inconclusive. A recent review of SCS in the treatment of PLP showed clinically significant pain relief in 7/12 studies reviewed; the remaining 5 studies showed no benefit.[23] Inadequate pain management is one of the primary reasons for device removal,[24] with annual explant rates of up to 11% in implanted subjects.[25] PNS has shown promise in the treatment of localized PAP, albeit in limited numbers. The one placebo-controlled study we are aware of reported substantial (>50%) pain relief in a small cohort of subjects receiving PNS (N=18/24) at two months.[26] This reduction in pain was maintained for 12 months in 6/9 subjects.[27] Despite this, the use of PNS in the treatment of PAP has been limited due to the technical complexity of surgical intervention with currently available devices and its association with high rates of device revision (27%) and explant (15%) procedures.[28] To date, studies have not identified a reliable, durable, and dramatically effective treatment option for PAP.

High-frequency alternating currents (HFAC) have recently been used investigationally to block nerve conduction.[29] Preclinical studies have demonstrated that the application of HFAC within the 5–50 kHz range resulted in a reversible conduction block.[30] Similar to lidocaine, HFAC achieves nerve conduction block through its action on VGSCs. HFAC provides an electrical, rather than chemical, nerve block through sustained membrane depolarization, leading to inactivation of VGSCs and subsequent reduction in signal transduction.[31] From this, a novel implantable device was developed to deliver HFAC directly to targeted damaged nerve fibers and block the propagation of pain signals (high-frequency nerve block (HFNB)) in PAP. An early iteration was studied in 10 subjects with chronic PAP, with 7/10 achieving ≥ 50% pain reduction in ≥ 50% of their self-initiated treatment

sessions for the three-month endpoint.[32] The treatment efficacy was sustained for up to 12-months with an average pain reduction of 73%. These preliminary data provided the framework and justification for a larger pivotal study to evaluate bioelectric HFNB for the treatment of chronic PAP – the QUEST study (ClinicalTrials.gov identifier: NCT02221934; trial design introduced previously).[33] The subjects were studied for 12-months, however herein, we report the 3-month primary endpoint comparison between the Treatment and Control groups.

Materials and Methods

QUEST is a prospective, multicenter, double-blind, randomized, active-sham-controlled clinical trial designed to evaluate the safety and effectiveness of the Altius® System (Figure 1) for the treatment of severe chronic PAP. The study was conducted in compliance with the US Code of Federal Regulations and recommendations/guiding principles in biomedical research by the Declaration of Helsinki. The study protocol and informed consent forms were approved by the Western Investigational Review Board and Institutional Review Board of each study site (IRB).

