Biosense Webster Inc.

STATISTICAL ANALYSIS PLAN (SAP)

Study Title: WAVECREST PMCF Study

Protocol Number: CHX_IP015 Revision D

SAP Version:	Date:
Version 1.0	05JUL2022

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1.0 REVISION HISTORY

Version	Date	Author(s)	List of Changes
1.0	05JUL2022	PPD	Original Creation of Document

2.0 INTRODUCTION

This is the Statistical Analysis Plan (SAP) for the final analysis of data collected under Clinical Investigation Plan (CIP) CHX_IP015. This SAP describes in detail the statistical methodology and statistical analyses for the above-mentioned protocol.

2.1 Study Objectives

This trial is designed to confirm the safety and performance of the Coherex WaveCrest LAA Occlusion System in current medical practice through 45 days (± 15 days) follow-up following minor system enhancements.

2.2 Study Design Overview

The WAVECREST PMCF Study is a prospective, multicenter, non-randomized, post-market clinical follow-up study to confirm safety and performance of the Coherex WaveCrest® Left Atrial Appendage Occlusion System in current medical practice in patients with non-valvular atrial fibrillation

Up to 65 subjects will be enrolled in the study at up to 15 study sites in Europe.

Enrollment in the study will be concluded in approximately 18 - 20 months after the first subject is enrolled. Total duration including follow-up visits is expected to be 22 months.

3.0 STUDY ENDPOINTS

Safety and performance of the WaveCrest device through 45 days (± 15 days) follow-up will include the following endpoints:

- Composite rate of:
    - All-cause mortality
    - Pericardial effusion requiring intervention
    - Device embolization (major)
    - Device thrombus
    - Ischemic stroke
- Device Success - Device deployed and implanted in the correct position
- Technical Success at implant
    - Occlusion of the LAA
    - No device-related complications
    - No leak >5mm on color Doppler TEE
- Procedural Success
    - Technical success
    - No procedure-related complications except uncomplicated (minor) device embolization (resolved by percutaneous retrieval during the procedure without surgical intervention or damage to surrounding cardiovascular structures)

4.0 SUBJECT DISPOSITION

Subject disposition will be summarized with counts and percentages in total. Categories summarized will include the number of enrolled subjects (i.e., subjects who signed informed consent), number of screen failures, and the number completed, and discontinued, as well as reasons for discontinuation. The summary of disposition will also include the number and percentage of subjects included in each analysis set described in Section 6 below.

5.0 ANALYSIS SETS

Statistical analyses will be carried out on the following analysis sets.

5.1 Intention-to-Treat (ITT) Analysis Set

The ITT analysis set consist of all subjects who signed the informed consent form, have met all of the inclusion criteria and none of the exclusion criteria, and the Coherex Delivery sheath has been inserted into the subject's femoral vein.

5.2 As-Treated Analysis Set

The As-Treated analysis set consists of all ITT subjects who received the WaveCrest LAA occlusion device.

6.0 GENERAL STATISTICAL CONSIDERATIONS

6.1 Summary Statistics

Subject data will be summarized using listings and tables. All critical electronic case report form (eCRF) data will be listed per subject for all enrolled subjects. For continuous variables, descriptive statistics will include, at a minimum, the number of observations, mean, standard deviation, median, minimum, and maximum. For categorical variables, the number and percentage of subjects will be presented.

For all analyses, the baseline observation is defined as the last available measurement on or before the date of the implantation procedure.

6.2 Reporting of Numerical Values

Raw data will be presented with the exact precision that it was collected on the eCRF or other external data sources.

The number of decimal places to display for calculated data will be determined by the scale of measurement. No decimal places will be displayed if the smallest calculated value is 100; 1 decimal place will be displayed when all calculated values are within the interval (10, 100), with 10 being inclusive; 2 decimal places are displayed when all calculated values are within (1, 10), with 1 being inclusive; 3 decimal places are displayed for calculated values within (0.1, 1), with 0.1 being inclusive; and so on for even smaller scales of measurement.

Percentages will be reported with exactly one decimal place. For summary statistics, means, medians, and confidence intervals will be displayed to one more decimal place than was determined above, dispersion statistics will have 2 more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as determined by the rules above. Blank fields on an eCRF will be displayed as blank fields in corresponding listings.

6.3 Handling of Missing Data

Unless otherwise explicitly specified, missing data will not be imputed; observed cases will be used in the analyses.

6.4 Statistical Software

Statistical analyses will be performed using SAS version 9.4 or higher.

