Statistical Analysis Plan

[redacted]

Infinity MRI PMCF

A Post-Market Study Evaluating the Safety of Infinity DBS System with MR Conditional Labeling

Statistical Analysis Plan (SAP)

Version [redacted]

December 18, 2020

[redacted]

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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 [redacted], the Infinity MRI PMCF clinical investigation. This plan is based on the Version [redacted], Jan 16, 2019 Clinical Investigation Plan.

1.2 Clinical Investigation Objectives

The primary objective of the Infinity MRI PMCF is to support the safety of the Infinity™ deep brain stimulation (DBS) systems with MR Conditional labeling.

1.3 Clinical Investigation Design

This study will be conducted as an international, multicenter, observational, prospective, single-arm, post-market clinical follow-up (PMCF). The study will evaluate the safety of the Infinity DBS system with MR Conditional labeling when an MRI procedure is performed according to the approved guidance. The results of this study will be submitted to the notified body.

The study will be conducted at centers that are qualified to participate and will enroll up to [redacted] subjects at up to [redacted] centers in geographies where Infinity DBS systems with MR Conditional labeling are approved including the European Union and the United States. A minimum of [redacted] centers will be included to ensure a range of MRI equipment brands, including a minimum of 6 in the European Union. Each site will have a maximum enrollment capped at 20% of total enrollment. Subjects who have a leads-only configuration or a full system configuration will participate in the study. Subjects may be enrolled when an MRI procedure is prescribed per standard of care.

Each subject will be limited to one MRI procedure during the course of the study. Selected sites will have this protocol approved to allow for data collection of the MRI parameters and any adverse events (AEs) that occur during the procedure and through 1-month following the procedure. An office visit will be added for all subjects for a [redacted] ([redacted]) post-MRI follow-up visit after the initial MRI procedure is performed.

The clinical investigation has been designed to involve as little pain, discomfort, fear, and any other foreseeable risk as possible for subjects. Refer to the Risks Analysis section of this clinical investigation plan for details.

1.4 Endpoints

1.4.1 Primary Endpoint

The primary endpoint is the rate of MRI-related adverse events. This endpoint was selected as the primary goal of the study is to support safety of Infinity DBS systems with MR Conditional labeling when undergoing an MRI procedure according to the approved guidelines defined in the MRI Procedure Information Clinician's Manual.

1.4.2 Secondary Endpoints

The following secondary endpoints are for subjects undergoing an MRI procedure with the full system configuration.

- Rate of successful MRI mode 'turn on/off' functionality of the MRI mode
- Rate of successful 'turn on/off' functionality for the stimulation
- Rate of successful adjustments to the stimulation amplitude
- Rate of successful interrogation and download of the IPG parameters
- Rate of successful ability to obtain lead impedance measurements

1.4.3 Additional Safety Endpoint

- Characterization of all MRI-related adverse events.

1.5 Randomization

This is an open label observational study, so no randomization is needed.

1.6 Blinding

This is an open label observational study, so no blinding is needed.

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

2.1.1 Primary Analysis Population

The primary analysis population will include the subjects who are [redacted] and who meet all of the following criteria:

- [redacted]
- [redacted]
- [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, and where specified in the table mockups, with median, quartiles, minimums, maximums, and 95% confidence intervals for the means.

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.

[redacted]

2.3 Endpoint Analysis

2.3.1 Primary Endpoint

The primary endpoint is the event rate of MRI-related adverse events through [redacted] post-MRI procedure.

Any adverse event will be included in the primary endpoint analysis if it:

- Is classified as being MRI-related (as determined by the CEC), occurs during or after the MRI procedure, and cannot be attributed to any other cause; **and**
- Is classified as being related to the device (implanted or external component) (as determined by the Investigator); **and**
- Meets the criteria for serious adverse event **or** is a non-serious adverse event that is the result of irrecoverable failure of therapy delivery or device communication.

The clinical acceptance criterion for the rate of MRI-related adverse events is 7%, [redacted]
The primary analysis will be performed on Primary Analysis Population. The primary endpoint will be summarized as number of events, number of subjects who experienced these events and percentage. The clinical acceptance criterion is satisfied if the event rate is less than 7% in both groups (leads-only and full system).

