Statistical Analysis Plan

SJM-CIP-10113/ CRD_810
TARGET (DRG) Post-Approval Study

TARGET: A Post-Approval Study to Evaluate Targeted SCS (DRG) Stimulation for the Management of Moderate to Severe Chronic, Intractable, Pain of the Lower Limbs Due to CRPS Types I and II

Statistical Analysis Plan (SAP)

Version B

January 28, 2021

[redacted]

Statistical Analysis Plan

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1.0 SYNOPSIS OF STUDY DESIGN

1.1 Purpose of the Statistical Analysis Plan

This statistical analysis plan (SAP) is intended to provide a detailed and comprehensive description of the planned methodology and analysis to be used for the TARGET (DRG) post approval clinical investigation. [redacted]

1.2 Clinical Investigation Objectives

The primary objective of this study is to demonstrate that the proportion of serious adverse events at 12 months for subjects who receive the permanent DRG IPG is lower than a pre-specified performance goal. The secondary objectives of this study are to evaluate the change in overall pain intensity, change in physical function and change in quality of life at 12 months.

1.3 Clinical Investigation Design

This study is a prospective, multicenter, single arm, observational, post-approval study with follow-ups at 1, 3, 6 and 12 months post-permanent implant. [redacted]

After the subject signs the informed consent, s/he will be screened according to the inclusion/exclusion criteria and will undergo a baseline evaluation. Those subjects who meet the criteria for participation will undergo a trial of the DRG Neurostimulation System to assess response to DRG stimulation. For purposes of accounting, subjects are considered enrolled in the study only after they receive the trial system implant. Subjects who fail the trial procedure are considered as screen failures. Only subjects who report a 50% or greater reduction in overall pain intensity through direct patient-reported percentage of pain relief at the of trial evaluation period will receive the permanent implant. Device activation will occur according to the site's standard of care and may occur at the time of permanent system implant. Subjects will then return to the office for follow-up at 1, 3, 6 and 12 months post-permanent implant.

1.4 Endpoints

1.4.1 Primary Endpoint

The primary endpoint is the 12-month serious adverse event rate for subjects receiving the permanent DRG IPG.

1.4.2 Secondary Endpoints

Secondary endpoints include:

- Percent change from baseline to 12 months post-permanent implant for overall pain intensity measured using the Visual Analog Scale (VAS)

- Change from baseline to 12 months post-permanent implant for physical function measured using the PROMIS-29 Profile
- Change from baseline to 12 months post-permanent implant for quality of life measured using the PROMIS Global Health Scale

1.4.3 Descriptive Endpoints

Safety

- Proportion of subjects with device, procedure or stimulation-related serious adverse events and non-serious adverse events among subjects who receive the permanent implant
- Proportion of subjects who have adverse events related to the trial implant procedure among subjects who fail the trial neurostimulator phase
- Summary of procedure-related serious adverse events and non-serious adverse events by implanter experience

Effectiveness

- Percent change from baseline to 1, 3, and 6 months post-permanent implant for overall pain intensity measured using the Visual Analog Scale (VAS)
- Change from baseline to 1, 3, and 6 months post-permanent implant for physical function measured using the PROMIS-29 Profile
- Change from baseline to 1, 3, and 6 months post-permanent implant for quality of life measured using the PROMIS Global Health Scale
- Change from baseline to 1, 3, 6 and 12 months post-permanent implant for neuropathic pain measured using the Neuropathic Pain Scale (NPS)
- Change from baseline to 1, 3, 6 and 12 months post-permanent implant for sleep disturbance anxiety, depression, fatigue, ability to participate in social roles and activities, pain interference and pain intensity measured using the PROMIS-29 Profile Patient Global Impression of Change (PGIC) at 1, 3, 6 and 12 months post-permanent implant

1.5 Randomization

This is a single-arm study and no randomization is administrated.

1.6 Blinding

There is no blinding for the subjects or the Investigators.

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

2.1.1 Primary Endpoint Analysis Population `

[redacted]

2.2 Statistical Methods

2.2.1 Descriptive Statistics for Continuous Variables

For continuous variables, results will be summarized with the numbers of observations, means, and standard deviations, with quartiles, minimums, maximums. The normality test may be performed for selected variables as appropriate.

2.2.2 Descriptive Statistics for Categorical Variables

For categorical variables, results will be summarized with subject counts and percentages/rates, and where specified in the table mockups, with exact 95% Clopper-Pearson confidence intervals, or otherwise will be specified.

