Statistical Analysis Plan Cover Page

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AMPLATZER™ LAA Occluder Post Approval Study (PAS)
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SJM-CIP-10122
Amplatzer LAAO PAS
Amplatzer LAA Occluder Post-Approval Study (PAS)

Statistical Analysis Plan (SAP)

Version B

09SEP2020

[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 SJM-CIP-10122, the Amplatzer LAA Occluder Post Approval Study (PAS) clinical investigation. This plan is based on the version C, 19NOV2018, clinical investigation plan.

1.2 Clinical Investigation Objectives

The study is a post-approval study to compile real world outcome data on the use of the Amplatzer Cardiac Plug ("ACP") and the next generation Amplatzer Amulet left atrial appendage occluder ("Amulet") upon its approval by Health Canada, in subjects with non-valvular atrial fibrillation who are at increased risk for stroke and systemic embolism. [redacted]

1.3 Clinical Investigation Design

The Amplatzer family of left atrial appendage ("LAA") occluder devices (ACP and Amulet) will be clinically evaluated through this post-approval study. This is a prospective, multicenter, non-randomized, observational, post-approval study on subjects who will undergo the implant of an Amplatzer LAA occluder.

1.4 Endpoints

As the coronavirus disease 2019 (COVID-19) has spread around the world, Abbott has taken steps to minimize the potential confounding effect of the disease. In alignment with the guidance documents "FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Public Health Emergency," updated 03JUN2020, "Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency," dated June 2020, and EU "Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic," updated 28APR2020, additional consideration was given to the impact of COVID-19 on the primary and secondary endpoint analysis. [redacted]

1.4.1 Primary Safety Endpoint

The primary safety endpoint is the occurrence of one of the following events between the time of implant and 7 days post-procedure or hospital discharge (whichever is later): all cause death, ischemic stroke, systemic embolism, or device- or procedure-related events requiring open cardiac surgery or major endovascular repair.

Percutaneous catheter drainage of pericardial effusion, snaring of an embolized device, thrombin injection to treat femoral pseudoaneurysm, and nonsurgical treatments of access site complications will not be included in the assessment of the primary safety endpoint.

1.4.2 Primary Efficacy Endpoints

Primary effectiveness endpoint 1 is the occurrence of stroke (including ischemic or hemorrhagic), systemic embolism, cardiovascular death, or unexplained death through 24 months.

Primary effectiveness endpoint 2 is the occurrence of ischemic stroke or systemic embolism through 24 months.

1.4.3 Secondary Endpoint

The secondary endpoint is a comparison of the observed rate of ischemic stroke or systemic embolism at 24 months with the CHA_2DS_2-VASc predicted rate.

1.4.4 Descriptive Endpoints

- Oral anticoagulant use over time
- Device closure
- Procedure success
- Technical success
- Procedure duration
- Device thrombosis
- Transient ischemic attack (TIA)
- Major bleeding
- Death

See section 3.5 for additional details.

1.5 Randomization

N/A

1.6 Blinding

N/A

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

[redacted]

- [redacted]
- [redacted]

2.2 Statistical Methods

2.2.1 Descriptive Statistics for Continuous Variables

Continuous variables will be summarized with statistics to include sample size, mean, median, standard deviation, minimum, and maximum.

2.2.2 Descriptive Statistics for Categorical Variables

Categorical variables will be summarized by frequency (count) and percent of subjects.

2.2.3 Survival / Event Rate Analysis

Kaplan-Meier analysis will be used to estimate event rate. [redacted]

2.3 Endpoint Analysis

2.3.1 Primary Endpoints

The performance goals for each primary endpoint are identical to those used in the US post-approval study for Bostin Scientific's Watchman device. In each primary endpoint, H_0 must be rejected in order to declare success.

2.3.1.1 Primary Safety Endpoint

The primary safety endpoint will be assessed in the attempt population. The hypothesis is formally stated:

$$H_0: P \geq 2.66\%$$

$$H_a: P < 2.66\%$$

where P is the proportion of subjects who experience a primary safety endpoint event. P will be estimated by the 97.5% upper confidence bound (UCB) of the event rate [redacted]

2.3.1.2 Primary Effectiveness Endpoint 1

Primary effectiveness endpoint 1 will be assessed in the implant population. The hypothesis is formally stated:

$$H_0: \lambda_1 \geq 9.6\%$$
$$H_a: \lambda_1 < 9.6\%$$

where λ_1 is the endpoint event rate. λ_1 will be estimated by the 97.5% UCB of the Kaplan-Meier event rate.

