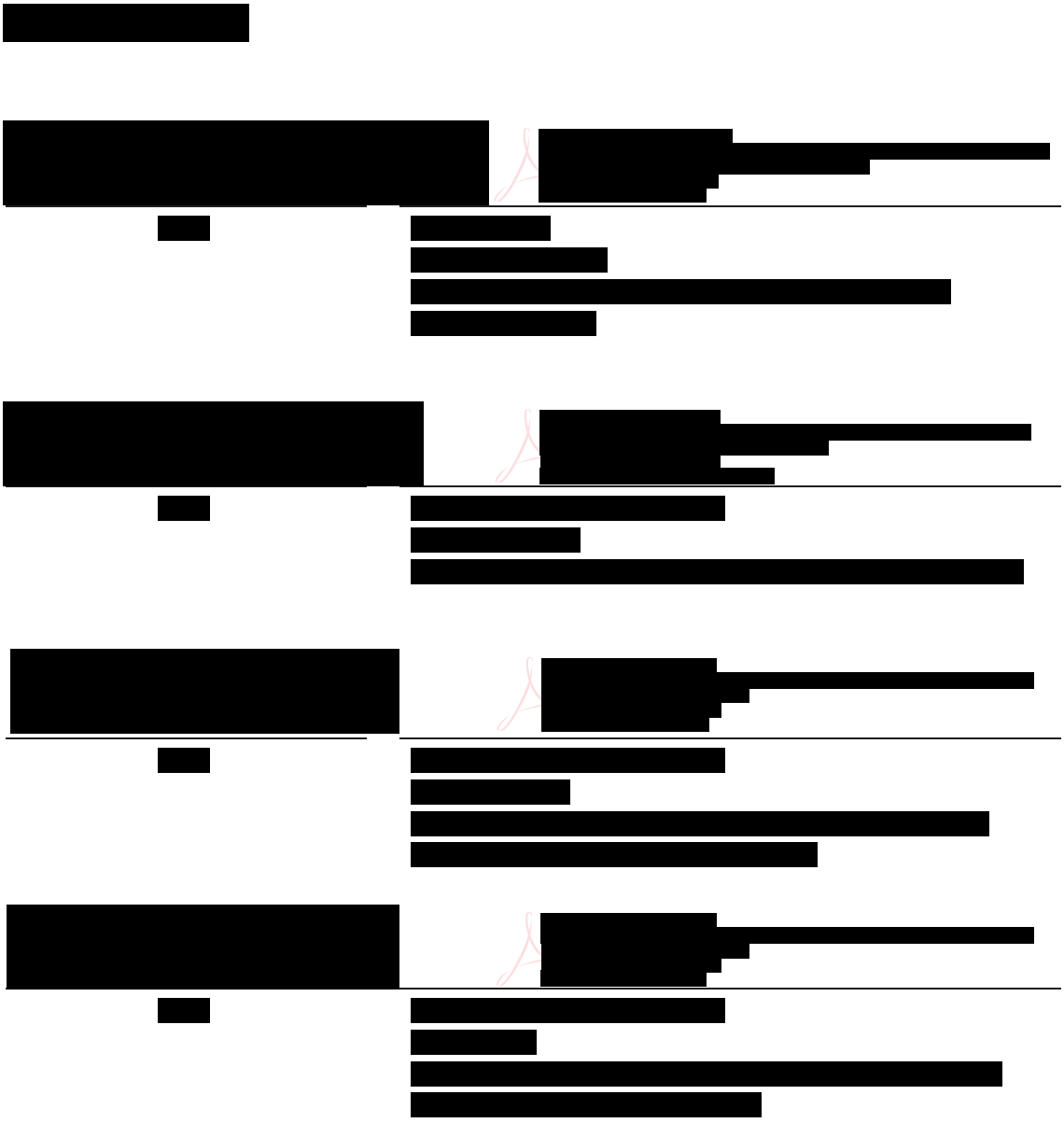
Biosense Webster Inc.

STATISTICAL ANALYSIS PLAN (SAP)

Study Title: WAveCrest Vs. Watchman TranssEptal LAA Closure to REduce AF-Mediated STroke 2

Protocol Number: CHX_IP014 Revision H

SAP Version:	Date:
Version 3.0	17APR2020



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1.0 REVISION HISTORY

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

2.0 INTRODUCTION

This is the Statistical Analysis Plan (SAP) for the final analysis of data collected under Clinical Investigation Plan (CIP) CHX_IP014. 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 demonstrate non-inferiority of the Coherex WaveCrest LAA occlusion device to the Boston Scientific Watchman LAA occlusion device for both effectiveness and safety endpoints.