2.2.3 Survival Analyses

Survival analysis will be conducted to analyze the primary endpoint. Subjects without events will be censored at their last known event-free time point. Survival curves will be constructed using Kaplan-Meier estimates. The 95% confidence interval will be estimated using log-log transformation.

2.3 Endpoint Analysis

2.3.1 Primary Endpoint

The hypothesis is stated as follows:

[redacted]

where p is the 12-month serious adverse event rate for subjects who receive the permanent Axium or Proclaim DRG IPG. The hypothesis will be tested at the 5% significance level.

The primary endpoint analysis will be conducted using Kaplan-Meier method on subjects who received the permanent Axium or Proclaim DRG IPG (primary analysis population). The serious adverse events include adverse events which occur after permanent implant and CEC adjudicates as serious events.

The primary endpoint includes all serious adverse events, including ones related to the neurostimulation device or procedure as well as any unrelated serious adverse events. [redacted]

[redacted]

[redacted]

The 12-month (365 days) serious adverse event rate will be estimated using Kaplan-Meier method with a 95% upper confidence bound (UCB) estimated using log-log transformation. If the 95% UCB is less than the [redacted], the null hypothesis will be rejected.

[redacted]

[redacted]

2.3.2 Secondary Endpoints

2.3.3 Reduction in pain intensity (VAS)

The endpoint will test whether subjects achieve a clinically relevant change (mean percentage reduction of at least [redacted]) in VAS score at 12 months from baseline.

Percentage change in VAS score is calculated within each subject as:
% Change in VAS score = (VAS at baseline – VAS at 12-month)/VAS at baseline*100%

The following hypothesis will be tested:

[redacted]

The hypothesis will be tested at the 5% significance level. The analysis will be carried out by calculating the 95% lower confidence bound (LCB) on the mean % Change in VAS from baseline to 12-month visit based on a t-distribution. If the 95% LCB is greater than [redacted], the null hypothesis is rejected. The analysis population of this secondary endpoint will include primary analysis population subjects who complete both baseline and 12-month VAS scales.

2.3.4 Change in Physical Function (PROMIS Physical Function score)

The endpoint will test whether there is a change in mean PROMIS-29 Physical Function domain scores at 12 months from baseline. Change in PROMIS-29 Physical Function domain score is calculated as:

Change in PROMIS-29 Physical Function domain score = (PROMIS-29 Physical Function domain score at 12-Month – PROMIS-29 Physical Function domain score at Baseline)

The following hypothesis will be tested:

[redacted]

The hypothesis will be tested at the 5% significance level. The analysis will be carried out by calculating the 95% LCB on the mean change in PROMIS-29 Physical Function domain score from baseline to 12-month visit based on a t-distribution. If the 95% LCB is greater than [redacted], the null hypothesis is rejected. [redacted]

2.3.5 Change in Global Health (PROMIS Global Health score)

The endpoint will test whether there is a change in mean PROMIS Global Health Score from baseline to 12 months. Change in PROMIS Global Health Sore is calculated as:

Change in PROMIS Global Health Score = (PROMIS Global Health Score at 12-Month – PROMIS Global Health Score at Baseline)

The following hypothesis will be tested:

[redacted]

The hypothesis will be tested at the 5% significance level. The analysis will be carried out by calculating the 95% LCB on the mean change in PROMIS Global Health Score from baseline to 12-month visit based on a t-distribution. If the 95% LCB is greater than [redacted], the null hypothesis is rejected. The analysis population for this secondary endpoint will include subjects who complete both baseline and 12-month PROMIS Global Health questionnaire, irrespective of IPG types.

2.4 Sample Size Calculations

[redacted]

[redacted]

2.5 Interim Analysis

No formal interim analyses are planned for this study. As such, no formal statistical rule for early termination of the trial is defined. [redacted]

[redacted]

2.6 Timing of Analysis

After the last subject with a permanently implanted Axium or Proclaim IPG reaches the 12-month study visit or crosses the 12-month study visit window, the primary endpoint analysis will be conducted and reported to the FDA.

2.7 Study/Trial Success

[redacted]

2.8 Subgroups for Analysis

[redacted]

2.9 Handling of Missing Data

[redacted]

2.10 Poolability

[redacted]

2.11 Multiplicity

There is no multiplicity adjustment planned for this study.

2.12 Adjustments for Covariates

Unless otherwise specified, no adjustments for covariates will be made for any of the variables in the analyses.

2.13 Sensitivity Analysis

[redacted]

3.0 DESCRIPTIVE ENDPOINTS AND ADDITIONAL DATA

3.1 Baseline and Demographic Characteristics

The following baseline and demographic variables will be summarized for the subjects enrolled: gender, age, ethnicity, race, primary diagnosis, visual analog scale (VAS), etc.

