Statistical Analysis Plan

17-518
MitraClip® EXPAND Study
A Contemporary, Prospective Study Evaluating Real-world Experience of Performance and Safety for the Next Generation of MitraClip® Devices

Statistical Analysis Plan (SAP)

Version A

July 9th, 2020

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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 Clinical Investigation Plan (CIP) ABT-CIP-10236, the MitraClip EXPAND study. This plan is based on the [redacted].

1.2 Clinical Investigation Objectives

The primary objective is to confirm the safety and performance of the next generation MitraClip® NTR and MitraClip® XTR Systems within a contemporary real-world setting.

1.3 Clinical Investigation Design

This is a Prospective, Multi-Center, Single-Arm, International, Post Market, Observational Study designed to collect real-world data on the use of the next generation MitraClip NTR and MitraClip XTR Systems. Up to 1,000 commercial subjects from the EU or US will be included in the analysis for the MitraClip EXPAND Study. Follow-up echocardiograms will be collected at 30 days and 12 months post-procedure visits with an additional clinical follow-up visit or phone call at 6 months.

The study will group subjects into cohorts for analysis based upon select pre-defined mitral valve anatomic criteria. This approach is supported by recent literature that shows an evolution of the use of MitraClip in which a significant percentage of cases presented in post-market studies differ in patient selection from the cases included in early clinical studies (i.e. EVEREST, EVEREST II). The analysis of these cohorts will allow for the evaluation of outcomes and identification of trends in patient selection and outcomes in contemporary real-world use in the context of historical MitraClip data.

1.4 Endpoints

1.4.1 Safety and Performance Measures

- Safety
  The assessment of safety will include all occurrences through 30 days post procedure.

  Occurrence of Major Adverse Events (MAE) at 30 days

  MAE is defined as a composite of all-cause Death, Myocardial Infarction, Stroke, or non-elective Cardiovascular (CV) surgery for device related complications (CEC adjudicated).

- Performance
  The assessment of performance measures will include all data reported at 30-day visits for this study.

  MR Reduction to ≤2+ at 30 days

1.4.2 Acute Measures

- Acute Procedural Success (APS) defined as successful implantation of the MitraClip® device with resulting MR severity of 2+ or less on discharge Echocardiogram (30-day echocardiogram will be used if

discharge is unavailable or uninterpretable). Subjects who die or undergo mitral valve surgery before discharge are considered to be an APS failure

- Acute Device Success defined as successful implant of the MitraClip device without the occurrence of a Device-Related Complication (including mitral valve stenosis, device embolization, Single Leaflet Device Attachment (SLDA), Iatrogenic atrial septal defect, or myocardial perforation) through discharge.
- Use of MitraClip NTR or MitraClip XTR: to include the percentage of cases with each device and an assessment of reason for device selection
- Procedure Time: defined as the time elapsed from the first intravascular catheter placement or trans-esophageal echocardiogram (TEE) to the removal of the last catheter and TEE
- Number of Clips Implanted
- Number of Attempted Grasps defined as the number of attempts to stabilize leaflets by the open Clip
- User feedback
- Device-Related Complications defined as the occurrence of one the following adverse events that is determined by investigator assessment to be probably, possibly or definitely related to the MitraClip device.
  – Mitral valve stenosis
  – SLDA
  – Device Embolization
  – Iatrogenic atrial septal defect
  – Myocardial perforation
  – Need for mitral valve replacement instead of repair due at least in part to the MitraClip procedure or the presence of the MitraClip device
- In-hospital MAE defined as the number of MAEs that occur prior to discharge from hospitalization in which MitraClip Procedure was performed
- MR Reduction to ≤1+ at 30 days

1.4.3 Clinical Measures (Discharge, 30-day, 6-month and 12-month):

- All-cause Mortality
- Heart Failure Hospitalization
- MAE
- Device-Related Complications

1.4.4 Functional Improvement Measures (Baseline, Discharge and 12-month)

- New York Heart Association (NYHA) functional class improvement
- Quality of Life (QOL) assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ)

1.4.5 Site Reported Echocardiographic Measures (Baseline, Post Procedure, 30-day and 12- month)

- MR Severity Grade
- Effective Regurgitant Orifice Area (EROA) as measured by measured by PISA method
- Coaptation Measures (depth/length)
- Flail Measures (gap/width)
- Grasping Area Anatomy (measure cleft or scallop if significant)
- Assess chordal support
- Regurgitant Jet(s) Position and Quantity
- TR Severity: None, Mild, Moderate or Severe

1.4.6 **Echocardiographic Measures from echo core lab (Baseline, Post Procedure, 30-day and 12- month)**

- MR Severity Grade
- Effective Regurgitant Orifice Area (EROA) as measured by measured by PISA method
- Coaptation Measures (depth/length)
- Flail Measures (gap/width)
- Grasping Area Anatomy (measure cleft or scallop if significant)
- Assess chordal support
- Regurgitant Jet(s) Position and Quantity
- TR Severity: None, Mild, Moderate or Severe

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

2.1.1 Analysis Population

[redacted]

2.2 Statistical Methods

2.2.1 Descriptive Analyses

Descriptive analysis will be performed to summarize baseline characteristics, acute measures, functional improvement, echocardiographic, clinical measurements, safety and performance measurements. Depending on the type of data (e.g., continuous or categorical), statistical methods described in the following sections will be used.

