STUDY TITLE

Clinical Study Of a Micro-Implantable Pulse Generator For The Treatment of Peripheral Neuropathic Pain (COMFORT)

CLINICAL TRIALS REGISTRATION NUMBER (NCT NUMBER)

NCT05287373

PROTOCOL VERSION

Version 3.0, 20 November 2023

SAP VERSION

Version 2.0, 20 November 2023

DocuSign Envelope ID: 953A31CA-8D30-4CD3-AE0C-1104F85BFAFF

Nalu Medical

Clinical Study Of A Micro-Implantable Pulse Generator For the Treatment of Peripheral Neuropathic Pain (COMFORT)

NAL-01-2021-US, Version 2.0

Statistical Analysis Plan

Version 2.0, 20 November 2023

DocuSign Envelope ID: 953A31CA-8D30-4CD3-AE0C-1104F85BFAFF

Sponsor	Study	Version
Nalu Medical	**Clinical Study Of A Micro-Implantable Pulse Generator For the Treatment of Peripheral Neuropathic Pain (COMFORT)**	**2.0**

Version History

Version	Version Date	Author/Title	Summary of Key Changes
1.0	15Februrary2022	Chris Mullin / Dir. Product Dev. Strategy	Initial Release
2.0	20 November 2023	Shilpa Kottalgi/Dir Clin Ops	Update for long term follow-up

DocuSign Envelope ID: 953A31CA-8D30-4CD3-AE0C-1104F85BFAFF

Sponsor	Study	Version
Nalu Medical	**Clinical Study Of A Micro-Implantable Pulse Generator For the Treatment of Peripheral Neuropathic Pain (COMFORT)**	**2.0**

Document Approval

Author	
Authored By	Shilpa Kottalgi
Signature	Shilpa Kottalgi 1030749392BA499...
Date	Nov 20, 2023
Role	Director, Clinical Ops

Approval	
Approved By	Patrick Martin
Signature	Patrick Martin 6DA282CA10844F3...
Date	Nov 20, 2023
Role	Vice President, Clinical Affairs

Approval	
Approved By	
Signature	
Date	
Role	

DocuSign Envelope ID: 953A31CA-8D30-4CD3-AE0C-1104F85BFAFF

Table of Contents

1 Introduction 5
2 Study Objectives 5
2.1 Study Endpoints 5
3 Study Design 6
3.1 Randomization 7
3.2 Blinding 7
3.3 Sample Size Determination 7
4 Statistical Analyses 7
4.1 General Considerations 7
4.1.1 Descriptive Statistics 7
4.1.2 Visit Windows 8
4.2 Analysis Populations 8
4.3 Handling of Missing Data 8
4.4 Subject Disposition 8
4.5 Demographics and Baseline Characteristics 8
4.6 Analysis of Study Endpoints 8
4.6.1 Primary Safety Endpoint Analysis 9
4.6.2 Primary Effectiveness Endpoint Analysis 9
4.6.3 Secondary Endpoint Analysis 9
4.7 Sensitivity Analysis 10
4.8 Poolability Analyses 10
4.9 Safety Analyses 10
4.10 Subgroup Analyses 11
4.11 Interim Analyses 11
4.12 Protocol Deviations 11
5 Changes from Planned Analyses 11

DocuSign Envelope ID: 953A31CA-8D30-4CD3-AE0C-1104F85BFAFF

1 Introduction

This statistical analysis plan (SAP) describes the planned statistical methods to be used during the reporting and analysis of data collected under the Clinical Study Of A Micro-Implantable Pulse Generator For the Treatment of Peripheral Neuropathic Pain (COMFORT).

The Nalu PNS system incorporates a battery-free, micro implantable pulse generator (mIPG), powered by an externally worn device (Therapy Disc). All PNS therapies, including the Nalu device, utilize mild electrical pulses to create an energy field that act to modulate the transmission of pain signals to the brain. The study sponsor manufacturers the Nalu PNS system, which has US market clearance (K191435, K183579) for the treatment of chronic pain originating from peripheral nerves. This study will be limited to patients who will receive the Nalu PNS system in order control for variables related to the specific product used for therapy, device programming, and training.