- The primary effectiveness objective is to demonstrate non-inferiority of the WaveCrest device to the Watchman device for the composite rate of ischemic stroke or systemic embolism. If non-inferiority is demonstrated, superiority will be evaluated.
- The primary safety objective is to demonstrate non-inferiority of the WaveCrest device to the Watchman device for the composite rate of all death, procedure- and device-related complications requiring percutaneous or surgical intervention through 45 days post-procedure, and major bleeding throughout the duration of the trial. If non-inferiority is demonstrated, superiority will be evaluated.

[redacted]

2.2 Study Design Overview

The WAVECREST2 trial is a prospective, multicenter, randomized, active controlled, clinical trial to evaluate the effectiveness and safety of the Coherex WaveCrest LAA device compared to the Watchman® LAA device for the reduction in risk of ischemic stroke or systemic embolism in patients with non-valvular atrial fibrillation who have an appropriate rationale to seek a non-pharmacologic alternative to chronic oral anticoagulation.

Subjects will be randomized in a 1:1 ratio to the Treatment Arm (Coherex WaveCrest LAA Occlusion System) or the Control Arm (Boston Scientific's Watchman LAA Device). The trial is designed to demonstrate that effectiveness and safety of the WaveCrest device are non-inferior to the Watchman device.

[redacted]

The enrollment phase is expected to last between 2 and 3 years, and maximum follow-up duration is 5 years, resulting in a total trial duration of up to approximately 8 years.

2.3 [redacted]

[redacted]

2.4 Data Monitoring Committee

The Data Monitoring Committee (DMC) will review accumulating data from the trial on a regular basis. The DMC will advise the Sponsor regarding the continuing safety of trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial. Based on accumulating data from the trial, the DMC will recommend whether to continue, suspend, modify or stop the trial. The DMC will be composed of at a minimum one statistician and two physicians. The composition, responsibilities, frequency of DMC meetings, handling of emergency situations and documentation of DMC meetings will be specified in a Data Monitoring Committee Charter.

3.0 STUDY ENDPOINTS

3.1 Primary Endpoints

The primary safety endpoint is the composite rate of death, procedure- or device-related complications requiring percutaneous or surgical intervention, through 45 days post-procedure, and major bleeding throughout the duration of the trial.

The primary effectiveness endpoint is the composite rate of ischemic stroke or systemic embolism.

3.2 Secondary Endpoints

The first secondary effectiveness endpoint is the rate of ischemic stroke or systemic embolism with the WaveCrest device in comparison to the CHA_2DS_2-VASc imputed risk of ischemic stroke or systemic embolism in the absence of anticoagulant therapy.

The second secondary effectiveness endpoint is the percentage of subjects in the WaveCrest arm who have achieved effective LAA closure at 45 days (defined as having residual flow ≤ 5 mm based on the 45-day TEE).

[redacted]

4.0 SUBJECT DISPOSITION

Subject disposition will be summarized with counts and percentages for each treatment group and in total. Categories summarized will include the number of subjects who signed informed consent, number of screen failures, and the number randomized, 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 ENROLLMENT AND ACCOUNTABILITY

The number and percentage of subjects completing each study visit will be summarized for all randomized subjects by randomized treatment group and in total. Following implantation, subject office visits are scheduled at 45 days, 6 months and annually through 5 years. Subjects are also scheduled to complete phone visits at 1.5, 2.5, 3.5, and 4.5 years after implantation.

[redacted]

6.1 [redacted]

[redacted]

6.2 [redacted]

[redacted]

6.3 [redacted]

[redacted]

[redacted]

6.5 Roll-in Subjects Cohort

This cohort will consist of all subjects identified as roll-in subjects per the CIP who had vascular access attempted.

6.6 As-Treated Cohort

This cohort will consist of all randomized subjects who received the LAA occlusion device independently of which treatment group they were randomized to.

7.0 GENERAL STATISTICAL CONSIDERATIONS

7.1 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. All listings will include the subject number and the randomized treatment arm (or identification of roll-in subjects as appropriate). 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.

