| Abbott | Statistical Analysis Plan Cover Page |
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| Amulet IDE Trial |
| AMPLATZER™ Amulet™ Left Atrial Appendage Occluder Randomized Controlled Trial |
| Study Document No: SJM-CIP-10114 |
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# AMPLATZER™ Amulet™ Left Atrial Appendage Occluder

# Randomized Controlled Trial

(SJM-CIP-10114)

**Statistical Analysis Plan (SAP)**

Date: 20 – Sept – 2021

Author: Hong Zhao

| Abbott | Study Document No: CL1016823 Ver. A<br>Study Name: AMPLATZER™ Amulet™ Left Atrial Appendage Occluder Randomized Controlled Trial |
|---|---|
| **Statistical Analysis Plan** | |

## Table of Contents

## 1.0 INTRODUCTION

This document is a statistical analysis plan for the AMPLATZER™ Amulet™ Left Atrial Appendage Occluder Randomized Controlled Trial (refer to CIP [redacted] for the clinical investigational plan).

## 2.0 TRIAL OBJECTIVES

The objective of this clinical trial is to demonstrate that the safety and effectiveness of the Amulet device is non-inferior to that of the Boston Scientific LAA closure (LAAC) device in subjects with non-valvular atrial fibrillation. The trial will test whether the device meaningfully improves health outcomes through evaluation of the primary safety endpoint, primary effectiveness endpoint, and mechanism of action endpoint. The intended patient population for this trial would be those already indicated for the Control device, therefore, a randomized device-to-device comparator trial is appropriate for evaluating the outcomes of those with non-valvular atrial fibrillation and an increased risk of stroke.

## 3.0 TRIAL DESIGN

This is a prospective, randomized, multi-center active control trial intended to demonstrate non-inferiority of the Amulet device to the commercially available Boston Scientific LAAC device in subjects with non-valvular atrial fibrillation.

[redacted]

[redacted] The trial is expected to take approximately 3 years to enroll, and each subject will be followed for 5 years. Follow-up visits may occur as part of a post-approval study, should the Amulet device gain approval for commercial distribution prior to the subject's 5-year visit.

The trial will utilize a Clinical Events Committee (CEC) to review adverse events for adjudication of trial endpoints.

## 4.0 TRIAL ENDPOINTS

### 4.1 Primary Safety Endpoint

The primary safety endpoint is a composite endpoint of CEC adjudicated procedure-related complications (refer to Appendix P in the CIP for definition), or all-cause death or major bleeding (defined as Type 3 or greater based on the Bleeding Academic Research Consortium (BARC) definition) through 12 months.

### 4.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint is a composite endpoint of ischemic stroke or systemic embolism through 18 months.

### 4.3 Mechanism of Action Primary Endpoint

Device closure (defined as residual jet around the device ≤ 5 mm) at the 45-day visit documented by transesophageal echocardiogram (TEE/TOE) defined by Doppler flow.

### 4.4 Secondary Endpoints

The trial has the following secondary endpoints:

- A composite of all stroke, systemic embolism, or cardiovascular/unexplained death through 18 months
- Major bleeding rate through 18 months (defined as Type 3 or greater based on BARC definition)
- A composite of procedure-related complications, or all-cause death, or major bleeding through 12 months (superiority analysis)
- A composite of ischemic stroke or systemic embolism through 18 months (superiority analysis)
- Device closure (defined as residual jet around the device ≤ 5 mm) at the 45-day visit documented by TEE/TOE, defined by Doppler flow (superiority analysis)

### 4.5 Descriptive Endpoints

The trial has a number of descriptive endpoints. See Section 5.3 for a full listing.

## 5.0 STATISTICAL METHODS

### 5.1 Primary Endpoints

This trial has one primary safety endpoint, one primary effectiveness endpoint, and one mechanism of action primary endpoint.