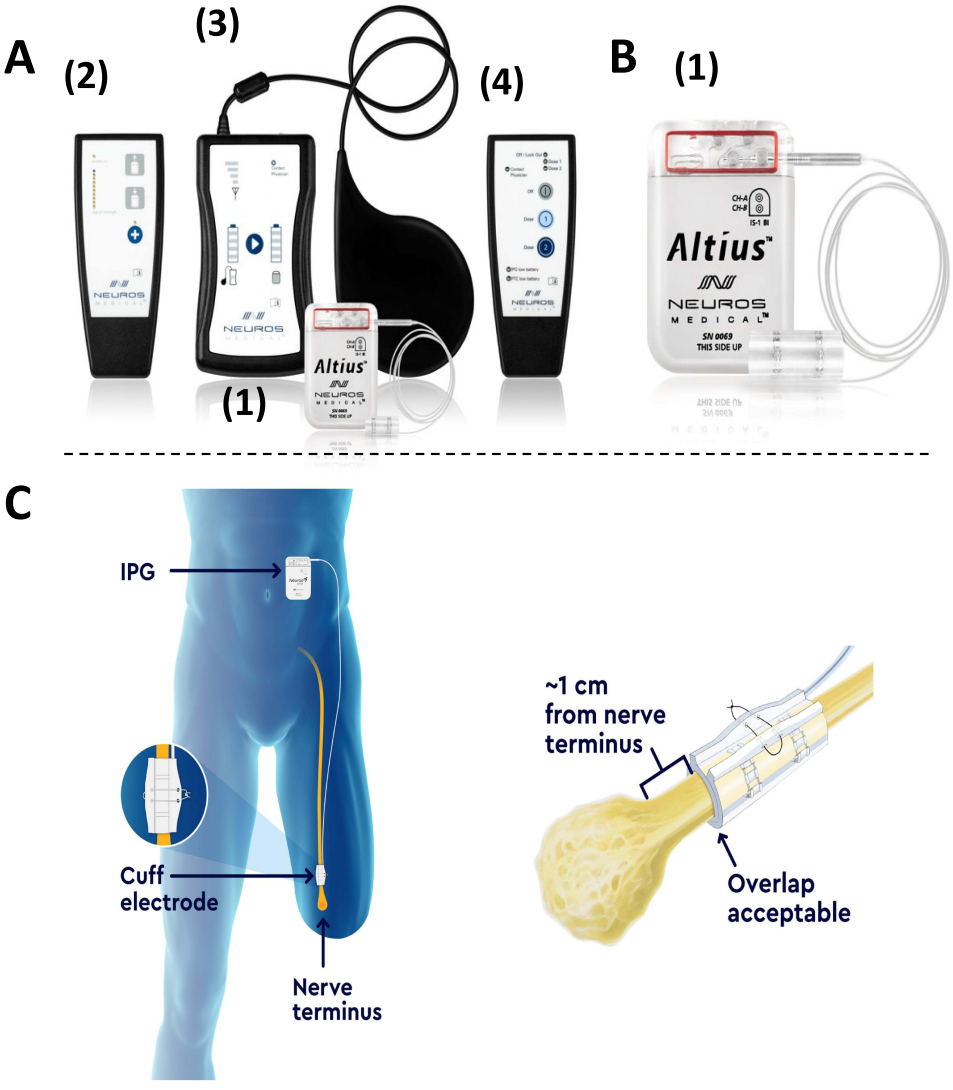

Figure 1 The Altius Bioelectric Nerve Block System and Implantation schematic. (**A**) The Altius Bioelectric Nerve Block System is designed to deliver high frequency nerve block (HFNB) to relieve chronic PAP. Implantable Pulse Generator (IPG) shown in the foreground connected to a single nerve cuff electrode (1). Implanted system components shown in the background: Physician Programming Wand (2), IPG Battery Charger (3), Patient Controller (4). (**B**) Increased magnification of the IPG and nerve cuff electrode. (**C**) Surgical implantation schematic showing the cuff electrode wrapped around the distal end of the target nerve and connected to the IPG which is typically implanted in a subcutaneous pocket in the abdomen. Adapted with permission from Dove Medical Press. Kapural L, Syed Shah N, Fang Z-P, Mekhail N. Multicenter, Double-Blinded, Randomized, Active-Sham Controlled Clinical Study Design to Assess the Safety and Effectiveness of a Novel High Frequency Electric Nerve Block System in the Treatment of Post-Amputation Pain (The QUEST Study). *J Pain Res*. 2022;15:1623–1631.[33]

Study Population and Study Screening

Adult unilateral amputees with chronic PAP were enrolled and implanted at 25 centers in the US. Key inclusion criteria were chronic PAP (≥ 6-months with exacerbations lasting ≥ 60-minutes with a frequency of ≥ 4 episodes per week with >5 Numerical Rating Scale (NRS)), and agreement to maintain a stable drug regimen for ≥ 4 weeks. Key exclusion criteria included previously implanted active medical devices, confounding pain sources that would interfere with limb pain reporting, underlying or concomitant conditions requiring MRI, uncontrolled diabetes (HbA1c > 8.0), and a history of substance abuse or untreated psychological conditions.

Following enrollment, the participants were screened for their ability to report their end-of-day pain levels, medication use, and prosthetic use. The subjects were provided with an eDiary for four weeks and were required to demonstrate two consecutive weeks of compliant reporting and adequate pain severity and frequency to qualify. Next, subjects were evaluated for their ability to report pain reduction and their likelihood of responding to Altius treatment through injection screening with a local anesthetic peripheral nerve block ("Injection Evaluation"; Figure 2A). The subjects received an ultrasound-guided injection of saline into the sciatic nerve or its major branches. If there was no response to the sham