[redacted]

7.2 [redacted]

[redacted]

7.3 [redacted]

[redacted]

[redacted]

8.0 STATISTICAL METHODS

8.1 Demographics and Baseline Characteristics

A minimum of the following demographic and baseline characteristics will be summarized and compared between the WaveCrest and Watchman arms [redacted]

8.2 Primary Safety Endpoint

The primary safety endpoint is the composite rate of death, procedure- or device-related complications requiring percutaneous or surgical intervention, through 45 days post-procedure, and major bleeding throughout the duration of the trial.

The primary analysis of this endpoint for establishing trial success will occur in the ITT cohort and will apply Bayesian methods. [redacted].

Let $q_{WAVECREST}$ be the primary safety endpoint rate at 24 months in the WaveCrest arm, while $q_{CONTROL}$ is the corresponding rate in the Watchman arm.

[redacted]

[redacted]

[redacted] = [redacted]

= [redacted] − [redacted] + [redacted]

[redacted] = [redacted]

= [redacted] − [redacted] + [redacted]

[redacted] The following null and alternative hypotheses will be tested:

$$H_0: q_{WAVECREST}/q_{CONTROL} \geq 1.0 \text{ vs.}$$
$$H_a: q_{WAVECREST}/q_{CONTROL} < 1.0$$

[redacted]

8.2.1 Justification of the Non-inferiority Margin for the Safety Endpoint

Complications requiring percutaneous or surgical intervention through 45 days will likely consist of pericardial effusion/tamponade, vascular repair, and embolized device retrieval. The WaveCrest device has been designed to avoid the most serious of these complications, namely device embolization and life-threatening LAA perforations which may require surgery. These events are rare and while clinically important, are expected to contribute little to the composite endpoint. [redacted]

8.3 Primary Effectiveness Endpoint

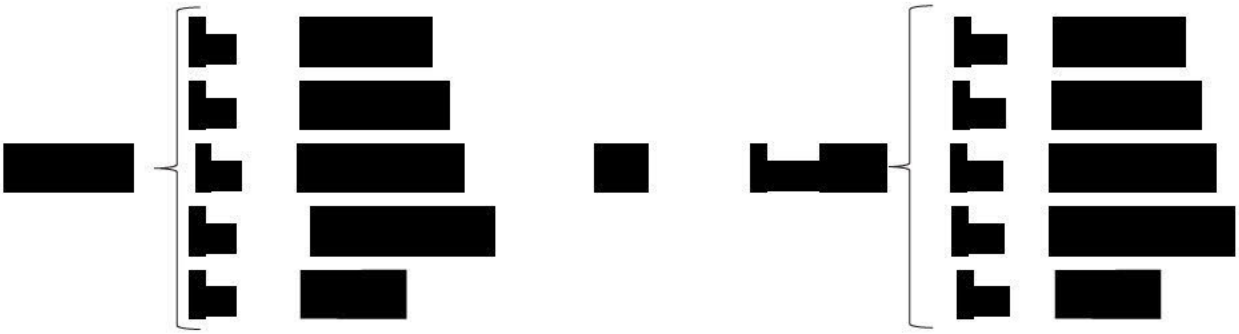
The primary effectiveness endpoint is the composite rate of ischemic stroke or systemic embolism.

[redacted]

Let $p_{WAVECREST}$ be the primary effectiveness endpoint rate at 24 months in the device arm, while $p_{CONTROL}$ is the corresponding rate in the control arm.

[redacted]

[redacted]



[redacted]

[redacted]

If non-inferiority is established for both the primary safety, the primary effectiveness endpoints and the second secondary effectiveness endpoint, the primary safety endpoint will then be tested for superiority, and if superiority is established for the primary safety endpoint, then the primary effectiveness endpoint will be tested for superiority. The following null and alternative hypotheses will be tested:

$$H_0: p_{WAVECREST} - p_{CONTROL} \geq 0.0\%$$
$$H_a: p_{WAVECREST} - p_{CONTROL} < 0.0\%$$

[redacted]

8.3.1 Justification of the Non-inferiority Margin for the Effectiveness Endpoint

By demonstrating statistical non-inferiority to Watchman, the WAVECREST2 Trial is designed to make the WaveCrest device available as an additional alternative to oral anticoagulation for patients with a reason to seek a non-pharmacologic alternative to chronic oral anticoagulation.