This SAP should be read in conjunction with the study clinical investigation plan (CIP) and case report forms (CRFs). This version of the SAP has been developed with respect to the Clinical Investigation Protocol NAL-01-2021-US Version 3.0 dated 20Nov2023. Any revisions to the protocol or CRFs that impact the planned analyses may require updates to the SAP.

2 Study Objectives

The primary objective of this post-market, open-label, minimal risk, randomized clinical study is to document the comparative effectiveness and safety of peripheral nerve stimulation (PNS) plus conventional medical management (CMM) versus CMM alone in the treatment of chronic, intractable peripheral neuralgia of post-traumatic or post-surgical origin.

Secondary objectives of the study are:

- To evaluate the comfort, compliance and usability of the wearable component of the system.
- Evaluate patient satisfaction and response to the system using patient reported outcomes

2.1 Study Endpoints

The primary effectiveness endpoint is the percentage of responders (Responder Rate) at 3-months post device activation. Comparisons will be made between randomized arms. Responders are defined as subjects with ≥ 50% reduction in average Numeric Rating Scale (NRS), for the area of pain from baseline,

DocuSign Envelope ID: 953A31CA-8D30-4CD3-AE0C-1104F85BFAFF

based on the Brief Pain Inventory-Q5 (BPI-SF-Q5) where, 0= no pain and 10= pain as bad as you can imagine.

The primary safety endpoint is the rate of serious and non-serious adverse device events, at 3-months.

The following secondary effectiveness endpoints are planned:

- Percent change in pain from baseline to 3, 6, 12, 18, 24, 30 and 36 months for both arms. Comparisons between arms will be made (NRS-BPI-SF-Q5)
- Percentage of responders at 6, 12, 18, 24, 30 and 36 months in both arms (NRS-BPI-SF-Q5)
- Percentage of responders and percent change from baseline, in the cross-over group, at 3, 6, 12, 18, 24, 30 and 36 months post-device activation (NRS-BPI-SF-Q5).
- Change in patient reported outcomes (PGIC, medication use, patient satisfaction, ODI, BDI, EQ-5D, PCS) at 3, 6, 12, 18, 24, 30 and 36 months, in both groups and cross over arms.
- Comfort, compliance and usability of the external wearable components at 3, 6, 12, 18, 24, 30 and 36 months, post-device activation, in both arms and cross-over arm (Stimulator Usability Questionnaire).
- Rate of serious and non-serious adverse device events at 6, 9, 12, 18, 24, 30 and 36 months.
- Rate of adverse procedure effects and unanticipated serious adverse device effects at 3, 6, 9, 12, 18, 24,30 and 36 months.

3 Study Design

The study is designed as a multi-center, prospective, open-label, randomized controlled trial (RCT) comparing PNS plus CMM with CMM alone. Subjects will be randomized to receive:

Arm 1: Nalu Neurostimulation System for PNS plus CMM

Arm 2: CMM alone

Consented subjects will receive a baseline evaluation and then be randomized 2:1 into one of two arms: 1) PNS+CMM arm or 2) CMM arm. Subjects assigned to Arm 1 will undergo a trial implant period using best clinical practices. Those subjects who pass the trial implant will receive the permanent implant. At the 3-month point, subjects in the Arm 2 will be given the option to crossover into the Arm 1. All patients will be followed for a total of 36 months after permanent implant. The study duration is expected to be 5.5 years from first enrollment to last follow up of last patient and subsequent study closure.

DocuSign Envelope ID: 953A31CA-8D30-4CD3-AE0C-1104F85BFAFF

3.1 Randomization

On confirmation of eligibility, subjects will be randomized into one of the two arms i.e. active arm or control arm. Randomization will be performed using a random permuted block design with a 2:1 allocation ratio (treatment versus control). Randomization will be stratified by investigational site. Randomized treatment will be assigned via a centralized electronic system.

3.2 Blinding

Owing to the nature of the treatments in the study, specifically an implanted device compared to CMM, blinding subjects, investigators or other study personnel, is not feasible.

3.3 Sample Size Determination

Sample size for the study is based on power requirements for the primary effectiveness endpoint.