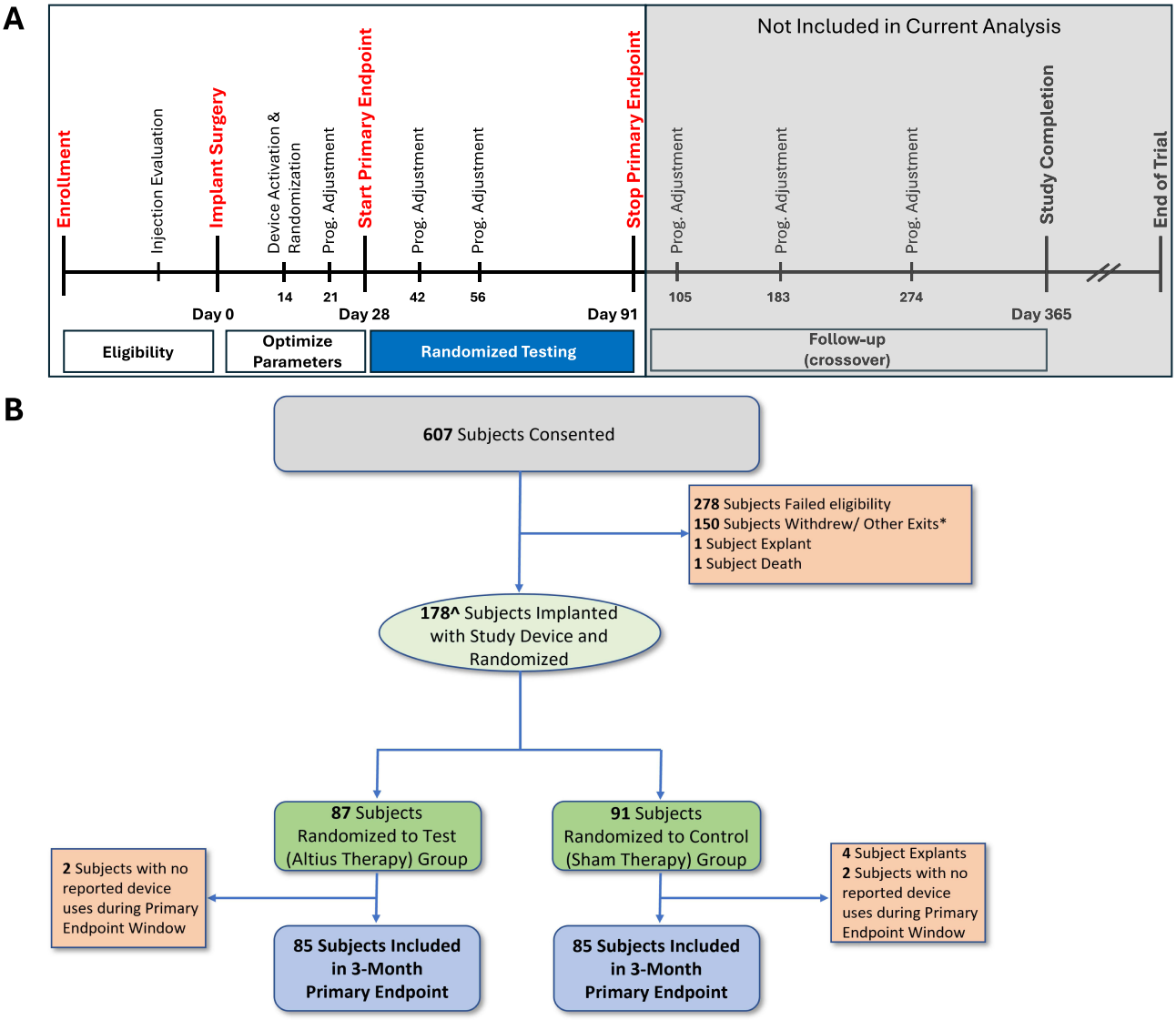

Figure 2 QUEST subject study schedule and subject flow chart. (**A**) QUEST study schedule. (**B**) QUEST subject flow chart. ^1 Subject failed eligibility but proceeded to implant; *Subject Withdrew/Other Exits included voluntary, investigator withdrawing subject, subject failing to keep in contact with site, exit post-enrollment, or exit after an unsuccessful implant of the study device. (**A**) is adapted with permission from Dove Medical Press. Kapural L, Syed Shah N, Fang Z-P, Mekhail N. Multicenter, Double-Blinded, Randomized, Active-Sham Controlled Clinical Study Design to Assess the Safety and Effectiveness of a Novel High Frequency Electric Nerve Block System in the Treatment of Post-Amputation Pain (The QUEST Study). *J Pain Res*. 2022;15:1623–1631.[33]

(saline), an injection of 2% lidocaine was administered. Subjects who reported <30% pain relief after sham injection and ≥50% pain relief after lidocaine injection passed the screening and proceeded to implantation of the investigational device ("Implant Surgery"; Figure 2A).

Investigational Device and Implant Procedure

The Altius® Bioelectric Nerve Block System (Neuros Medical, Inc., Aliso Viejo, CA, USA) consists of an implantable pulse generator (IPG) with an integrated rechargeable battery connected to one or two cuff electrodes wrapped around the target nerve(s) (Figure 1A and B). The cuff electrodes come in three sizes (4-6 mm, 6-9 mm, or 9-11 mm) to accommodate a range of nerve diameters. The IPG was programmed to deliver 30 min of HFNB treatment when the subject initiated therapy with their (external) Patient Controller.

The subjects were implanted with Altius under general anesthesia (Day 0; Figure 2A). The target nerve was exposed proximal to the damaged nerve ending and the cuff electrode was wrapped around the nerve and sutured in place (Figure 1C). Subjects with above-the-knee amputations (AKA) typically received a single electrode on the sciatic nerve, whereas those with below-the-knee amputations (BKA) typically received two electrodes, one each on the tibial and common peroneal nerves. The lead from the electrode(s) was tunneled and connected to the Altius IPG implanted subcutaneously in the abdominal wall.

Randomization and Treatment Parameters

Approximately two weeks after implantation, the subjects returned to the clinic for device activation and initial programming ("Device Activation"; Day 14; Figure 2A) and were randomized (1:1) to receive either Treatment or Control programs. Randomization was stratified by clinical site using random permuted blocks (block size concealed from site personnel) to achieve an approximate balance of treatment allocation within each site. The subjects, investigators, and site personnel were blinded to the randomization. Approximately one week later, subjects returned to the clinic for additional programming settings optimization by Neuros field personnel ("Prog. Adjustment"; Day 21; Figure 2A). Programming adjustment visits were used to adjust current and voltage settings to optimize therapy for the subject.

On Day 28, the subjects began the randomized testing period ("Randomized Testing"; Day 28–91; Figure 2A) and activated their devices for pain management. Subjects in the Treatment group received HFNB (5–10 kHz) for a 30-minute treatment duration. The Control group received an ultra-low frequency (0.1 Hz) that was sub-therapeutic yet physically discernable to the subject. On Day 91, the randomized study period ended, and control subjects crossed over to receive the treatment program for the remainder of the 12-month study period . Subjects who were initially assigned to the treatment group remained on the treatment program ("Follow-up Crossover" to "Study Complete"; Day 91–365; Figure 2A). The subjects completed two blinding questionnaires prior to any parameter adjustments at the time of visit, along with Month-1, and −3, and were assessed for potential unblinding. The complete study schedule is shown in Figure 2A.

Data Collection and Outcome Measures

Participants activated their Altius system as needed for pain management. The therapy sessions lasted for 30 min, followed by a 30-minute lockout for nerve recovery. Subjects were instructed to record their pain intensity using a 0–10 NRS score before therapy and 30-min and 120-min after therapy in the eDiary application (Axiom, Inc., Toronto, Canada) on a study-provided, secure mobile phone (Samsung, Seoul, South Korea). Subjects were also required to report their daily current pain score and their past 24-hour average, least and worst pain scores, pain medication use, and prosthesis use. The participants' use of Altius was automatically recorded in an electronic log stored on the IPG and retrieved at each follow-up and programming visit. If the subjects were on as-needed medications for pain, they were instructed to report the frequency/amount in their eDiary, similar to their Altius device usage.

The Primary Effectiveness Endpoint was the difference in responders between the Treatment and Control (active-sham) groups. A "Responder" was defined as a subject who attained ≥50% pain reduction (30 minutes post-treatment initiation compared to just before treatment) in ≥50% of the treatment sessions. The Primary Safety Endpoint was the

incidence of all serious adverse events (SAEs) including serious adverse device events (SADEs) and unanticipated adverse device events (UADEs). Secondary Endpoints included differences in Responder Rate 120-minutes after therapy, change in opioid Morphine Equivalent Dose (MED), and change in pain interference to activities of daily living via the Brief Pain Inventory (BPI).

Statistical Analysis

This study was powered by the primary effectiveness endpoint. The total sample size calculation used a normal approximation multiplied by an inflation factor for the group sequential design, a statistical power of 0.90, and an expected responder rate to Treatment and Control groups of 0.50 and 0.25 respectively (PASS 15 Power Analysis and Sample Size Software (2017), NCSS, LLC, Kaysville, Utah, USA). With an estimated attrition rate of up to 10%, to account for subjects who were implanted but not randomized, the sample size was 180.