[redacted]

8.4 Secondary Effectiveness Endpoints

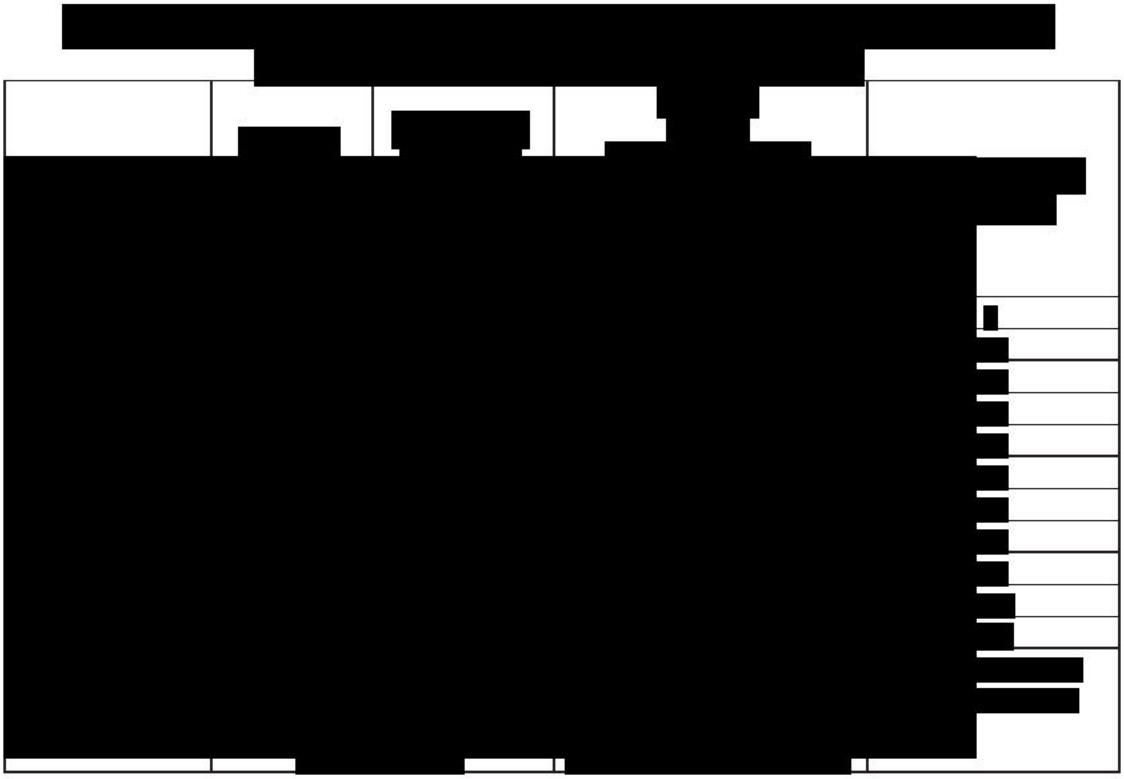
The first secondary effectiveness objective is to establish non-inferiority of the rate of LAA closure at 45 days for the WaveCrest arm compared to the control arm. Let $r_{WAVECREST}$ be the 45-day LAA closure rate in the device arm, while $r_{CONTROL}$ is the corresponding rate in the control arm. [redacted]

$$H_0: r_{WAVECREST} - r_{CONTROL} \geq 6.0\% \text{ vs.}$$
$$H_a: r_{WAVECREST} - r_{CONTROL} < 6.0\%.$$

The rate will be calculated as the number of subjects who have residual flow ≤ 5 mm based on the 45-day TEE divided by the number of subjects in each group with a 45-day TEE.

The second secondary effectiveness endpoint is the rate of ischemic stroke or systemic embolism with the WaveCrest device in comparison to the CHA_2DS_2-VASc imputed risk of ischemic stroke or systemic embolism in the absence of anticoagulant therapy.

[redacted]



[redacted] rate of ischemic stroke in subjects receiving the WaveCrest device in the Treatment Arm will be tested against the performance goal. The hypotheses to be tested are as follows:

