Statistical Analysis Plan

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Trevisio PAS
Trevisio Post-Approval Study
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Sponsor

Abbott
5050 Nathan Lane N
Plymouth, MN 55442, USA
USA

[redacted]

Trevisio Post-Approval Study

A single-arm, non-randomized, multi-center clinical study of the Amplatzer™ Trevisio™ Intravascular Delivery System for facilitating percutaneous, transcatheter implantation of the Amplatzer™ Occluder Devices

Statistical Analysis Plan (SAP)

Version A

3/22/2021

Joshua Rapkin

Statistical Analysis Plan

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[redacted]

1.0 SYNOPSIS OF STUDY DESIGN

1.1 Purpose of the Statistical Analysis Plan

This statistical analysis plan (SAP) is to provide a detailed and comprehensive description of the planned methodology and analysis to be used for ABT-CIP_10319, the Trevisio PAS clinical investigation. This plan is based on the Version A, 03 June 2020 Clinical Investigation Plan.

1.2 Clinical Investigation Objectives

The primary objective of this clinical study is to characterize the safety and effectiveness of the Amplatzer Trevisio Delivery System for facilitating percutaneous, transcatheter implantation of the Amplatzer PFO Occluder, Amplatzer ASO, Amplatzer ASD-MF Occluder, Amplatzer Muscular VSD Occluder, and Amplatzer Post-Infarct Muscular VSD Occluder. The Amplatzer Trevisio Delivery System is CE-Marked and commercially available.

1.3 Clinical Investigation Design

This post-approval study (PAS) is a non-randomized, multi-center, single arm clinical study to evaluate the safety and effectiveness of the Amplatzer Trevisio Delivery System for facilitating percutaneous, transcatheter implantation of the Amplatzer PFO Occluder, Amplatzer ASO, Amplatzer ASD-MF Occluder, Amplatzer Muscular VSD Occluder, and Amplatzer Post-Infarct Muscular VSD Occluder.

[redacted] Subjects will be evaluated at baseline (pre-procedure), implant procedure, and prior to discharge or 7 days after the procedure, whichever occurs first. [redacted]

1.4 Endpoints

The study has a primary effectiveness endpoint, a primary safety endpoint, and a number of descriptive endpoints.

1.4.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is technical success, which is defined as successful deployment and release of at least one device.

[redacted]

1.4.2 Primary Safety Endpoint

The primary safety endpoint is device- or procedure-related serious adverse events through discharge or 7 days, whichever occurs first, including:

- Cardiac perforation
- Sustained atrial fibrillation requiring intervention
- Device thrombus
- Device erosion
- Device embolization
- Vascular complication requiring surgical intervention
- Device- or procedure related serious adverse event leading to death

1.4.3 Descriptive Endpoints

The study has several descriptive endpoints, which are as follows:

- The number of times the device is recaptured
- The number of times the device is repositioned
- Total fluoroscopy time
- Ease of use – investigators will be asked survey questions about their first experience with the Amplatzer Trevisio Delivery System.

1.5 Randomization

This study is a single-arm trial; therefore, there is no randomization implemented in the study.

1.6 Blinding

This study is a single-arm trial; therefore, there is no blinding procedure implemented in the study.

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

2.1.1 Attempted Procedure Population

[redacted]

2.1.2 Per-Protocol (PP) Population

[redacted]

2.2 Statistical Methods

2.2.1 Descriptive Statistics for Continuous Variables

For continuous variables, results will be summarized with the numbers of observations, means, and standard deviations and may include quartiles, minimums, maximums, and 95% confidence intervals for the means as needed.

2.2.2 Descriptive Statistics for Categorical Variables

For categorical variables, results will be summarized with subject counts and percentages/rates, and exact 95% Clopper-Pearson confidence intervals as needed.

2.3 Endpoint Analysis

2.3.1 Primary Effectiveness Endpoint Analysis

2.3.1.1 PFO and ASD Closure Groups

The performance goal for the primary effectiveness endpoint for the PFO and ASD closure groups is set at 95% [redacted]

Let π_1 be the proportion of subjects who experience successful deployment and release of at least one device.

The following hypothesis will be tested:

H_0: $\pi_1 \leq 95\%$
H_a: $\pi_1 > 95\%$

[redacted]

[redacted] The hypothesis will be tested at a one-sided significance level of 2.5% [redacted]

[redacted]

2.3.1.2 Muscular and Post-Infarct Muscular VSD Closure Groups

The performance goal for the primary effectiveness endpoint for the muscular VSD and post-infarct muscular VSD closure groups is set at 80% [redacted]

Let π_2 be the proportion of subjects who experience successful deployment and release of at least one device.

