Statistical Analysis Plan

CIP 10407
GEMINI

Study of Gemini Rechargeable Spinal Cord Stimulation (SCS) System

Statistical Analysis Plan (SAP)

Version A

July 14, 2021

[redacted]

Statistical Analysis Plan

Contents

Statistical Analysis Plan

1.0 SYNOPSIS OF STUDY DESIGN

1.1 Purpose of the Statistical Analysis Plan

This statistical analysis plan (SAP) is to provide a detailed and comprehensive description of the planned methodology and analysis to be used for Clinical Investigation Plan (CIP) 10407, the GEMINI study (CRD_1030). This plan is based on CIP Version A, April 2021.

1.2 Clinical Investigation Objectives

The objective of this study is to collect confirmatory data to show that the Gemini SCS neuromodulation system functions as intended in a clinical setting.

1.3 Clinical Investigation Design

This is a pre-market, prospective, single-arm, non-randomized, open-label multi-center clinical study designed to show that the Gemini SCS neurostimulation system functions as intended in a clinical setting.

The study is designed to report on 20 subjects who receive a Gemini SCS implant and complete follow-up. [redacted]

1.4 Endpoints

1.4.1 Confirmatory Safety Endpoint

The confirmatory safety endpoint is the rate of serious adverse events adjudicated as related to the investigational IPG and/or charging system. No formal hypothesis test will be evaluated, but data for the endpoint will be used to confirm whether Gemini SCS system functions as intended.

1.4.2 Additional Endpoints

Additional endpoints are reported using descriptive statistics, without hypothesis testing:

- Serious adverse events other than confirmatory endpoint with their relatedness (such as device, procedure, stimulation, charging, COVID, or MRI)
- Non-serious adverse events related to device, procedure, stimulation, charging, COVID, or MRI (investigational device and on-market devices)

Additional data collected:

- Patient satisfaction
- Patient experience with charging
- NRS for pain intensity
- PROMIS-29
- Charging history
- Stimulation programs used
- Stimulation programs available

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

A subject is considered enrolled in the study when the following conditions are met:

1. Subject has provided written informed consent, and
2. Subject has been determined to meet all inclusion and do not meet any exclusion criteria.

The following populations will be used in the analysis for this study.

[redacted]

2.2 Statistical Methods

2.2.1 Descriptive Statistics for Continuous Variables

For continuous variables (e.g., age), results will be summarized as number of observations, means, and standard deviations, and where applicable, with quartiles, minimums, maximums, and 95% confidence intervals for the means. Difference between baseline and 6-week follow-up, when specified, will be summarized with the means of the difference, and the 95% confidence interval of the differences.

2.2.2 Descriptive Statistics for Categorical Variables

For categorial variables (e.g. gender), results will be summarized with subject counts and percentages/rates, and where applicable, with exact 95% Clopper-Pearson[1] confidence intervals.

2.3 Endpoint Analysis

2.3.1 Confirmatory Safety Endpoints

The confirmatory safety endpoint for this study is the rate of Serious Adverse Events (SAEs) related to the IPG and/or charging system.

No formal hypothesis is formulated for this study. The confirmatory endpoint will be summarized as the number and percentage of subjects with IPG and/or charging system related SAEs, along with exact 95% Clopper-Pearson confidence intervals.

The confirmatory endpoint will be analyzed using safety population defined in 2.1. The evaluable subjects will include those who complete their 6-week visit or had IPG and/or charging related SAE at/prior to their termination before 6 weeks visit.

Charging system related SAE(s) will also be analyzed separately using safety population defined in 2.1. The evaluable subjects will include those who complete their 6-week visit or had charging system related SAE at/prior to their termination before 6 weeks visit.

2.4 Sample size Calculation

[redacted]

2.5 Interim Analysis

[redacted]

2.6 Timing of Analysis

The analysis will be performed after all enrolled subjects have completed their 6-week visits or withdrawn from study.

2.7 Handling of Missing Data

Confirmatory endpoint analysis will be based on available data. No imputation for missing data will be performed.

3.0 DESCRIPTIVE ENDPOINTS AND ADDITIONAL DATA

3.1 Baseline and Demographic Characteristics.

Baseline and demographic variables will be summarized using the methods defined in 2.2 based on the safety population defined in 2.1. Adverse Events (AE)

3.2 Safety population defined in 2.1 will be included in this analysis. Serious adverse events (SAEs) and AEs, will be summarized using number of events, the percentage of subjects with events and by the relatedness (such as related to device, procedure, stimulation, charging, COVID, or MRI) of events. Subject Early Termination

Subject early termination reasons including deaths, withdrawals, lost-to-follow-up, etc. will be summarized for all enrolled subjects.

3.3 Protocol Deviation

Protocol deviations will be summarized by category for subjects in whom a protocol deviation was reported. Number of protocol deviations and number of subjects with deviation will be summarized by deviation category.

3.4 Descriptive Performance Endpoints or Additional Data

Descriptive Endpoints

The descriptive endpoints will be analyzed using the methods defined in 2.2 based on implanted population defined in 2.1. The descriptive endpoints will be analyzed at baseline and at 6 weeks if applicable.

Descriptive endpoints include:

- Patient satisfaction
- Patient experience with charging
- NRS score change
- PROMIS-29 change
- Charging history

  The following charging history will be summarized using the methods defined in 2.2
  - Time between implant and first charging session in days
  - Number of charging sessions
  - The rate of charging sessions per follow-up week
    The numerator will be the total number of charging sessions. The denominator will be the total follow-up duration (in weeks) from the date of first charging started to the last follow-up date
  - Average duration of charging (in hours) per charging session
  - Average charging interruptions per charging session
  - Rate of charging sessions with Overheat protection events, which is defined as total number of sessions with overheating protection flag/total number of charging sessions
  - The average percent of battery at end of the charging sessions per charging session

- Stimulation programs used
- Stimulation programs available

3.4.1 Additional Analyses

Battery consumption per day will be summarized using the method defined in 2.2.1.

The battery consumption per day is calculated as

$$\frac{\sum(Battery\ (\%)\ usage\ between\ two\ consecutive\ charging\ sessions)}{\sum(days\ between\ the\ two\ consecutive\ charging\ sessions)}$$

For example, the first charging is on Mar 27th, 2021, the battery (%) is 85% at the end of the charging session. The next charging is April 10 h, 2021 and the battery is 29% at beginning of charging. The battery usage is calculated as 85%-29%=56%. There are 14 days between the two charging sessions.

Other additional analysis may be needed for exploratory purposes.

4.0 DOCUMENTATION AND OHER CONSIDERATIONS

[redacted]

5.0 ACRONYMS AND ABBREVIATIONS

AE	Adverse Event
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
CLBP	Chronic Low Back Pain
CMM	Comprehensive Medical Management
CRF	Case Report Form
CT	Computed Tomography
DMP	Data Management Plan
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
FAS	Full Analysis Set
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
HIPPA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IFU	Instructions for Use
IRB	Institutional Review Board
MHRA	Medicines and Healthcare Products Regulatory Agency
MRI	Magnetic Resonance Imaging
NRS	Numerical Rating Scale
ODI	Oswestry Disability index
PCS	Pain Catastrophizing Scale
PGIC	Patient Global Impression of Change
PRO	Patient Reported Outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
SAE	Serious Adverse Event
SCS	Spinal Cord Stimulation
UADE	Unanticipated Adverse Device Effect
US	United States

6.0 REFERENCES

1. Clopper C. J., Pearson E. S., The Use of the Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Biometrika, 1934, 26, 404-413.

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