H_0: $l_W \geq 6.0$

H_1: $l_W < 6.0$

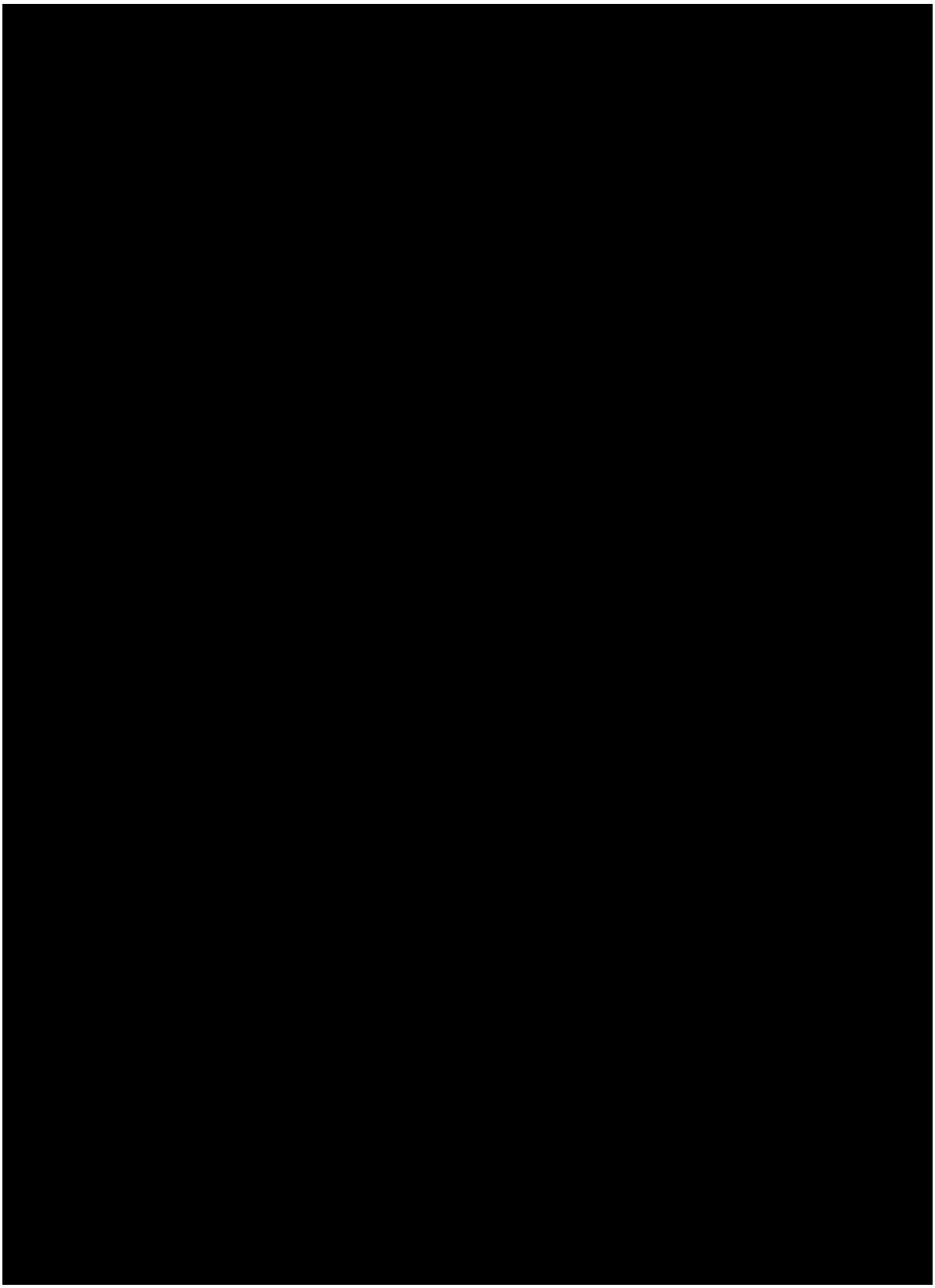
where l_W is the true rate of ischemic stroke or systemic embolism per 100 patient-years for the WaveCrest device. [redacted]

8.5 Sample Size and Power

A minimum sample size of 1250 subjects will be randomized in the trial up to a maximum of 1550 randomized subjects.

[redacted]

[redacted]



[redacted]

[redacted]

[redacted]

8.6 Multiplicity Adjustment

The trial will be considered successful if both the primary effectiveness and primary safety endpoints are met. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.7 Additional Endpoints

A number of descriptive effectiveness and safety endpoints are included in this trial, and will be summarized by randomized arm (WaveCrest or control). [redacted] Summary statistics and 95% confidence intervals will be provided, and p-values will be provided as a descriptive measure of difference between the treatment groups, though no labeling indications will be sought for any of these endpoints.

8.7.1 Descriptive Safety Endpoints

Descriptive safety endpoints will be summarized and presented as detailed below.

- **Components of the primary safety composite endpoint**

  The number and percentage of subjects who experience each component of the primary safety endpoint through 45 days will be presented.