The primary analysis population for the effectiveness endpoint included subjects who were randomized and had documented device use during the randomized period. Each participant's individual responder rate at both 30- and 120-minutes were calculated using all sessions captured. The responder rate was compared between the Treatment and Control groups using logistic regression, controlling for the following covariates: etiology (vascular, trauma, other), location (AKA, BKA), pain type (phantom, stump, both), baseline pain intensity (5–6, 7–10) from the subject's eDiary compliance eligibility window, and baseline pain duration (episodic, persistent). Significance was evaluated using a one-sided test, with an alpha level of 0.025. Study success was determined using a superiority test of the difference between responder rates in the Control and Treatment groups. Subject sessions in which a 30-minute pain score was not reported were considered failures. Subject responder rates at 120 minutes were also calculated using logistic regression; however, pain scores that were not reported were not imputed or included in the analysis. Analyses were based on the available data, with no imputation of missing data for secondary endpoints due to premature withdrawal. The primary safety analysis population included all subjects who underwent implant surgery.

Clinical oversight included an expert Independent Physician Adjudicator who adjudicated all AEs (including deaths, device- or procedure-related SAEs, and SAEs associated with the target limb or implant site) and a Data Monitoring Committee that monitored AE rates and provided safety and futility reviews throughout enrollment.

Results

Study Subjects and Baseline Pain Characteristics

Between October 2014 and September 2021, 607 patients were evaluated for inclusion in QUEST, with 180 proceeding through device implantation and 178 proceeding through randomization (two subjects were not randomized, one died, and one could not be activated). 87 subjects were randomized to receive HFNB (Treatment Group) and 91 subjects were randomized to receive active-sham therapy (Control Group). During the randomized testing period, four subjects were explanted (two infections, two subject requests), and four subjects reported no device use (two subject compliance, one insufficient pain, one device discomfort) for a total of 170 subjects (85 in each group) included in the 3-month Primary Endpoint (Figure 2B).

The patient demographics, co-morbidities, and amputation characteristics are presented in Table 1. The subjects were primarily male, with an average age of 58 years at the time of consent, and were well matched between the groups. Of the 170 subjects included in the analysis, 73 (43%) had AKA compared to 97 (57%) BKA with the primary causes of amputation being trauma (42%) or vascular disease (42%). Consistent with the proportion of vascular amputees, approximately one-third of the subjects had a history of diabetes and peripheral vascular disease.

QUEST subjects suffered from substantial PAP, and their characteristics were similar between the groups (Table 1). The subjects rarely reported isolated PLP or RLP, and most subjects regularly reported experiencing both conditions. Pain was typically persistent, with an average duration of approximately 8 years prior to enrollment (93.2 ± 107.5 months). The average pain intensities (daily worst, average, and least ± SD) across all the subjects were 9.1 ± 1.0, 6.0 ± 1.5, and 3.1 ± 2.2, respectively. At baseline, most participants used non-opiates (N=52 Treatment, N=51 Control), opiates

Table 1 Subject Demographics, Comorbidities, Amputation Characteristics, and Post-Amputation Pain

	Treatment (N=85)	Control (N=85)	P-value*
Demographics and Co-morbidities			
Age (yr), mean (SD)	58.1 ± 12.2	57.9 ± 12.6	0.916
Sex Male (%)	60.0	60.0	>0.999
DM – Current or Previous (%)	41.2	29.8	0.237
PVD – Current or Previous (%)	30.6	33.4	0.915
Race (%)			0.899
American Indian or Alaska Native	2.4	1.2	
Asian	0.0	0.0	
Black or African American	14.1	11.8	
Native Hawaiian or Other Pacific Islander	1.2	0.0	
White	77.6	83.5	
Other	0.0	0.0	
Multiple	2.4	1.2	
Unknown	2.4	2.4	
Ethnicity (%)			>0.999
Hispanic or Latino	1.2	0.0	
Not Hispanic or Latino	97.6	98.8	
Not Reported	1.2	0.0	
Unknown	0.0	1.2	
Amputation Characteristics			
Location (N)			0.757
AKA	38	35	
BKA	47	50	
Cause (%)			0.839
Vascular	42.4	41.2	
Trauma	43.5	41.2	
Other	14.1	17.6	
Pain Characteristics			
Location of Pain (%)			0.833
Phantom Only	9.5	7.1	
Residual Limb Only	6.0	3.6	
Both Phantom and Residual	84.5	89.3	

(*Continued*)

Table 1 (Continued).

	Treatment (N=85)	Control (N=85)	P-value*
Duration of Pain (%)			0.873
Persistent	63.1	64.7	
Episodic	36.9	35.3	
Severity of Pain (mean ± SD)			
Daily Worst Pain	9.1 ± 1.0	9.1 ± 1.0	>0.999
Daily Average Pain	6.1 ± 1.5	5.9 ± 1.5	0.224
Daily Least Pain	3.2 ± 2.2	3.1 ± 2.2	0.945

Notes: *Statistical comparisons between treatment groups for categorical variables were performed using two-sided Fisher's exact test. Significance is evaluated at the 0.05 level. Statistical comparisons between treatment groups for continuous variables were performed using a two-sided two-sample *t*-test. Significance is evaluated at the 0.05 level. Daily limb pain scores were obtained using the PASS window during the eDiary eligibility assessment.
Abbreviations: DM, Diabetes mellitus; PVD, peripheral vascular disease; AKA, above-The-knee; BKA, below-The-knee.

(N=39 Treatment, N=25 Control) or both (N=29 Treatment, N=19 Control). 51 subjects reported no pain medication use (N=23 Treatment, N=28 Control).

