VPA "Closure of Muscular Ventricular Septal Defects with the AMPLATZER™ Muscular VSD Occluder Post-Approval Study"

(NCT Number: NCT00647387)

Statistical Analysis Plan (SAP)

Contents

1.0 INTRODUCTION

This document is a statistical analysis plan for the VPA "Closure of Muscular Ventricular Septal Defects with the AMPLATZER™ Muscular VSD Occluder Post-Approval Study" trial ([redacted]).

2.0 TRIAL OBJECTIVES

The primary safety objective is to evaluate the proportion of subjects experiencing a serious adverse event within 12 months of the procedure.

The effectiveness objective is to evaluate the proportion of subjects who experience technical success, acute procedure success, and shunt closure success.

3.0 TRIAL DESIGN

This is a prospective, non-randomized, multi-site clinical trial designed to evaluate the safety and effectiveness of the AMPLATZER Muscular VSD Occluder. The primary safety and effectiveness endpoints of this trial are intended to be evaluated against the corresponding endpoints of the High Risk Cohort of the Muscular VSD trial.

This study will enroll a maximum of 100 subjects at a maximum of 50 sites in the United States and additional sites in Europe and Canada. Each study subject receiving a device will be followed for 60 months post-procedure, unless the device is explanted. If subject follow-up drops below 80%, additional subjects will be enrolled to ensure a final population of 80 subjects either meet a defined endpoint or will be followed for five years.

A subject is considered enrolled in the trial after he/she has provided informed consent, meets all inclusion criteria, meets no exclusion criteria, and the delivery system enters the subject's body in an attempt to implant the AMPLATZER Muscular VSD Occluder (Implant Attempt). A subject could be enrolled in the trial prospectively or retrospectively (refer to CIP Section I.H).

4.0 TRIAL ENDPOINTS

4.1 Primary Safety Endpoint

The primary safety endpoint is the proportion of subjects experiencing a serious adverse event (SAE) within 12 months of the procedure.

4.2 Primary Effectiveness Endpoints

There are three primary effectiveness endpoints including technical success, acute procedure success, and shunt closure success.

4.2.1 Primary Effectiveness Endpoint 1: Technical Success

Primary effectiveness endpoint 1 is the proportion of subjects who have technical success. Technical success is defined as a device is successfully deployed in the ventricular septal defect.

4.2.2 Primary Effectiveness Endpoint 2: Acute Procedure Success

Primary effectiveness endpoint 2 is the proportion of subjects who have acute procedure success. Acute procedure success is defined as a defect with ≤ two millimeters residual shunt at the time of the post procedure evaluation.

4.2.3 Primary Effectiveness Endpoint 3: Shunt Closure Success

Primary effectiveness endpoint 3 is the proportion of subjects who have shunt closure success. Shunt closure success is defined as a defect with ≤ two millimeters residual shunt at the one-year follow-up visit.

4.3 Descriptive Endpoints

The trial has a number of descriptive endpoints. See Sections 5.2 for a full listing.

5.0 STATISTICAL METHODS

5.1 Primary Endpoints

This trial has one primary safety endpoint and three primary effectiveness endpoints.

5.1.1 Primary Safety Endpoint

The primary safety endpoint is the proportion of subjects experiencing a serious adverse event (SAE) within 12 months of the procedure.

5.1.1.1 Hypothesis

Let π_{SAE} be the probability of subjects experiencing a serious adverse event within 12 months of the procedure. In the high risk cohort of the muscular VSD trial, [redacted] in the intent-to-treat population experienced a serious adverse event. Since the subject selection criteria will be similar to that used in the High Risk Cohort of the Muscular VSD Occluder trial, π_{SAE} will be compared against the observed major adverse event rate from the High Risk Cohort with a margin of [redacted].

The following hypothesis will be tested:

$$H_0: \pi_{SAE} \geq 63.2\%$$

$$H_a: \pi_{SAE} < 63.2\%$$

5.1.1.2 Analysis Method

The probability of π_{SAE} will be estimated as a [redacted]. The hypothesis will be tested at the [redacted] significance level. [redacted].

5.1.1.3 Sample Size

The primary safety endpoint event rate within 12 months of [redacted].

5.1.1.4 Analysis Population

The analysis of the primary safety endpoint will [redacted].

5.1.1.5 Sensitivity Analysis

[redacted]

5.1.2 Primary Effectiveness Endpoints

5.1.2.1 Primary Effectiveness Endpoint 1: Technical Success

Primary effectiveness endpoint 1 is the proportion of subjects who have technical success. Technical success is defined as a device is successfully deployed in the ventricular septal defect.

Hypothesis

Let π_{Tech} be the probability of subjects who have technical success. [redacted] the technical success rate π_{Tech} will be compared against the observed technical success rate [redacted].

The following hypothesis will be tested:

$$H_0: \pi_{Tech} \leq 64.0\%$$

$$H_a: \pi_{Tech} > 64.0\%$$

Analysis Method

The probability of π_{Tech} will be estimated [redacted]. The hypothesis will be tested at the [redacted] significance level. The null hypothesis will be rejected [redacted].

