Statistical Analysis Plan

[redacted]

ROSTRA
Real-World Outcomes Study on Subjects Treated with Radiofrequency Ablation

Statistical Analysis Plan (SAP)

[redacted]

30 November 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 [redacted], the ROSTRA clinical investigation. This plan is based on the Version [redacted] Clinical Investigation Plan.

1.2 Clinical Investigation Objectives

The objective of this study is to collect real-world safety and effectiveness data on Abbott's IonicRF™ Generator and compatible accessories.

1.3 Clinical Investigation Design

This is an international, prospective, non-randomized, single-arm, multi-center, and post-market study. Subjects will be assessed at baseline and post implant using questionnaires. Specifically, assessments will include pain intensity as assessed by the Numeric Rating Scale (NRS), quality of life as assessed by EuroQol-5 Dimensions (EQ-5D) and PROMIS-29, and procedure satisfaction as assessed by the Patient Global Impression of Change (PGIC) and patient satisfaction level. The Oswestry Disability Index (ODI), Neck Disability index (NDI), and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) index score will be completed for specific indications only.

Subjects will be followed via clinic visit or remote follow-up at [redacted]. The study will enroll up to [redacted] subjects at up to [redacted] sites in Europe and the United States. No site may enroll more than [redacted] of the total subjects. This study uses a sample size that allows inclusion of multiple indications. Additional centers may be approached for participation in the study as needed.

It is recommended that subjects should limit increases in their prescribed chronic pain medications from Baseline to the assessment of the primary endpoint at [redacted]. Both the types of medication and the prescribed maximum daily dosage of pain medication for their chronic pain condition should not increase significantly (at the discretion of the investigator). If a rescue medication is required, subjects will be allowed additional aspirin or Tylenol (Acetaminophen) at a maximal dose of 2 g within a 24-hour period. (NOTE: Post-operative pain medications prescribed only for acute management of post-procedural pain are allowed.)

Subject enrollment is expected to be completed within [redacted]; subjects will be followed for [redacted]. The total duration of the study is expected to be [redacted], including enrollment, data collection from all subjects, and study close out.

1.4 Endpoints

1.4.1 Primary Safety Endpoint

The primary safety endpoint is the incidence of device- and procedure-related serious adverse events by [redacted]

1.4.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint is the relative change in Numeric Rating Scale (NRS) [redacted] follow-up visit. NRS is the patient's self-rating of average pain intensity for the area being treated over [redacted] from 0 "no pain" to 10 "worst pain imaginable". This will be calculated for each represented indication.

1.4.3 Secondary Endpoint

There are no specific secondary endpoints of this clinical investigation.

1.4.4 Descriptive Endpoints

Refer to Section 3.5 in this SAP.

1.5 Randomization

This is a non-randomized clinical investigation.

1.6 Blinding

This is a unblinded clinical investigation.

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

1. Full Analysis Set (FAS): [redacted]
2. As-treated Population (AT): [redacted]

The safety endpoints will be performed on the FAS. The effectiveness endpoints will be performed on the AT.

2.2 Statistical Methods

2.2.1 Descriptive Statistics for Continuous Variables

For continuous variables (e.g., age, change in NRS, improvement in patient outcome measures, etc.), results will be summarized with the numbers of observations, means, standard deviations, medians, 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, race, etc.), results will be summarized with subject counts and percentages/rates, and where specified in the table mockups, with exact 95% Clopper-Pearson confidence intervals.

2.2.3 Survival Analyses

Survival analysis will be conducted to analyze time-to-event variables, if applicable. Subjects without

events will be censored at their last known event-free time point. Survival curves will be constructed using Kaplan-Meier estimates.

2.3 Endpoint Analysis

2.3.1 Primary Endpoint(s)

The primary effectiveness endpoint is [redacted].

The null and alternative hypotheses are as follows:

$$H_0: \mu = 0$$

$$H_1: \mu \neq 0$$

[redacted]

This endpoint will be evaluated [redacted]t at the 5% significance level. The endpoint will be analyzed based on AT population described in Section 2.1.

The primary safety endpoint is the incidence of device- and procedure-related serious adverse events [redacted]

The device- and procedure-related serious adverse events will be summarized as frequency, proportion, and number of events per patient years of follow-up. The analysis will be performed on FAS as described in Section 2.1.

2.3.2 Descriptive Endpoints

Summary statistics will be presented for the descriptive endpoints. Refer to 2.2 for the descriptive summary statistics.

2.4 Sample Size Calculations

[redacted] 180 subjects [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 report with descriptive analysis may be performed on an ad-hoc basis to assess continuing safety and effectiveness and provide routine updates to applicable authorities as necessary.

2.6 Timing of Analysis

The primary effectiveness and safety endpoints will be conducted when all enrolled subjects have [redacted]. The final analysis will be conducted, and final report will be written when the enrolled subjects [redacted]

2.7 Study/Trial Success

Success will be declared when the primary endpoint is met.