Primary Effectiveness Endpoint and Responder Comparison

The primary effectiveness endpoint was the difference in responder rate between the Treatment and Control groups 30-minutes following initiation of therapy. The Responder rates are presented in Table 2. At 30-min post treatment, 24.7% of the Treatment subjects were classified as responders, compared with 7.1% of the control group, with a treatment effect size of 17.6% (p=0.002). Compared to 30-min post-treatment, responder rates increased in both groups at 120-minutes post-treatment, however a more robust and significant treatment effect was observed (25.8%; p=0.001). At 120-minutes post-treatment, the responder rate was 46.8% in the Treatment group and 22.2% in the control group.

QUEST uniquely assessed longitudinal pain relief by defining Responders on repeated treatment sessions. A post-hoc visual representation of a Responder's individual experience with HNFB is shown in Figure 3A. In 78 self-initiated treatment sessions, this subject achieved ≥50% pain reduction compared to the baseline pain score in 87% of the sessions. In the remaining 13% of the sessions, the subject achieved ≥30% pain reduction, which was considered a moderate clinical improvement per IMMPACT.[34] In contrast, Figure 3B shows the experience of a non-Responder over the 58 treatment sessions. The subject experienced ≥50% pain reduction in 47% of sessions but ≥30% pain reduction in 100% of

Table 2 Responder Rates for Primary and Secondary Effectiveness Endpoints

30-minutes post treatment **– Primary Endpoint**				
	Treatment (N=85)	**Control (N=85)**	**Treatment Effect**	**P-value***
Responders	24.7% (21/85)	7.1% (6/85)	17.6%	0.002
Unadjusted 95% CI	(15.5, 33.9)	(1.6, 12.5)	(7.0, 28.3)	
120-minutes post treatment **– Secondary Endpoint**				
	Treatment (N=77)	**Control (N=81)**	**Treatment Effect**	**P-value**
Responders	48.1% (37/77)	22.2% (18/81)	25.8%	<0.001
Unadjusted 95% CI	(36.9, 59.2)	(13.2, 31.3)	(11.5, 40.2)	

Notes: Responders: ≥50% pain reduction in ≥50% of sessions. Missing 30-min reports were treated as failures, and missing 120-min reports were treated as excluded. *P-value calculated using logistic regression analysis.

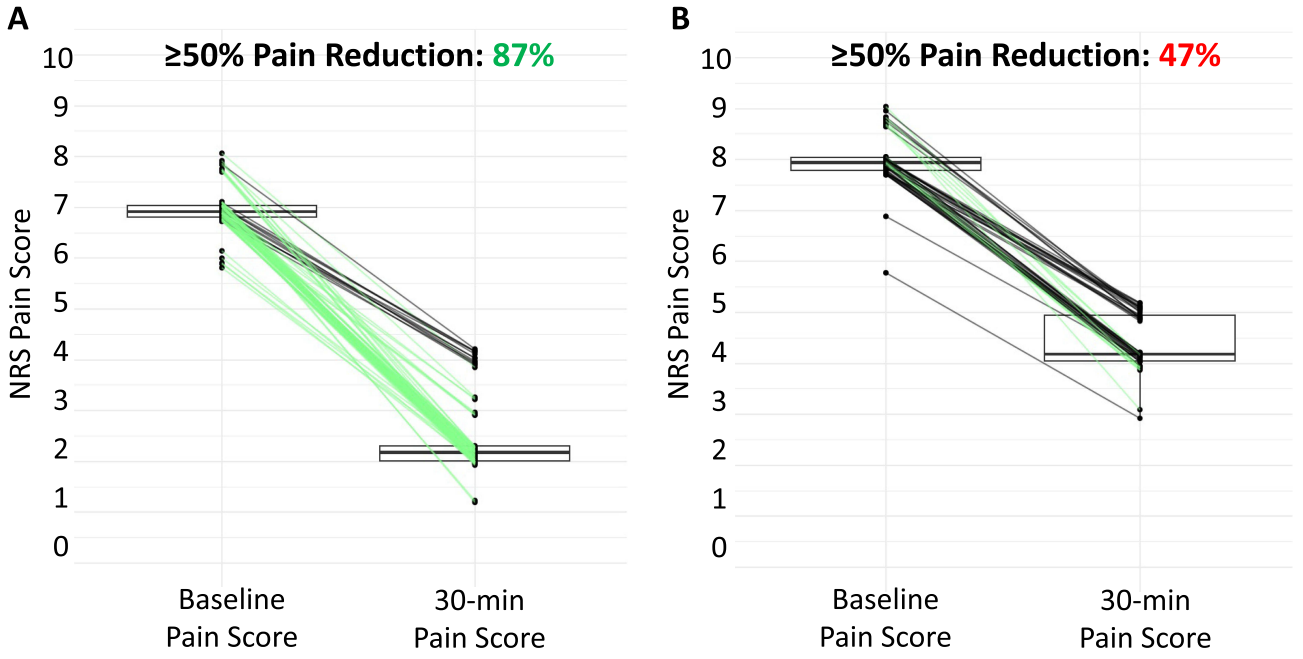

Figure 3 Examples of self-initiated treatment sessions demonstrate meaningful pain reduction in both Responders and Non-Responders. (**A**) Pain scores prior to device activation (baseline) and directly after treatment (30-min) throughout the randomized period for an example QUEST Responder. (**B**) Same as in A, only for an example QUEST Non-Responder. Green lines represent a single session with ≥50% pain reduction; black lines represent a single session with 30–50% pain reduction. The box-plot diagram represents the 75th percentile (top bar), 25th percentile (bottom bar), and median (middle dark bar).

sessions, demonstrating notable pain reduction despite not meeting the Responder criteria. This further highlights the arbitrary nature of responder categorizations, which may mask any treatment effect that does not fall into the predefined definition of a responder.[35] To "unmask" this treatment effect across all levels of pain reduction, we plotted the cumulative proportion of sessions against all possible levels of pain reduction (Figure 4A and B). Over half of all sessions by treatment subjects resulted in >30% pain reduction.