7.0 STATISTICAL METHODS

7.1 Sample Size Justification

Based on the results presented in Section 3.4 of CIP for Version 1.3 of the WaveCrest device in the WAVECREST 1 study and during limited market release, a total of 7 (4.2%) subjects out of 165 implanted subjects have experienced an occurrence of the composite safety endpoint of all-cause mortality, pericardial effusion requiring intervention, device embolization from the LAA, device thrombus, or ischemic stroke. If the expected rate of occurrence of the composite safety endpoint is 5%, then a sample size of 56 subjects will result in the upper bound of a two-sided exact 95% confidence interval being less than 15%. Assuming a drop-out rate of ten percent, total enrollment in this study will be at least 63 subjects (56/0.9 rounded up).

7.2 Demographics and Baseline Characteristics

A minimum of the following demographic and baseline characteristics will be summarized by each analysis set: age at enrollment, sex, race, ethnicity, weight, height, body mass index, prior cardiovascular history, baseline $CHADS_2$ score, baseline CHA_2DS_2-VASc score, baseline HAS-BLED score, baseline QVSFS score, modified Rankin Scale score, congestive heart failure, hypertension, diabetes, previous stroke/TIA, NYHA Class, type of atrial fibrillation, time of onset of atrial fibrillation (summarized continuously in years as well as categorically with cut points of < 1 year or ≥ 1 year), left ventricular ejection fraction (LVEF), left atrial appendage anatomy shape and morphology, and use of antiplatelet and anticoagulation medications.

7.3 Safety Endpoint

The safety endpoint for the investigation is a composite of the following through 45 days follow-up post implant:

- All-cause mortality
- Pericardial effusion requiring intervention
- Device embolization (major)
- Device thrombus
- Ischemic stroke

All safety events occur within the 45 days follow up visit window (up to Day 60) will be adjudicated by the Sponsor. The safety endpoints analysis will be based on Sponsor Assessment of Adverse Events data. No formal statistical inference will be made. The analysis will be descriptive for the ITT analysis set. The number and percentage of subjects experiencing any occurrence of the composite safety endpoint will be summarized assuming binomial distribution. The exact two-sided 95% confidence intervals will be constructed for the composite endpoint. A similar analytical approach will be performed for each component as well.

7.4 Clinical Performance Endpoints

Descriptive clinical performance endpoints through 45 days (+15 days) follow-up will be summarized and presented as detailed below for both ITT and As-Treated analysis sets. No formal statistical inference will be made and the exact two-sided 95% confidence intervals will be constructed.

- **Device success**

  Device success will be calculated as the proportion of subjects who have the device deployed and implanted in the correct position.

- **Technical Success**
  The technical success rate will be calculated as the proportion of subjects who experience successful placement and release of the occluder in the LAA with LAA closure (defined as no leak > 5mm on color Doppler TEE) and discharge from the cardiac catheterization laboratory without the occurrence of device-related complications.
- **Procedural success**
  The procedural success rate will be calculated as the proportion of subjects who experience successful placement and release of the occluder in the LAA with LAA closure (defined as no leak > 5mm on color Doppler TEE) and discharge from the cardiac catheterization laboratory without device-related complications and without procedure-related complications other than minor device embolization (defined as device embolization that can be resolved by percutaneous technique without surgical intervention or damage to surrounding cardiovascular structures).

7.5 Other Safety Analysis - Adverse events (AEs)

Site reported adverse events (AEs) during the study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects reporting adverse events will be summarized by MedDRA system organ class and preferred term for both ITT and As-Treated analysis sets. Separate summaries will also be provided for device-related AEs and procedure-related AEs. All serious adverse events (SAEs), device-related SAEs, and procedure-related SAEs will also be summarized by system organ class and preferred term. All adverse events occurring through the 45-day (+15 days) follow-up will be summarized.

7.6 Procedural Results

The following characteristics of implant procedure, which are not study endpoints, will be summarized descriptively (n, mean, standard deviation, median, minimum, maximum, and 95% confidence interval, as appropriate) based on the As-Treated analysis set:

- Device deployment duration, defined as the difference in minutes between time of removal of delivery sheath and time of transseptal puncture,
- Procedural duration, defined as the difference in minutes between time of removal of delivery sheath and time of venous puncture,
- Catheterization lab duration, defined as the difference in minutes between time patient left catheterization lab and time patient arrived in catheterization lab,
- Anesthesia type, and

- Contrast volume

7.7 **Protocol Deviations**

All protocol deviations, including rationale for deviation, recorded during the study will be classified by the Sponsor as minor or major and will be listed.