2.3.1.3 Primary Effectiveness Endpoint 2

Primary effectiveness endpoint 2 will be assessed in the implant population. The hypothesis is formally stated:

$$H0: \lambda_2 \geq 6.6\%$$
$$Ha: \lambda_2 < 6.6\%$$

where λ_2 is the endpoint event rate. λ_2 will be estimated by the 97.5% UCB of the Kaplan-Meier event rate.

2.3.2 Secondary Endpoint

The secondary endpoint will be assessed [redacted]

[redacted]

2.4 Sample Size

[redacted]

2.5 Interim Analysis

No formal interim analysis is 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

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

The database will be locked for the final report after all subjects have completed 24-month follow-up visits, withdrawn prior to 24 months, or passed the 24-month visit window without a 24-month visit (i.e. a missed visit).

2.7 Study/Trial Success

[redacted]

2.8 Handling of Missing Data

There will be no imputation of missing data. It is anticipated that there will not be missing data for the primary safety endpoint, and the primary efficacy endpoints will be censored when data is unavailable. The secondary endpoint, descriptive endpoints, and other data will be analyzed as available.

2.9 Poolability

[redacted]

2.10 Multiplicity Issues

[redacted] No adjustments will be made for multiplicity.

3.0 DESCRIPTIVE ENDPOINTS AND ADDITIONAL DATA

3.1 Baseline and Demographic Characteristics

Baseline and demographic variables will be summarized, including but not limited to: gender, age, ethnicity, race, medical history, CHA_2DS_2-VASc score, and HAS-BLED score.

3.2 Adverse Events

Safety reporting begins when vascular access of an enrolled subject is initiated. Serious adverse events (SAE) and serious adverse device effects (SADE) will be summarized in terms of frequency and percent of subjects with events. Adverse events related to COVID-19 will be summarized separately.

3.3 Subject Early Termination

Subject early termination reasons including death, withdrawal, lost-to-follow-up, and others. They will be summarized with description and days to termination.

3.4 Protocol Deviation

Deviations from the protocol will be summarized by type. Deviations related to COVID-19 will be summarized separately.

3.5 Descriptive Endpoints

Oral anticoagulant use over time:

The count and proportion of subjects using oral anticoagulants will be summarized at each follow-up visit. [redacted]

Device closure:

The number and proportion of subjects in whom device closure is achieved at the 45-day follow-up visit will be summarized. Device closure is defined as residual jet around the device < 5mm at the 45-day visit documented by transoesophageal echocardiogram (TOE). [redacted]

Procedure success:

The count and proportion of subjects with a successful implant will be summarized. A successful implant procedure is defined as implantation of the Amplatzer LAA occluder during the procedure with no SAE prior to hospital discharge. [redacted]

Technical success:

The count and proportion of subjects with a successful implant will be summarized. Technical success is defined as delivery and release of the Amplatzer LAA occluder. [redacted]

Procedure duration:

Procedure duration will be summarized using descriptive statistics including mean, standard deviation, median and range. Procedure duration is defined as the time from the transeptal

puncture until the delivery sheath is removed. [redacted]

Device Thrombosis:

The count and proportion of subjects with a device thrombus will be summarized. [redacted]

Transient Ischemic Attack:

Kaplan-Meier analysis will be used to estimate the rate of TIA. [redacted]

Death:

Kaplan-Meier analysis will be used to estimate the rate of all-cause death. [redacted]

Major Bleeding:

Kaplan-Meier analysis will be used to estimate the rate of major bleeding events. Major bleeding is defined as type 3 based on the BARC definition. [redacted]

4.0 DOCUMENTATION AND OHER CONSIDERATIONS

All analysis will be performed using SAS® for Windows, version 9.4 or higher.

5.0 ACRONYMS AND ABBREVIATIONS

Acronym or Abbreviation	Complete Phrase or Definition
CRF	case report form
SAE	serious adverse event
SAP	statically analysis plan
TIA	Transient ischemic attack
UCB	Upper confidence bound

6.0 REFERENCES

[redacted]