In addition to acute pain relief, subjects reported reduced end-of-day pain levels relative to the baseline window, indicating a lasting effect of Altius treatment on a subject's pain profile. The average worst end-of-day pain levels were significantly reduced by 22% in the treatment group (7.6 at baseline vs 6.0 at Month-3) versus 12% in the control group (7.7 vs 6.7) (p=0.049). The mean average end-of-day pain score decreased by 32% in the Treatment (6.1 at baseline vs 4.2 at Month-3) versus 17% (5.9 vs 4.9) in the control group, which was also significant (p=0.003).

Opioid Utilization and Quality of Life Improvement

In the Treatment group, the average MED decreased by 6.9 MED/day at 3-months compared to the baseline versus a 3.6 MED/day reduction in the control group (p=0.157). Tracking opioid utilization was not the primary objective of QUEST; thus, baseline MED was not equally distributed between groups. Only 35 treatment subjects and 24 control subjects reported taking opioids at baseline and had 3-month data for comparison and dosage was not consistent between groups. When analyzing only those subjects, opioid users in the treatment group experienced a 56.4% reduction in the average MED/day (−6.9 MED/day) compared with a 44.5% reduction in the control group (−3.6 MED/day; p = 0.160; Figure 5A). Individual subject-level MED changes are shown in Figure 5B and highlight the dramatic MED reduction in most treatment subjects. A post hoc review identified two significant outliers (one Treatment and one Control subject) with a change in MED/day of ≥8 SD from the mean due to the speed, magnitude, and timing of reduction. Removing these two outliers from analysis resulted in a statistically significant decrease in MED of 5.3 MED/day in the Treatment group compared to 1.3 MED/day in the Control group (p=0.012).

The functional impact of pain on a subject's life was assessed using the BPI and average pain interference scores (Figure 6A). Treatment subjects reported an average improvement in BPI interference score of 2.4 ± 0.29 which

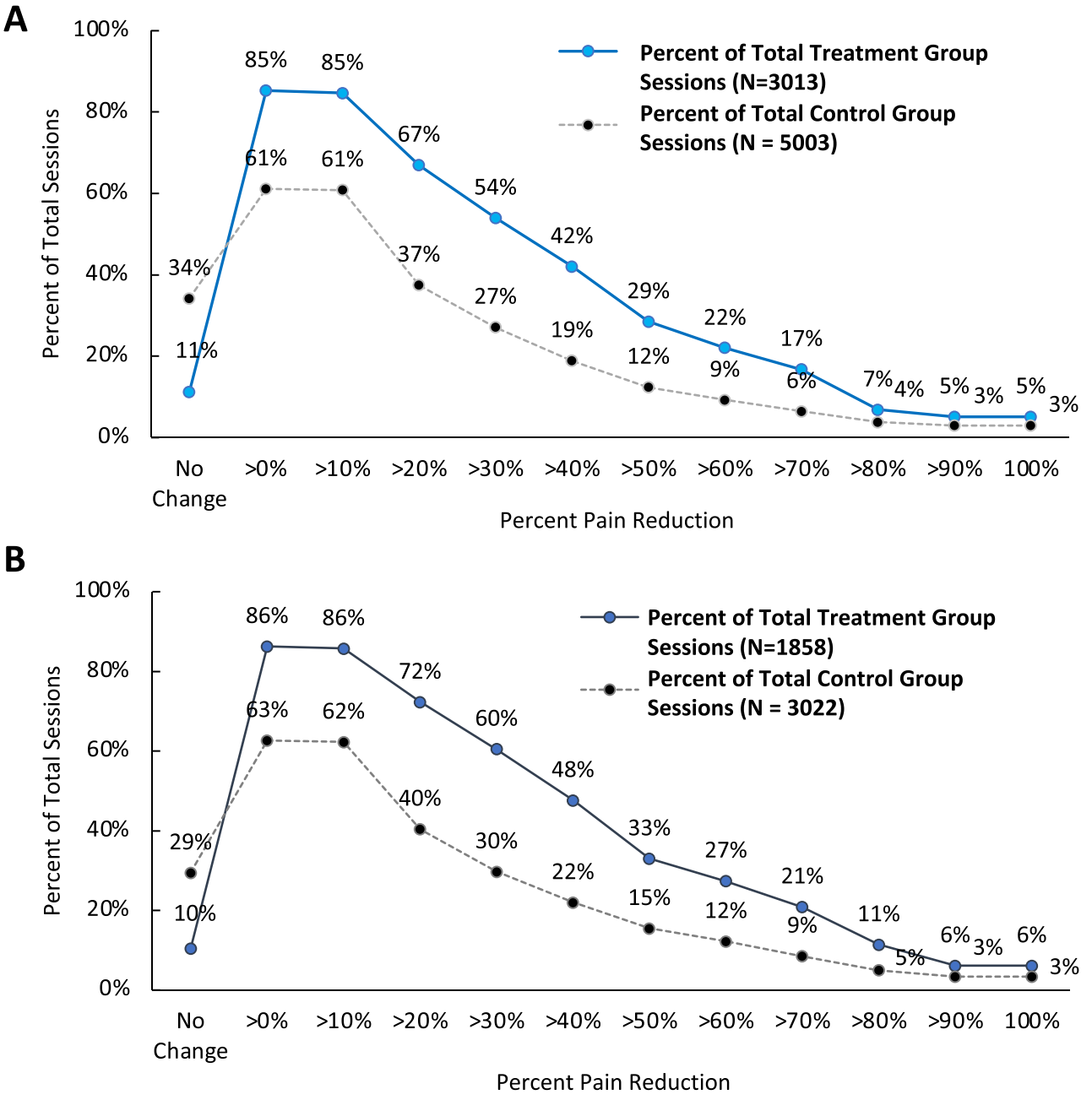

Figure 4 Cumulative percent pain reduction across all Altius treatment sessions. (**A**) Percent pain reduction as a function of total treatment sessions in the Treatment group (solid blue; N=3013 total sessions) and Control group (dashed; N=5003 total sessions) 30-min post-treatment demonstrating a robust treatment effect across all possible pain reduction thresholds. (**B**) Same as A, only at 120-min post-treatment. Treatment Group (solid blue; N=1858 total sessions) and Control Group (dashed; N=3022 total sessions).

was significantly greater than the 1.4 ± 0.26-point improvement reported in the Control group (p = 0.01; Figure 6B).