#### 5.1.1 Primary Safety Endpoint

The primary safety endpoint is a composite endpoint of procedure-related complications, or all-cause death or major bleeding (defined as Type 3 or greater based on the Bleeding Academic Research Consortium (BARC) definition) through 12 months. The primary safety endpoint will be reported and analyzed based on event adjudication by the CEC.

##### 5.1.1.1 Hypothesis

Let $p_1$(Amulet) be the probability of a primary safety endpoint event with the Amulet device, while $p_1$(Control) is the corresponding probability with the Control device. The following hypothesis will be tested:

$$H_0: p_1(\text{Amulet}) - p_1(\text{Control}) \geq \Delta_1$$

$$H_1: p_1(\text{Amulet}) - p_1(\text{Control}) < \Delta_1$$

where $\Delta_1$ is the absolute value of the non-inferiority margin for the safety endpoint. [redacted]

[redacted]

[redacted]

[redacted]

### 5.1.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint is a composite endpoint of ischemic stroke or systemic embolism (SE) through 18 months.

#### 5.1.2.1 Hypothesis

Let $p_2$(Amulet) be the probability of a subject experiencing a primary effectiveness endpoint event in the Amulet group, while $p_2$(Control) is the corresponding probability in the Control group. The following hypothesis will be tested:

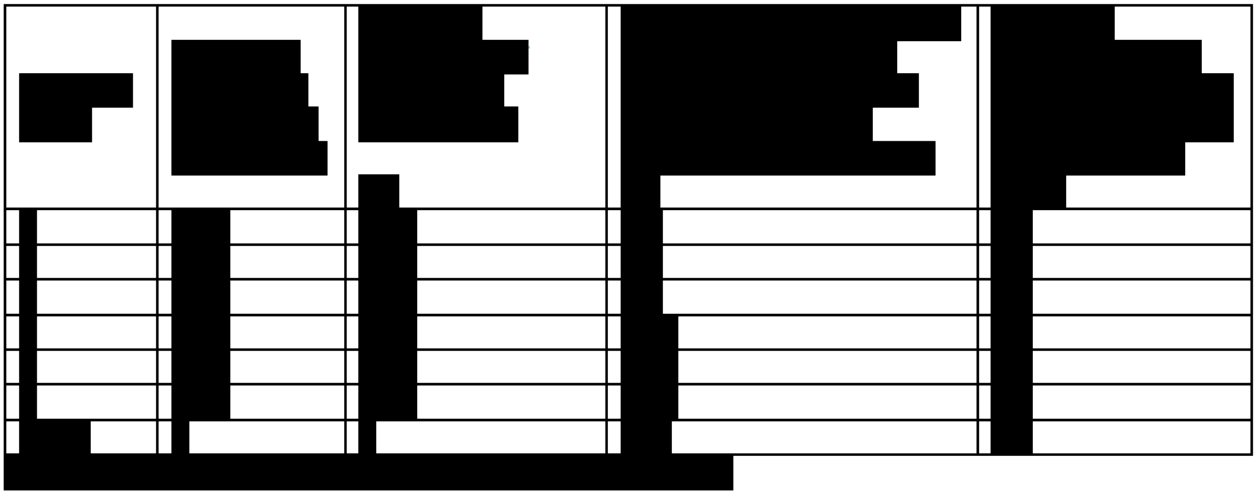
$$H_0: p_2(\text{Amulet}) - p_2(\text{Control}) \geq \Delta_2$$

$$H_1: p_2(\text{Amulet}) - p_2(\text{Control}) < \Delta_2$$

where $\Delta_2$ is the absolute value of the non-inferiority margin for the effectiveness endpoint. [redacted]

[redacted]

[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

### 5.1.3 Mechanism of Action Primary Endpoint

The primary endpoint of device closure is the device closure rate at the 45-day visit. Device closure is defined as residual jet around the device ≤ 5 mm, documented by TEE/TOE. Closure will be determined by Doppler flow and adjudicated by an independent Echocardiography Core Laboratory.