3.2 Adverse Events

All the adverse device effects, serious adverse device effects, UADEs, USADEs will be summarized for all subjects who enrolled in this trial in terms the number of events, the percentage of subjects with events and event rate as # event/patient-month per CEC adjudication. [redacted]

3.3 Subject Early Termination

Subject early termination reasons will be summarized.

3.4 Protocol Deviation

Protocol deviations will be summarized for subjects in whom a protocol deviation was reported.

3.5 Descriptive Endpoints or Additional Data

3.5.1 Descriptive endpoints

The following descriptive endpoints will be reported:

Safety

- Proportion of subjects with device, procedure or stimulation-related serious adverse events and non-serious adverse events among subjects who receive the permanent implant
- Proportion of subjects who have adverse events related to the trial implant procedure among subjects who fail the trial neurostimulator phase
- Summary of procedure-related serious adverse events and non-serious adverse events by implanter experience

Effectiveness

- Percent change from baseline to 1, 3, and 6 months post-permanent implant for overall pain intensity measured using the Visual Analog Scale (VAS)
- Change from baseline to 1, 3, and 6 months post-permanent implant for physical function measured using the PROMIS-29 Profile
- Change from baseline to 1, 3, and 6 months post-permanent implant for quality of life measured using the PROMIS Global Health Scale
- Change from baseline to 1, 3, 6 and 12 months post-permanent implant for neuropathic pain measured using the Neuropathic Pain Scale (NPS)
- Change from baseline to 1, 3, 6 and 12 months post-permanent implant for sleep disturbance, anxiety, depression, fatigue, ability to participate in social roles and activities, pain interference and pain intensity measured using the PROMIS-29 Profile
- Patient Global Impression of Change (PGIC) at 1, 3, 6 and 12 months post-permanent implant

The analysis population for these descriptive endpoints will include primary analysis population subjects with available data and no imputation will be implemented.

3.5.2 Additional data

[redacted]

4.0 DOCUMENTATION AND OHER CONSIDERATIONS

4.1 Change in Analysis and Justification

4.1.1 Imputation

[redacted]

4.2 Analysis software

All analyses will be performed using SAS® for Windows, version 9.4 or higher.

5.0 ACRONYMS AND ABBREVIATIONS

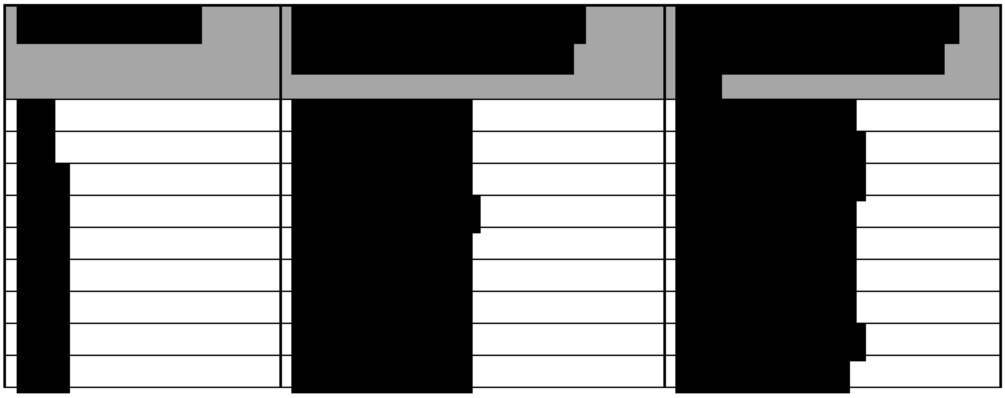
Acronym or Abbreviation	Complete Phrase or Definition
ADE	non-serious **A**dverse **D**evice **E**ffects, which include device, procedure or stimulation related non-serious adverse events
AE	Non-serious **A**dverse **E**vents not related to device, procedure or stimulation
CEC	**C**linical **E**vents **C**ommittee
CIP	**C**linical **I**nvestigation **P**lan
CRF	**C**ase **R**eport **F**orm
LCB	**L**ower **C**onfidence **B**ound
SADE	**S**erious **A**dverse **D**evice **E**ffects, which include device, procedure or stimulation related serious adverse events
SAE	**S**erious **A**dverse **E**vents not related to device, procedure or stimulation
SAP	**S**tatically **A**nalysis **P**lan
UCB	**U**pper **C**onfidence **B**ound
VAS	**V**isual **A**nalog **S**cale (mm)

6.0 REFERENCES

[redacted]

[redacted]

[redacted]



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