Primary Safety Endpoint and Study-Related AEs

The primary safety endpoint was the difference in SAEs including serious device- and procedure-related AEs. Protocol-defined SAEs were reported in 28.7% of treatment subjects and 24.2% of control subjects (p = 0.502). Most AEs were unrelated to the study device or index procedure (N=19/33 events in Treatment; N=17/31 in Control) and were not significantly different between the groups. Of the treatment subjects, 3.4% had serious device-related AEs compared with

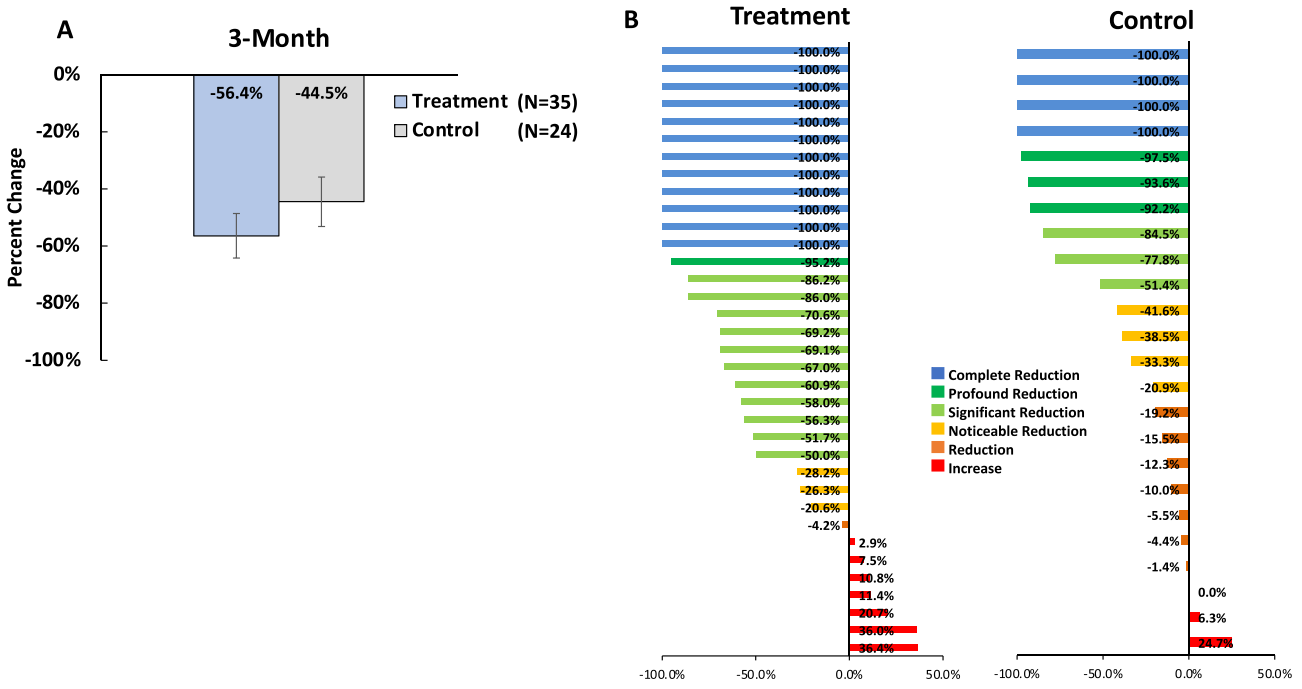

Figure 5 Group- and Subject-level Average Daily Morphine Equivalent Dose (MED) Percent Change at 3-Month relative to Baseline – (**A**) Mean Percent Change of Average Daily MED for Treatment (blue) and Control (gray) groups. Data is presented as Mean Percent Change of Average Daily MED ± SEM for subjects that reported using opioids for 2 Weeks at Baseline and 2 Weeks immediately before 3-Month visit. (**B**) Tornado Plots of the Mean Percent Change of Average Daily MED for each Treatment and Control subjects used to generate (**A**). Colors on each figure indicate degree of reduction or increase: *Complete Reduction* = 100% from baseline; *Profound Reduction* = ≥90% to <100% from baseline; *Significant Reduction* = ≥50% to <90% from baseline; *Noticeable Reduction* = ≥20% to <50% from baseline; Reduction = <20% from baseline. Reduction is indicated as negative (-) percent change, an increase as a positive percent change. N= 35 subjects in Treatment Group and N=24 subjects in Control Group.