- **Stroke (all types) or pericardial effusion**

  The number and percentage of subjects who experience a stroke (ischemic, hemorrhagic, or indeterminant) or pericardial effusion through 45 days post-procedure

- **Pericardial effusion requiring surgical drainage**

  The number and percentage of subjects who undergo pericardial effusion requiring surgical drainage through 7 days post-procedure or at hospital discharge, whichever is later, will be presented by intervention type (surgical vs. percutaneous).

- **All-cause mortality**

  Event rates per subject-year for all-cause mortality will be estimated assuming a one-parameter exponential survival model. [redacted]

- **Cardiovascular mortality**

  Event rates per patient-year for cardiovascular mortality will be estimated assuming an exponential survival model. [redacted]

- **Adverse events**

  Adverse events (AEs) reported 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 by treatment group and in total. Separate summaries will also be provided for device-related AEs and procedure-related AEs. [redacted]

8.7.2 Descriptive Effectiveness Endpoints

Descriptive effectiveness endpoints will be summarized and presented as detailed below.

- **Primary effectiveness event rate at 6 months, 3 years, 4 years and 5 years**
  After the primary analysis, primary effectiveness event rates will be estimated at 6 months, 3 years, 4 years and 5 years under the Bayesian piecewise exponential model. [redacted]

[redacted]

- **Composite of all stroke, systemic embolism, or TIA**

  Event rates per subject-year for the composite of all stroke, systemic thromboembolism or TIA (as well as for each component) will be estimated assuming a one-parameter exponential survival model. [redacted]

- **Landmark analysis of primary effectiveness endpoint**

  A landmark analysis of the primary effectiveness endpoint will be carried out with subject exposure start times beginning at the 45-day visit [redacted]

- **Landmark analysis of the incidence of ischemic stroke from 6 months following device implantation and discontinuation of oral anticoagulant and dual antiplatelet therapy**

  Event rates per subject-year for ischemic stroke will be estimated assuming a one-parameter exponential survival model. [redacted]

- **Composite of all-cause stroke**
  Event rates per subject-year for strokes of any etiology (ischemic, hemorrhagic, or other) will be estimated assuming a one-parameter exponential survival model. [redacted]

- **Incidence of thrombus formation on the left atrial surface of the implant**
  Event rates of thrombus on the left atrial surface of the implant through all available follow-up based on TEE examination as reported by the Echocardiography Core Laboratory (ECL) will be summarized.

- **Strokes adjudicated as ischemic, hemorrhagic, or indeterminate**

  Event rates per subject-year for ischemic, hemorrhagic, or indeterminate strokes will be estimated assuming a one-parameter exponential survival model. [redacted]

- **Strokes adjudicated as major or minor**

  Event rates per subject-year for major and minor strokes will be estimated assuming a one-parameter exponential survival model. [redacted]

- **Strokes adjudicated as cardioembolic in origin**

  Event rates per subject-year for cardioembolic strokes will be estimated assuming an exponential survival model. [redacted]

- **Freedom from oral anticoagulants**

  The proportion of subjects free from oral anticoagulants after each scheduled follow-up visit will be summarized. [redacted]

- **Number of devices used per subject**

  The number of devices used (i.e., attempted) will be summarized. The number of devices used will be summarized by the proportion of subjects in whom 0, 1, 2 or >2 devices were attempted. [redacted]

- **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 color flow Doppler flow > 5mm) and discharge from the cardiac catheterization laboratory without procedure-related complications [redacted]

- **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 color flow Doppler flow > 5mm) and discharge from the cardiac catheterization laboratory without the occurrence of a device-related adverse event.

- **Device success**

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

- **LAA closure rate at 45 days, 6 months, and 1 year**

  LAA closure will be assessed in subjects whose 45-day, 6-month and 1-year TEEs have been evaluated by the Echocardiography Core Lab for residual leak/gap measurement. As defined in the protocol, LAA closure is defined as no residual leak or if leak is present, residual gap ≤ 5mm. [redacted]

8.7.3 Procedural Results

The following procedural data, which are not trial endpoints, will be summarized by randomized arm for the mITT population. Summary statistics (n, mean, standard deviation, median, minimum, maximum, and 95% confidence interval) will be provided.

- Device deployment duration
- Procedural duration
- Catheterization lab duration
- Anesthesia duration
- Contrast volume

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.10 Sensitivity Analyses

Sensitivity analyses will be performed for the primary results that will be used to support a pre-market approval application. [redacted]

[redacted]

8.11 [redacted]

[redacted]