A total sample size of 100 randomized subjects is planned, leading to 90 expected evaluable based on a 10% attrition rate. Based on a two-sample, one-sided 0.025 alpha level (equivalent to a two-sided 0.05 alpha level) exact binomial test, this sample size will provide 80% power for a difference in responder rate as small as approximately 25% (e.g. 75% vs. 50%, 35% vs. 10% etc.) for a wide range of possible treatment and control values. The sample size is considered conservative since a larger difference between groups in responder rates will provide additional power. Further, an interim analysis as described in Section 4.11 will allow for the potential for earlier conclusions in light of a large treatment effect.

4 Statistical Analyses

4.1 General Considerations

Except where otherwise specified, the following general principles apply to the planned statistical analyses. All statistical analysis will be conducted using SAS version 9.4 or later (SAS Institute Inc., Cary, NC) or other widely accepted statistical or graphical software as required.

4.1.1 Descriptive Statistics

Continuous data will be summarized with mean, standard deviation, median, minimum, maximum, and number of evaluable observations. Categorical variables will be summarized with frequency counts and percentages. Confidence intervals may be presented, where appropriate. Descriptive statistics for the endpoints will be summarized for subjects with evaluable data. Summary statistics will be presented by treatment group, as well as the difference between groups and its associated 95% confidence interval.

DocuSign Envelope ID: 953A31CA-8D30-4CD3-AE0C-1104F85BFAFF

4.1.2 Visit Windows

Unless otherwise specified, visit based assessments will be analyzed for each analysis time point according to the nominal visit entered in the Case Report Form (CRF) regardless of if it is out of window.

4.2 Analysis Populations

The following analysis populations are defined:

- **Modified Intent-to-treat (mITT):** All randomized subjects, receiving a permanent implant and having an implant at the time of analysis.
- **Completers Subset (CS):** All randomized subjects with evaluable 3-month data.
- **Per-Protocol Subset (PP):** All subjects without major protocol deviations.

The primary analysis cohort is the mITT cohort. Supportive analyses of primary and secondary endpoints will be performed for the remaining analysis populations.

4.3 Handling of Missing Data

Missing data will be minimized by rigorous follow-up and investigator and site training. Handling of missing data is described within study endpoint analysis sections.

4.4 Subject Disposition

The number of subjects in each analysis population will be presented along with reason for any exclusions. Subject accountability will be summarized by visit. The number of subjects who are enrolled, randomized, eligible for follow-up, and number completing clinical follow-up will be summarized for each protocol-required visit. In addition, the number of subjects who complete the study or exit early will be summarized by reason.

4.5 Demographics and Baseline Characteristics

Descriptive statistics will be presented for all clinically relevant baseline demographic, medical history, and clinical characteristic variables. Comparisons may be made between the test and control arm using either t-tests (continuous data) or Fisher's exact test (categorical data).

4.6 Analysis of Study Endpoints

DocuSign Envelope ID: 953A31CA-8D30-4CD3-AE0C-1104F85BFAFF

4.6.1 Primary Safety Endpoint Analysis

Analysis of the primary safety endpoint will be on based on descriptive statistics. The number and percentage of subjects with a primary safety event will be summarized for the randomized groups. Additionally, the total number of primary safety endpoints will be summarized. Kaplan-Meier analysis may be used to summarize the rate of events over time. Time for events will be based on days from randomization. Analysis will be focused on the MITT group. Subjects excluded from the MITT cohort (trial failures) will be reported separately.

4.6.2 Primary Effectiveness Endpoint Analysis

The hypothesis test for the primary effectiveness endpoint is as follows:

$$H_0: \pi_{PNS} \leq \pi_{CMM}$$

$$H_1: \pi_{PNS} > \pi_{CMM}$$

where π_{PNS} is the responder rate for subjects assigned to the NPS system and π_{CMMP} is the responder rate for subjects assigned to CMM. The test will be based on a two-sample exact binomial test of proportions, at the one-sided 0.025 alpha level. Analysis will be based on evaluable data without imputation for missing data.

Descriptive statistics for the endpoint will be summarized for subjects with evaluable data. Summary statistics will be presented by treatment group, as well as the difference between groups and its associated 95% confidence interval.

Study success is defined as successful rejection of the null hypothesis for the primary effectiveness endpoint.

4.6.3 Secondary Endpoint Analysis

The following secondary effectiveness endpoints will be analyzed:

- Percent change in pain from baseline to 3, 6, 12, 18, 24, 30 and 36 months, for both arms. Comparisons between arms will be made (NRS-BPI-SF-Q5)
- Percentage of responders at 6, 12, 18, 24, 30 and 36 months in both arms (NRS-BPI-SF-Q5)
- Percentage of responders and percent change from baseline, in the cross-over group, at 3, 6, 12, 18, 24, 30 and 36 months post-device activation (NRS-BPI-SF-Q5).