2.8 Subgroups for Analysis

Subgroup analyses may be performed on an ad-hoc basis to understand outcomes for specific indications and patient populations.

2.9 Handling of Missing Data

A subject may discontinue from the study[redacted]. If this situation occurs, reasons for missing data will be summarized to assess the plausibility if the missing data could affect subject's endpoint results.

Every effort will be made to collect all required data. All available safety-related data will be used without adjustment to account for missing data. For effectiveness and other measures, all available data will be used.

2.10 Multiplicity Issues

The analysis will be done by indication and no multiplicity adjustment will be applied.

3.0 DESCRIPTIVE ENDPOINTS AND ADDITIONAL DATA

3.1 Baseline and Demographic Characteristics

The following baseline and demographic variables will be summarized descriptively for the subjects enrolled in the full analysis population:

- Subject demographics (age, gender, ethnicity, race, etc.)
- Occupational and lifestyle information
- Subject medical history (pain history and other interventions for pain management)
- Subject pain diagnosis and pain location
- NRS score
- EQ-5D-5L
- PROMIS-29
- Opioid medication usage*
- ODI (only for subjects with back pain)
- NDI (only for subjects with neck pain)

- WOMAC index score (only for subjects with knee and hip pain)
- Serious adverse events resulting in death (if applicable)

*Opioid medication use will be standardized by converting each drug to morphine milligram equivalents (MMEs) using CDC validated conversion factors. See Appendix A for details.

3.2 Adverse Events

All deaths, serious adverse events related to device/procedure (SADE) and non-serious adverse event related to device/procedure (ADE) will be summarized for FAS population excluding deregistered patients, as frequency, proportion, and number of events per patient years of follow up.

3.3 Subject Early Termination

Subject early termination reasons including deaths, voluntary withdrawal, lost-to-follow-up, deregistration, receiving additional chronic pain treatment for the same anatomical region during the follow-up period, etc. will be summarized at all scheduled visits.

3.4 Protocol Deviation

Protocol deviations will be summarized by major and minor categories for subjects in whom a protocol deviation was reported.

3.5 Descriptive Endpoints or Additional Data

The following descriptive endpoints will be reported using summary statistics.

1. The following will be characterized at RFA procedure(s):
   - Overall procedure and RF time
   - A summary of Abbott RFA accessory model numbers used in the procedure

2. The following will be characterized at follow-up visits:
   - Patient reported (%) pain relief
   - Patient satisfaction
   - Patient Global Impression of Change (PGIC): to evaluate the subject's impression of change in his/her condition since the beginning of the study treatment
   - Device- and procedure-related adverse events
   - Device deficiencies

3. Change from baseline to each follow-up visit in
   - NRS (raw change); the raw change is defined as (Baseline NRS score– Follow-up NRS score)
   - EQ-5D quality of life survey, consisting of a descriptive system and the EQ VAS. The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ VAS records the patient's self-rated health on a vertical visual analogue scale

- PROMIS-29 assesses pain intensity using a single 0-10 numeric rating item and eight health domains (physical function, fatigue, pain interference, depressive symptoms, anxiety, ability to participate in social roles and activities, cognitive function/abilities, and sleep disturbance) using four items per domain
- Opioid medication usage
- Oswestry Disability Index (ODI): 10-item scale that evaluates disability related to low-back pain (only for back pain patients)
- Neck Disability index (NDI): 10-item scale that evaluates disability related to neck pain (only for neck pain patients)
- The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) index score: measures pain, stiffness, and functional limitations (only for knee and hip pain patients)

4. Relative change in NRS [redacted]

5. Responder analysis [redacted]
   - Proportion of subjects with ≥ 30% decrease on NRS
   - Proportion of subjects with ≥ 50% decrease on NRS

4.0 DOCUMENTATION AND OHER CONSIDERATIONS

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
AE	Adverse Event
ADE	Adverse Device Effect
AT	As-treated Population
CIP	Clinical investigation plan
EQ-5D	EuroQol – 5 Dimensions
FAS	Full Analysis Set
FDA	Food and Drug Administration
NDI	Neck Disability Index
NRS	Numerical Rating Scale
ODI	Oswestry Disability index
PGIC	Patient Global Impression of Change
PROMIS	Patient-Reported Outcomes Measurement Information System
RF	Radiofrequency
RFA	Radiofrequency Ablation
SAE	Serious Adverse Event

Acronym or Abbreviation	Complete Phrase or Definition
SADE	Serious Adverse Device Effect
SAP	Statistical Analysis Plan
VAS	Visual Analogue Scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

6.0 REFERENCES

[redacted]

7.0 APPENDICES

[redacted]

[redacted]

[redacted]