Abbott

Statistical Analysis Plan

ABT-CIP-10277/Ver. A

PROLONG (CRD_960)

Statistical Analysis Plan (SAP)

Version A

November 03, 2020

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Statistical Analysis Plan

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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 PROLONG (CRD_960) clinical investigation. This plan is based on the ABT-CIP-10277 Ver. A, January 23, 2019 Clinical Investigation Plan (CIP).

1.2 Clinical Investigation Objectives

The objectives of this study are to evaluate the effectiveness of Abbott neurostimulation devices in restoring pain relief, improving quality of life, and reducing related medication use for patients with failed SCS.

1.3 Clinical Investigation Design

This study is a prospective, multi-center, open-label, post-market study designed to evaluate the effectiveness of Abbott neurostimulation devices in restoring pain relief for patients who no longer receive adequate therapeutic benefit from SCS. The Investigator will select the most appropriate BurstDR or DRG implementation method according to their standard of care.

A trial of BurstDR or DRG may be performed as deemed appropriate by the Investigator. This includes the option for multiple trials to test both BurstDR and DRG therapy. Similarly, the permanent implementation method will be performed as deemed appropriate by the Investigator.

This clinical investigation will enroll up to 100 patients at up to 40 sites in the US. [redacted] subjects will be followed for 24 months after permanent implementation. [redacted]

1.4 Endpoints

The clinical investigation has the following end points which will be assessed and reported for all protocol defined visits:

- Numerical rating scale (NRS) for pain intensity
- Patient reported pain relief
- Patient satisfaction
- Physician satisfaction
- PROMIS-29
- Pain Catastrophizing Scale (PCS)
- Pain Vigilance and Awareness Questionnaire (PVAQ)
- Pain condition-related medication usage

1.5 Randomization

Not applicable.

1.6 Blinding

[redacted]

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

2.1.1 Full Analysis Set (FAS)

[redacted]

2.2 Statistical Methods

Descriptive analysis will be performed to summarize baseline, clinical, effectiveness and safety event data. Depending on the type of data (e.g., continuous or categorical), statistical methods described in the following sections will be used.

2.2.1 Descriptive Statistics for Continuous Variables

For continuous variables (e.g., age, etc.), results will be summarized with the numbers of observations, means, and standard deviations, with quartiles, minimums, maximums, and 95% confidence intervals for the means as per the table mockups.

2.2.2 Descriptive Statistics for Categorical Variables

For categorical variables (e.g. gender, etc.), results will be summarized with subject counts and percentages/rates, etc. Two-sided exact 95% Clopper-Pearson confidence intervals may be presented as appropriate.

2.3 Endpoint Analysis

2.3.1 Endpoints

The following endpoints will be successively evaluated in the order shown below at 0.05 significance level.

1. Change in NRS score for all subjects
2. Change in PCS Total score for all subjects
3. Change in NRS score for SCS therapy subjects
4. Change in NRS score for DRG therapy subjects
5. Change in Promis-29 Pain Interference T-score for all subjects
6. Change in Promis-29 Physical Function T-score for all subjects

Change is defined as change in score from baseline to 6 months and is calculated as:

Change in score = Score at Baseline – Score at 6-month

[redacted]

[redacted]

The analysis population will include all the subjects in the Full Analysis Set, who have both baseline and 6-month data available. [redacted]

2.3.2 Descriptive Endpoints

In addition to the above endpoints, data from additional descriptive endpoints or timepoints will be summarized. All analyses will be based on subjects in the Full Analysis Set.

- For NRS, descriptive statistics as defined in section 2.2.1 will be provided at baseline and all scheduled post-baseline visits. Absolute change from baseline summary will also be provided at each scheduled post-baseline visit.

- For Patient reported pain relief, percent change in NRS score from baseline to each scheduled post-baseline visit summary will be provided as defined in section 2.2.1.

- For PROMIS-29, PCS and PVAQ questionnaire data, descriptive statistics as defined in section 2.2.1 will be provided at baseline and all scheduled postbaseline visits. Change from baseline summary will also be provided for each scheduled post baseline visit. All the questionnaire data will be scored according to the scoring manuals prior to data analysis. The weblinks to the scoring manuals are provided in the reference section.

- For Patient and Physician Satisfaction, descriptive statistics as defined in section 2.2.2 will be provided for each satisfaction category.