DocuSign Envelope ID: 953A31CA-8D30-4CD3-AE0C-1104F85BFAFF

- Change in patient reported outcomes (PGIC, medication use, patient satisfaction, ODI, BDI, EQ-5D, PCS) at 3, 6, 12, 18, 24, 30 and 36 months, in both arms and cross over groups.
- Comfort, compliance and usability of the external wearable components at 3, 6, 12, 18, 24, 30 and 36 months, post-device activation, in both arms and cross-over arm (Stimulator Usability Questionnaire).
- Rate of serious and non-serious adverse device events at 6, 9, 12, 18, 24,30 and 36 months.
- Rate of adverse procedure effects and unanticipated serious adverse device effects at 3, 6, 9, 12, 18, 24, 30 and 36 months.

Analyses will be based on exact binomial tests for responder rates, and t-tests for continuous outcomes. Descriptive statistics as well as nominal p-values and confidence intervals will be reported. Repeated measures models maybe used to characterize data over the course of follow-up, using a compound symmetric covariance structure to account for within-subject correlation.

4.7 Sensitivity Analysis

Sensitivity analysis for the primary safety and effectiveness endpoint will be performed, including multiple imputation to address missing data.

4.8 Poolability Analyses

All study sites will follow the requirements of a common protocol and standardized data collection procedures and forms. The primary safety and effectiveness endpoints will be presented separately for each site using descriptive statistics. Poolability of the primary endpoints across investigational sites will be evaluated using a logistic regression model with fixed effects for treatment, site, and treatment by site interaction. The model will be based on subjects in the mITT population. Firth's correction may be used if needed to facilitate modeling for sparse data. If the p-value for the interaction effect is <0.15, additional exploratory analyses will be performed to understand any variations in outcomes by site.

4.9 Safety Analyses

Adverse events (AE) will be reported for all enrolled subjects. AEs will be tabulated with the number of events and subjects with event for each event type and overall. Rates will be reported as the number of subjects who experience at least one event during the analysis interval out of the total number of subjects with follow-up to the beginning of the analysis interval. Rates will be compared between the two study arms. Serious adverse events will also be tabulated. All AEs and SAEs will also be summarized by relatedness.

DocuSign Envelope ID: 953A31CA-8D30-4CD3-AE0C-1104F85BFAFF

4.10 Subgroup Analyses

Subgroup analysis of the primary safety and effectiveness endpoints will be performed for the following subgroups: sex, target area, and stimulation type. These analyses are intended to demonstrate consistency of results across subgroups.

Subgroup analyses will be performed on the primary analysis cohort with complete data. For each subgroup, a logistic regression model will be fit that includes fixed effects for treatment arm, subgroup, and treatment by subgroup interaction. If the p-value for the interaction term is less than 0.15, additional exploratory analysis may be performed to understand any variations in outcomes by subgroup. Firth's correction may be used if needed to facilitate modeling for sparse data.

For each subgroup analysis, the p-value for the treatment by subgroup interaction will be presented. Additionally, at each level of the subgroup of interest, the within group estimates will be summarized with frequency counts and percentages and presented with the estimate for treatment vs. control with 95% confidence interval.

4.11 Interim Analyses

Interim analyses may be performed under a Lan-DeMets implementation of a group sequential design. Type I error for the primary effectiveness endpoint will be controlled via use of an O'Brien-Fleming type alpha-spending function.

4.12 Protocol Deviations

Deviations from the procedures outlined in the CIP will be reported by investigational sites on the CRF. Protocol deviations will be summarized for all deviations and by type with event counts and number of subjects with at least one deviation. Protocol deviations will be classified as major and minor deviations.

5 Changes from Planned Analyses

Any changes to planned statistical analyses determined necessary prior to performing the analyses will be documented in an amended Statistical Analysis Plan and approved prior to the analysis when possible. Any other deviations or changes from the planned analyses deemed necessary due to violation of critical underlying statistical assumptions, data characteristics, or missing data will be clearly described in the clinical study report with justification and rationale.