#### 5.1.3.1 Hypothesis

Let $p_3$(Amulet) be the 45-day closure probability in the Amulet group, while $p_3$(Control) is the corresponding probability in the Control group. The following hypothesis will be tested:

$$H_0: p_3(\text{Amulet}) - p_3(\text{Control}) \leq -\Delta_3$$

$$H_1: p_3(\text{Amulet}) - p_3(\text{Control}) > -\Delta_3$$

where $\Delta_3$ is the absolute value of the non-inferiority margin. [redacted]

[redacted]

## 5.2 Secondary Endpoints

The following secondary endpoints will be tested if the primary safety and effectiveness non-inferiority null hypotheses are both rejected:

### 5.2.1 Composite endpoint of all stroke, systemic embolism, or cardiovascular/unexplained death through 18 months

The following hypothesis will be tested:

$$H_0: p_4(\text{Amulet}) - p_4(\text{Control}) \geq \Delta_4$$

$$H_1: p_4(\text{Amulet}) - p_4(\text{Control}) < \Delta_4$$

where $p_4$(Amulet) and $p_4$(Control) are the probabilities of subjects in the two groups experiencing a composite endpoint of all stroke, systemic embolism, or cardiovascular (CV)/unexplained death through 18 months and $\Delta_4$ is the absolute value of the non-inferiority margin. [redacted]

### 5.2.2 Major bleeding through 18 months

The following hypothesis will be tested:

$$H_0: p_5(\text{Amulet}) - p_5(\text{Control}) \geq 0$$

$$H_1: p_5(\text{Amulet}) - p_5(\text{Control}) < 0$$

where $p_5$(Amulet) and $p_5$(Control) are the 18-month major bleeding probabilities in the two groups [redacted]. Major bleeding is defined as Type 3 or greater based on the BARC definition. [redacted]

### 5.2.3 Superiority test of the primary safety endpoint

If non-inferiority of safety of Amulet over control is demonstrated, a reflex test for superiority will be performed to determine if the Amulet device is superior to the Control device. The hypothesis is as follows:

$$H_0: p_1(\text{Amulet}) - p_1(\text{Control}) \geq 0$$

$$H_1: p_1(\text{Amulet}) - p_1(\text{Control}) < 0$$

The hypothesis will be tested at the 2.5% significance level. [redacted]

### 5.2.4 Superiority test of the primary effectiveness endpoint

If non-inferiority of effectiveness of Amulet over Control is demonstrated, a reflex test for superiority will be performed to determine if the Amulet device is superior to the Control device. The hypothesis is as follows:

$$H_0: p_2(\text{Amulet}) - p_2(\text{Control}) \geq 0$$

$$H_1: p_2(\text{Amulet}) - p_2(\text{Control}) < 0$$

The hypothesis will be tested at the 2.5% significance level. [redacted]

### 5.2.5 Superiority test of device closure rate at the 45-day visit

If non-inferiority of device closure endpoint of Amulet over control is demonstrated, a reflex test for superiority will be performed to determine if the Amulet device is superior to the Control device. The following hypothesis will be tested:

$$H_0: p_3(\text{Amulet}) - p_3(\text{Control}) \leq 0$$

$$H_1: p_3(\text{Amulet}) - p_3(\text{Control}) > 0$$

The hypothesis will be tested at the 2.5% significance level. [redacted]

## 5.3 Descriptive Endpoints

The following descriptive endpoints will be summarized by treatment group:

- **Technical success rate (refer to Appendix P in the CIP for definition)**

  The numerator for the event rate is the number of subjects who have technical success. The denominator is the number of subjects having undergone an "implant attempt".

- **Procedural success rate (refer to Appendix P in the CIP for definition)**

  The numerator for the event rate is the number of subjects who have technical success with no procedure-related complications except for uncomplicated (minor) device embolization. The denominator is the number of subjects having undergone an "implant attempt".

- **Device success rate (refer to Appendix P in the CIP for definition)**

  The numerator for the event rate is the number of subjects who have a successful implant. The denominator is the number of subjects having undergone an "implant attempt".