The following hypothesis will be tested:

H_0: $\pi_2 \leq 80\%$
H_a: $\pi_2 > 80\%$

[redacted]

[redacted]. The hypothesis will be tested at a one-sided significance level of 5% [redacted]

2.3.2 Primary Safety Endpoint

The primary safety endpoint is device- or procedure-related serious adverse events through discharge or 7 days, whichever is earlier, including:

- Cardiac perforation
- Sustained atrial fibrillation requiring intervention
- Device thrombus
- Device erosion
- Device embolization
- Vascular complication requiring surgical intervention
- Device- or procedure-related serious adverse event leading to death

2.3.2.1 PFO and ASD Closure Groups

A performance goal of 6% was chosen [redacted]

[redacted]

[redacted]

Let π_3 be the proportion of subjects who experience device- or procedure-related serious adverse events through discharge or 7 days.

The following hypothesis will be tested:

H_0: $\pi_3 \geq 6\%$
H_a: $\pi_3 < 6\%$

[redacted]

[redacted] The hypothesis will be tested at a one-sided significance level of 2.5% [redacted]

2.3.2.2 Muscular and Post-Infarct Muscular VSD Closure Groups

There is no formal statistical hypothesis for the primary safety endpoint for the VSD closure groups. The primary safety endpoint will be reported descriptively in the VSD closure groups.

2.3.3 Descriptive Endpoints

Descriptive endpoints include:

- The number of times the device is recaptured
- The number of times the device is repositioned
- Ease of use – physicians will be asked survey questions about their experience with the Amplatzer Trevisio Delivery System compared to other device delivery systems
- Total fluoroscopy time

The descriptive endpoints will be analyzed in the AP population. For each descriptive endpoint, data will be presented using appropriate summary statistics. Continuous data will be summarized using descriptive statistics including mean, standard deviation, median and range. Categorical data will be summarized by the frequencies and percentages. Percentages will be based on the number of subjects in the analysis population as described in Section 2.2.

2.4 Sample Size Calculations

[redacted]

2.4.1 PFO and ASD Closure Groups

[redacted]

[redacted]

[redacted]

The sample size of 215 PFO and ASD closure subjects is therefore based on the primary safety endpoint.

2.4.2 Muscular and Post-Infarct Muscular VSD Closure Groups

[redacted]

The sample size of 44 VSD closure subjects is based on the primary effectiveness endpoint.

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 study reports with descriptive analysis may be produced for regulatory or reimbursement purposes.

2.6 Timing of Analysis

[redacted] The analyses will be completed for each cohort as the data for each cohort become available.

2.7 Study/Trial Success

[redacted]

2.8 Subgroups for Analysis

Subgroups analysis will be performed on the primary safety and effectiveness endpoints of the trial in the PFO and ASD closure group. The subgroups will include, but are not limited to sex, age [redacted] and PFO vs. ASD closure. [redacted] The test for the subgroup effect will be performed at the 0.05 level of significance.

Baseline characteristics, demographics, primary endpoints and clinical outcomes may be analyzed separately for each of the defect closure groups (i.e., PFO and ASD closure; muscular VSD and post-infarct muscular VSD closure).

[redacted]

2.9 Handling of Missing Data

All analyses will be based on available data with missing data excluded unless otherwise specified in the analysis population for each endpoint.

2.10 Poolability Issue

[redacted]

2.11 Multiplicity Issues

[redacted] there is no need for multiplicity adjustment in this trial.

2.12 Adjustments for Covariates

Unless otherwise specified, no adjustments for covariates will be made for any of the variables in the analyses.

3.0 DESCRIPTIVE ENDPOINTS AND ADDITIONAL DATA

3.1 Baseline and Demographic Characteristics

The baseline and demographic variables will be summarized for the subjects in the analysis population: sex, age, ethnicity, race, medical history, implant procedural characteristics, etc. The baseline and demographic variables will be analyzed separately PFO and ASD closure group and the muscular VSD and post-infarct muscular VSD group.

3.2 Adverse Events

All of the serious adverse events and device- and/or procedure-related adverse events will be summarized for all subjects in the analysis population in terms of the number of events and the percentage of subjects with events by the type of adverse event. The seriousness and relatedness to device/procedure of the adverse event will be determined by the investigator. In addition, adverse events related to COVID-19 will be summarized in a separate table in terms of the number of COVID-19 related adverse events events and the percentage of subjects with events by the type of adverse event.

[redacted]

3.3 Subject Early Termination

Subject early termination reasons including deaths, withdrawals, and lost-to-follow-up and will be summarized from the time the subject signs consent until they exit the study.

3.4 Protocol Deviation

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

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
ASD	Atrial Septal Defect
ASD-MF	Atrial Septal Defect - Multi-fenestrated
ASO	Atrial Septal Occluder
CIP	Clinical Investigation Plan
PAS	Post Approval Study
PFO	Patent Foramen Ovale
VSD	Ventricular Septal Defect
SAP	Statistical Analysis Plan