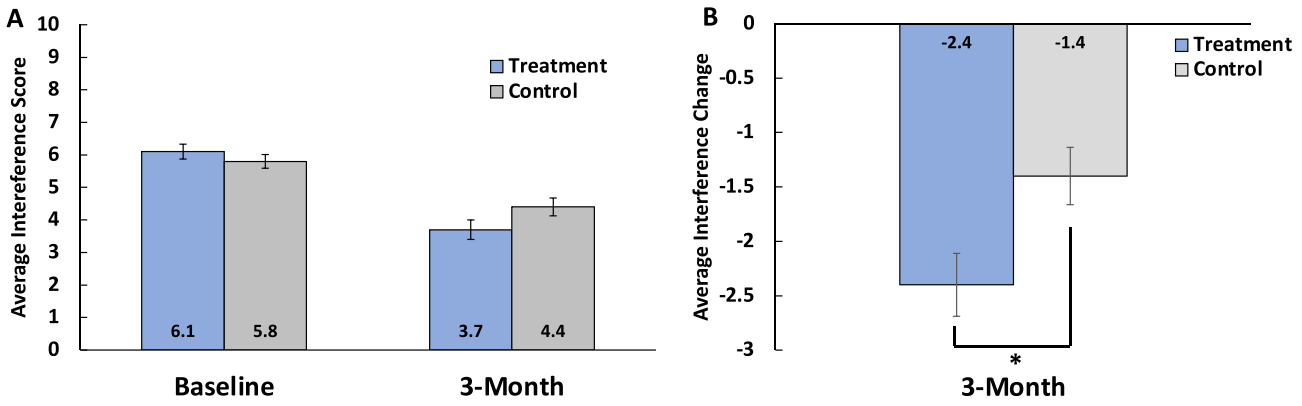

Figure 6 Change in Brief Pain Inventory (BPI) Pain Interference Score. (**A**). Average BPI Pain Interference scores at Baseline and 3-Month in Treatment (blue) and Control (gray) groups. Data is presented as Mean ± SEM. (**B**) Average BPI Interference *change* from Baseline to 3-Month in Treatment (blue) and Control (gray) groups. *Represents p=0.01.

5.5% of the control subjects (p = 0.721). The most common device-related AEs (N=8 total between groups) were device discomfort, site pain (N=3), and postoperative wound infections (N=2). Serious procedure-related AEs were reported in 9.2% of the treatment subjects compared with 7.7% of the control subjects (p = 0.791). The most common procedure-related AEs were infections (including implant site cellulitis/infection, postoperative wound infection, and pneumonia; N=8/15) and wound dehiscence (N=2/15).

Discussion

Here, we describe, for the first time, the initial 3-month outcomes of intermittent HFNB therapy for PAP treatment in the largest neuromodulation RCT to date for this indication. We demonstrated significant on-demand pain relief 30- and 120-

minutes after therapy initiation. More patients achieved relief at 120-min (secondary endpoint) than 30-min (primary endpoint), which could be explained by the complexity of the mechanism of action[29–31] and the time required for optimal pain relief. In both cases, device activation produced consistent and significant improvements in PAP in most patients who underwent HFNB.

The QUEST study had a unique double-blind, repeated-measures design which has not previously been employed to study PAP.[33] The introduction of a longitudinal approach using repeated measurements to investigate chronic PAP provides clearer details about daily changes in pain levels, and the consistency and durability of pain outcomes. On average, the subjects used Altius for 85 sessions during the randomized period. Most pain studies have employed periodic discrete assessments to determine effectiveness (eg, comparing baseline pain to the end of study pain), which fail to collect information on pain fluctuation between those timepoints. QUEST investigated pain as a continuous variable by repeatedly measuring outcomes over time in a population with difficult-to-treat PAP.[36] While pain cannot truly be tracked continuously, the repeated measurement approach performed in QUEST should be considered a new standard for pain-related study design.

Further rigor was introduced with a preprocedural assessment of pain relief using ultrasound-guided lidocaine injection.[33] In addition to controlling for potential placebo effects through differentiation of lidocaine from saline, lidocaine screening also assessed a subject's likelihood of responding to HFNB. Consistency of HFNB outcomes with pain relief after diagnostic lidocaine block was expected, considering similarities in the mechanisms of action, including inhibition of VGSC activity. Such diagnostic block assessment may be beneficial for selecting appropriate PAP subjects for therapy and future studies.

Maladaptive plasticity, resulting in central sensitization, is associated with persistent worsening of pain in PAP, eventually resulting in reorganization of the primary sensorimotor cortex.[37] The efferent central analgesic effects of peripheral nerve stimulation have been well described in the literature,[26,27,29–32] although the mechanisms are still being elucidated. PNS may modulate the prefrontal, somatosensory, anterior cingulate cortex, and parahippocampal pain pathways.[38–41] Here, the application of HFNB reduced acute pain levels almost immediately (30-minutes after treatment initiation), and the magnitude of relief increased over time, lasting hours after treatment initiation. Interestingly, acute pain exacerbations were reduced in time and intensity, resulting in an overall decrease in PAP, as evidenced by a significant reduction in end-of-day pain over the 3-month randomized period. Such effects from each self-administered therapy session of HFNB suggest reproducible pain relief not documented using any other noninvasive PNS, SCS, or DRG stimulation devices in patients with severe, long-standing, PAP.[42] QUEST subjects will continue to be closely followed for 1-year to see if the initial short-term findings are maintained in the long term.

We observed a significant difference in the QOL indices between the two groups, which was not surprising when considering the difference in pain levels. Opioid reduction was not significant between the groups over this short time interval; however, subjects receiving HFNB averaged more than a 50% reduction in opioid use despite no pre-specified weaning protocol. The lack of significance was likely due to the large between-group differences at baseline, where treatment subjects took nearly double the daily opioid dosage as control subjects, which makes comparison of percent reduction difficult to interpret. While these findings are promising in providing an alternative to long-term opioid use to treat PAP; a longer follow-up period and/or future studies are needed to properly assess the effects of HNFB on opioid reduction.

Conclusion

QUEST is a randomized, double-blind, active-sham-controlled pivotal study that demonstrated the efficacy and safety of high-frequency nerve block therapy with Altius for PAP. The statistically significant treatment effect indicates that the primary effectiveness endpoints of QUEST were met and that the bioelectric nerve block was superior to active-sham in the treatment of intractable PAP. Most treated patients experienced a substantial improvement in their PAP (regardless of meeting the study definition of a responder), which was accompanied by significant improvement in QOL metrics, and trend towards reduced opioid utilization compared to control patients. These data indicate that Altius treatment represents a significant therapeutic advancement for lower limb amputees suffering from chronic PAP where there are currently no viable, reliable, and effective treatment options.

Data Sharing Statement

The datasets for the current study are not publicly available due to the data being currently under FDA review for PMA approval.

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