- **Number of subjects on oral anticoagulant at each follow-up visit**

  The count and proportion of subjects who are on oral anticoagulant at each follow-up visit will be summarized.

- **Procedure duration**

  The procedure duration will be summarized using descriptive statistics including mean, standard deviation, median, and range.

- **Procedural complications by operator**

  The count and proportion of subjects who have procedural complications will be summarized by operator.

- **Device thrombosis**

  The count and proportion of subjects who have device thrombosis will be summarized.

- **Transient ischemic attack (TIA)**

  The count and proportion of subjects who experience TIA will be summarized.

- **Hemorrhagic stroke**

  The count and proportion of subjects who experience hemorrhagic stroke will be summarized.

- **Systemic embolism**

  The count and proportion of subjects who have systemic embolism will be summarized.

- **All-cause mortality**

  The number of deaths will be summarized by frequencies and percentages at 12 months. Kaplan-Meier survival curves will be used to present deaths through longer term follow-up.

- **Cardiovascular mortality**

  The number of cardiovascular mortality will be summarized by frequencies and percentages at 12 months. Kaplan-Meier survival curves will be used to present deaths through longer term follow-up.

- **Major bleeding, by site and severity (defined as Type 3 or greater based on BARC definition)**

  The count and proportion of subjects who have major bleeding by site and severity will be summarized.

- **Minor bleeding, by site and severity (defined as Type 1 or 2 based on BARC definition)**

  The count and proportion of subjects who have minor bleeding by site and severity will be summarized.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

## 6.0 ADDITIONAL DATA

### 6.1 Baseline and Demographic Characteristics

Descriptive statistics of continuous variables with be presented by treatment group and include sample size, mean median, standard deviation, minimum and maximum. For categorical variables, the number and percentage of subjects in each category will be presented by treatment group. Baseline characteristics will be tabulated and compared between the two treatment groups. Categorical variables will be tested using Fisher's exact test and continuous variables will be tested using two sample t-test.

### 6.2 Mortality

The number of deaths will be summarized by frequencies and percentages by treatment group at 12 months. Kaplan-Meier survival curves will be used to present deaths through longer term follow-up.

### 6.3 Adverse Events

Adverse events, serious adverse events and unanticipated adverse device effects (UADE) will be summarized from the time of consent in terms of number of events, the percentage of subjects with events, and event rate estimated as # event/patient-years.

### 6.4 Withdrawal

Withdrawals will be summarized for subjects who have withdrawn from the trial and will include days to withdrawal and reason for withdrawal.

### 6.5 Protocol Deviation

Protocol deviations will be summarized for subjects in whom a protocol deviation was reported. There is no plan to deviate from this Statistical Analysis Plan. If any deviations from the original statistical plan occur, such deviations will be documented in the clinical study report or statistical report containing the analysis results.

[redacted]

## 7.0 Bibliography

[redacted]

15 Boersma LV, [redacted] Implant success and safety of left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION registry. *European heart journal* (2016); [redacted]

## APPENDIX [redacted]

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| Abbott | Study Document No: CLxx Ver. xx<br>Study Name: AMPLATZER™ Amulet™ Left Atrial Appendage Occluder Randomized Controlled Trial |
|---|---|
| **Statistical Analysis Plan** | |

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| Abbott | Study Document No: CLxx Ver. xx<br>Study Name: AMPLATZER™ Amulet™ Left Atrial Appendage Occluder Randomized Controlled Trial |
|---|---|
| **Statistical Analysis Plan** | |

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|---|---|
| **Statistical Analysis Plan** | |

[redacted]

| Abbott | Study Document No: CLxx Ver. xx<br>Study Name: AMPLATZER™ Amulet™ Left Atrial Appendage Occluder Randomized Controlled Trial |
|---|---|
| **Statistical Analysis Plan** | |

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|---|---|
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|---|---|
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|---|---|
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|---|---|
| **Statistical Analysis Plan** | |

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