- For all Pain condition related medications, descriptive statistics as defined in section 2.2.2 will be provided for in Full Analysis Set

    - Subjects who took pain medication at baseline and stopped post-baseline
    - Subjects who did not take pain medication at baseline but started post-baseline
    - Subjects who increased dose from baseline to each post-baseline visit
    - Subjects who decreased dose from baseline to each post-baseline visit

  For pain condition related medication usage, the total morphine milligram equivalent (MME) dosage will also be calculated for each patient. The weblink for MME calculation is provided in the reference section of this SAP. Descriptive statistics as described in section 2.2.1 will be provided for total MME.

2.4 Sample Size Calculations

[redacted]

2.5 Interim Analysis

[redacted]

2.6 Timing of Analysis

The final analysis will take place once all subjects have exited the study.

2.7 Study/Trial Success

[redacted]

2.8 Subgroups for Analysis

Subgroup analysis using variables such as therapy (DRG vs SCS), salvage method and manufacturer type may be performed as needed for exploratory purposes.

2.9 Poolability Issue

No poolability analysis is planned for the study.

2.10 Multiplicity Issues

[redacted]

2.11 Adjustments for Covariates

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

2.12 Exploratory Analysis

Exploratory Analysis may be performed as appropriate per study teams' decision.

3.0 DESCRIPTIVE ENDPOINTS AND ADDITIONAL DATA

The following data will be summarized descriptively as outlined in Section 2.2 Statistical Methods in the SAP.

3.1 Baseline and Demographic Characteristics

The following baseline and demographic variables will be summarized for all subjects in the Full Analysis Set: age, gender, ethnicity, race, BMI, impact of pain, activity level, work status, etc. De-registered subjects will not be included in this summary.

[redacted]

3.2 Adverse Events

All adverse events related or unrelated to the device, serious and non-serious will be summarized for all subjects in the Full Analysis Set using the number of events, the number of subjects with event(s), and the percentage of subjects with event(s). All CEC adjudicated adverse events will also be summarized for all subjects in the Full Analysis Set with the number of events, the number of subjects with event(s), and the percentage of subjects with events.

3.3 Subject Early Termination

Subject early termination reasons including deaths, withdrawals, lost-to-follow-up, etc. will be summarized for subjects in the Full Analysis Set. A listing will also be provided for subjects who de-registered from the study with reasons for de-registration.

3.4 Protocol Deviation

Protocol deviations will be summarized descriptively by category for subjects in the Full Analysis Set in whom a protocol deviation was reported.

3.5 Additional Data

For PCS Total score, change from baseline to 6 months will be reported for subjects in Full Analysis Set, who are catastrophizing at baseline (PCS Total score at baseline >=30).

4.0 DOCUMENTATION AND OHER CONSIDERATIONS

4.1 Changes from Protocol Specified Analysis

Additional hypothesis testing is added in section 2.3.1 per study team's decision.

4.2 Analysis Software

All analyses will be performed using SAS® for Windows, version 9.2 or higher.

5.0 ACRONYMS AND ABBREVIATIONS

Acronym or Abbreviation	Complete Phrase or Definition
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
CRF	case report form
NRS	Numerical Rating Scale
PCS	Pain Catastrophizing Scale
PVAQ	Pain Vigilance and Awareness Questionnaire
PROMIS	Patient-Reported Outcome Measure Information System
SCS	Spinal Cord Stimulation
DRG	Dorsal Root Ganglion

[redacted]

Acronym or Abbreviation	Complete Phrase or Definition
AE	Adverse Event
SAP	Statistical Analysis Plan

6.0 REFERENCES

1. CRD_960 CIP ABT-CIP-10277 Ver. A, 23JAN2019
2. CRD_960 Prolong Case Report Form
3. Scoring Manual for PCS:

   https://sullivan-painresearch.mcgill.ca/pdf/pcs/PCSManual_English.pdf
4. Scoring Manual for PROMIS-29:
   http://www.healthmeasures.net/images/PROMIS/manuals/PROMIS_Adult_Profile_Scoring_Manual.pdf
5. PVAQ Reference:
   https://www.sciencedirect.com/science/article/abs/pii/S0005789497800470#:~:text=The%20results%20of%20this%20study,pain%2Drelated%20health%20care%20utilization.
6. MME Conversion Calculation:
   https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf

7.0 APPENDICES

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