Sample Size

[redacted]

Analysis Population

The analysis of the technical success effectiveness endpoint will include all prospectively enrolled subjects who have an attempted device placement (defined as the delivery system enters the subject's body in an attempt to place a device).

5.1.2.2 Primary Effectiveness Endpoint 2: Acute Procedure Success

Primary effectiveness endpoint 2 is the proportion of subjects who have acute procedure success. Acute procedure success is defined as a defect with ≤ two millimeters residual shunt at the time of the post procedure evaluation.

Hypothesis

Let π_{Acute} be the probability of subjects who have acute procedure success. [redacted] the acute procedure success rate π_{Acute} will be compared against [redacted].

The following hypothesis will be tested:

$$H_0: \pi_{Acute} \leq 61.3\%$$

$$H_a: \pi_{Acute} > 61.3\%$$

Analysis Method

The probability of π_{Acute} will be estimated [redacted].

Sample Size

The acute procedure success rate is assumed to be [redacted].

Analysis Population

The analysis of the acute procedure success effectiveness endpoint will [redacted].

5.1.2.3 Primary Effectiveness Endpoint 3: Shunt Closure Success

Primary effectiveness endpoint 3 is the proportion of subjects who have shunt closure success. Shunt closure success is defined as a defect with ≤ two millimeters residual shunt at the one-year follow-up visit.

Hypothesis

Let π_{Close} be the probability of subjects who have shunt closure success. [redacted] the shunt closure success rate π_{Close} will be compared against the shunt closure success rate [redacted].

The following hypothesis will be tested:

$$H_0: \pi_{Close} \leq 58.7\%$$

$$H_a: \pi_{Close} > 58.7\%$$

Analysis Method

The probability of π_{Close} will be estimated [redacted]

Sample Size

[redacted]

Analysis Population

The analysis of the shunt closure success effectiveness endpoint will include [redacted]

Sensitivity Analysis

A sensitivity analysis will be carried out to include [redacted]

5.2 Descriptive Endpoints

The following descriptive safety endpoints will be summarized using descriptive statistics:

- All unadjudicated events

- All adjudicated events
- Serious (Major) adverse events
- Device related events
- Procedure related events
- Events unrelated to the device or the procedure
- Deaths

All variables will be summarized by frequency and percentage. This analysis will include all enrolled subjects.

The following descriptive non-safety endpoints will be summarized using descriptive statistics:

- Procedure duration
- Fluoroscopy duration
- Size of defect
- Access site
- Medication taken at the time of procedure
- Anesthesia type
- Number of VSDs
- VSD location

Continuous variables will be summarized by mean, standard deviation, minimum, and maximum. Categorical variables will be summarized by frequency and percentage. Missing data will be omitted.

5.3 Overall Sample Size

The total sample size required for evaluation of the primary safety endpoint and primary effectiveness endpoints is 80 subjects. In order to ensure 80 subjects to have either an endpoint or 12-month follow-up, 100 subjects will be enrolled. Additional subjects will be enrolled as necessary to attain 80 subjects for the primary safety endpoint analysis.

5.4 Timing of Analysis

The analyses for the final report will be conducted on a dataset locked after all enrolled subject have had the 60-month follow-up visit (excepting deaths, withdrawals and loss-to-follow-up before 60 months) or crossed the 60-moth visit window without a visit (missed visit).

6.0 ADDITIONAL DATA

6.1 Demographic and Baseline Characteristics

The demographic baseline variables to be summarized include, but are not limited to:

- Age
- Gender

- Medical history
  - Recurrent respiratory infections
  - Contraindication to aspirin
  - Contraindication to anti-platelets
  - Previous thromboembolic stroke
  - Failure to thrive
  - Cyanosis
  - Pulmonary hypertension
  - Irreversible pulmonary vascular disease
  - Previous cardiac surgery
- Active bacterial infection
- Clinical symptoms of congestive heart failure
- Sepsis

Age will be summarized by mean, standard deviation, minimum, and maximum. Other variables will be summarized by frequency and percentage. Missing data will be omitted.

6.2 Procedural Data

The procedural variables to be summarized include but are not limited to:

- Procedure Time
- Fluoroscopy time
- Size of defect
- Access site
- Medication taken at procedure
- Anesthesia type
- Number of VSDs
- VSD Location

Descriptive statistics of continuous variables will be summarized using mean, standard deviation, minimum and maximum. For categorical variables, the frequency and percentage of subjects in each category will be summarized.

6.3 Mortality

The number of deaths will be summarized.

6.4 Adverse Events

Adverse events, serious adverse events and unanticipated adverse device effects (UADE) will be summarized in terms of number of events, the percentage of subjects with events.

6.5 Withdrawal

Withdrawals will be summarized for subjects who have withdrawn from the trial.

6.6 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 such a deviation occurs, such deviations will be documented in the clinical study report or statistical report containing the analysis results.