2.3.2 Secondary Endpoints

The following secondary endpoints will be analyzed for subjects who undergo an MRI procedure with a full system configuration. The endpoint “Rate of successful ability to obtain lead impedance measurements” will include only those subjects who had their IPG interrogated using the Clinician Programmer. Data (success or failure) for these endpoints will be collected immediately after the MRI procedure.

- Rate of successful MRI mode ‘turn on/off’ functionality of the MRI mode
- Rate of successful ‘turn on/off’ functionality for the stimulation
- Rate of successful adjustments to the stimulation amplitude
- Rate of successful interrogation and download of the IPG parameters
- Rate of successful ability to obtain lead impedance measurements

Rates will be reported as the percentage of subjects in which the device functionality could be successfully completed.

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. Interim study reports with descriptive analysis may be produced for regulatory or reimbursement purposes.

2.6 Timing of Analysis

Analysis of the primary endpoint and other endpoints will occur once all subjects have either completed the 1-month follow-up or withdrawn from the study.

2.7 Study/Trial Success

The clinical investigation is successful if the primary endpoint is met for both the lead-only configuration group and the full DBS system group.

2.8 Subgroups for Analysis

No subgroup analyses are planned for this clinical investigation.

2.9 Handling of Missing Data

No imputation techniques will be implemented in the analysis. The secondary endpoints will be evaluated in subjects who undergo an MRI procedure with a full system configuration. Subjects who don't have the IPG testing complete immediately after MRI procedure will be excluded from the related endpoint analysis.

2.10 Poolability Issue

No poolability analysis is planned for this clinical investigation.

[redacted]

2.11 Multiplicity Issues

Since there is no hypothesis testing in this study, no multiplicity adjustment will be considered.

2.12 Adjustments for Covariates

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

2.13 Sensitivity Analysis

No sensitivity analysis is planned for this clinical investigation.

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, medical condition indicated for MRI procedure and primary indication, etc.

3.2 Adverse Events

All the adverse events will be summarized descriptively for all subjects who are enrolled in this clinical investigation in terms the number of events and the percentage of subjects with events. The relationship with device (as determined by the Investigator), MRI procedure (as determined by the CEC) or COVID-19 (if applicable, as determined by the CEC) will be included.

3.3 Subject Early Termination

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

3.4 Protocol Deviation

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

3.5 Descriptive Endpoints or Additional Data

- Additional safety endpoint: The frequency of all MRI-related adverse events will be reported as the number of occurrences of each event and the percentage of subjects experiencing each event in table format.
- Data (success or failure) for these outcomes will be summarized at [redacted] post MRI Procedure visit
    - Rate of successful MRI mode ‘turn on/off’ functionality of the MRI mode
    - Rate of successful ‘turn on/off’ functionality for the stimulation
    - Rate of successful adjustments to the stimulation amplitude
    - Rate of successful interrogation and download of the IPG parameters
    - Rate of successful ability to obtain lead impedance measurements

Rates will be reported as the percentage of subjects in which the device functionality could be successfully completed.

4.0 DOCUMENTATION AND OHER CONSIDERATIONS

All analyses will be performed using SAS® for Windows, version 9.3 or higher.

5.0 ACRONYMS AND ABBREVIATIONS

Acronym or Abbreviation	Complete Phrase or Definition
CIP	Clinical Investigation Plan
SAP	Statistically Analysis Plan

6.0 DEVIATION FROM CIP

The following additional analyses are added to the SAP and not included in the CIP Rev B.

- Data (success or failure) for these outcomes will be summarized at [redacted] post MRI Procedure visit
    - Rate of successful MRI mode 'turn on/off' functionality of the MRI mode
    - Rate of successful 'turn on/off' functionality for the stimulation
    - Rate of successful adjustments to the stimulation amplitude
    - Rate of successful interrogation and download of the IPG parameters
    - Rate of successful ability to obtain lead impedance measurements

      Rates will be reported as the percentage of subjects in which the device functionality could be successfully completed.

7.0 REFERENCES

Infinity MRI PMCF clinical investigation CIP [redacted]