2.2.1.1 Descriptive Statistics for Continuous Variables

For continuous variables (e.g., age, etc.), results will be summarized as number of observations, means, and standard deviations, and where applicable, with quartiles, minimums, maximums, and 95% confidence intervals for the means. Differences between two groups, where specified, will be summarized with differences of the two means, and 95% confidence intervals for the difference between the means.

A two-sample t-test or Wilcoxon rank sum test, depends on the normality of the data, will be used to test the difference between subgroups. A paired t-test or Wilcoxon sign test will be used to test the difference of measurements between baseline and follow-ups.

2.2.1.2 Descriptive Statistics for Categorical Variables

For binary variables (e.g. gender, APS, etc.), results will be summarized with subject counts and percentages/rates, and where applicable, with exact 95% Clopper-Pearson[1] confidence intervals. Differences between the two groups, when specified, will be summarized with the difference in percent and the Newcombe[2] score 95% confidence interval for the difference of two percentages.

For endpoints of interest, relative risks (i.e., the ratio of rates), confidence interval for the relative risks, the difference in rates and the confidence interval for difference in rates, and p-values may also be presented for hypothesis generating purposes. [redacted]

[redacted]

2.2.2 Survival Analyses

Survival analysis will be conducted to analyze time-to-event variables. Subjects without events will be censored at their last known event-free time point. Subjects who withdrew from the study will be censored at the date of withdrawal. Survival curves will be constructed using Kaplan-Meier[4] estimates. Summary tables for events of interest will include event (failure) rates, Greenwood standard error and confidence interval for the event rates.

2.2.3 Logistic Regression

For the univariate analyses, coefficients, Wald's chi-square p-values, odds ratios, and 95% confidence intervals for the odds ratios will be displayed. Note that for variables created from subsets of subjects, only variables with at least 10 subjects in the given subset will be included in this analysis.

[redacted]

[redacted]

[redacted]

2.3 Endpoints Analyses

Study endpoints defined in section 1.4 will be summarized descriptively using methods described in Section 2.2.Sample

2.4 Size Calculations

A sample size of 1000 subjects is expected to adequately capture data on a wide range of subjects with primary or secondary MR, subjects with or without complex valve anatomy, and subjects from Europe and the United States.

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. Descriptive analysis based on accumulated data may be produced for publication and presentation purposes.

[redacted]

2.6 Timing of Analysis

The analysis will be performed after database lock per analysis population who complete their 1-year follow-up visits or terminated from study before their 1-year follow-up visits.

2.7 Subgroups for Analysis

The following subgroup analyses are to provide understanding and evaluation of the safety and performance of MitraClip treatment in a various patient populations, for exploratory purpose and the supports of publication and presentation.

[redacted]

[redacted]

2.8 Handling of Missing Data

All analyses will be based on available data. Missing data will not be imputed. Any unused or spurious data will be documented as appropriate in the clinical report. For APS endpoint, a 30-day echocardiogram will be used if discharge is unavailable or uninterpretable.

2.9 Multiplicity Issues

There are no multiplicity issues since we did not have hypothesis testing.

3.0 DESCRIPTIVE ENDPOINTS AND ADDITIONAL DATA

The following analises will be conducted based on analysis population define in 2.1.1

3.1 Baseline and Demographic Characteristics

The following baseline and demographic variables will be summarized: gender, age, height, weight, baseline risk factors, medical history, echocardiogram, implant procedural characteristics, device usage, quality of life and functional status, etc.

3.2 Adverse Events

All of the adverse events (AEs), serious adverse events (SAEs), adverse device effects (ADEs) and serious adverse device effects (SADEs) will be summarized using number of events, the percentage of subjects with events, and event rates per MedDRA coding.

All CEC adjudicated adverse events up to 30 days post index procedure will also be summarized using number of events, the percentage of subjects with events, and event rates.

3.3 Subject Early Termination

Subject early termination reasons including deaths, withdrawals, lost-to-follow-up, etc. will be summarized at all scheduled visits.

[redacted]

3.4 Protocol Deviation

Protocol deviations will be summarized by category for subjects in whom a protocol deviation was reported. Number of protocol deviations and number of subjects with deviation will be summarized by deviation categories.

3.5 Descriptive Endpoints or Additional Data

COVID-19 assessment will be listed.

4.0 DOCUMENTATION AND OHER CONSIDERATIONS

All analyses will be performed using SAS® for Windows, version 9.3 or higher.

5.0 ACRONYMS AND ABBREVIATIONS

Acronym or Abbreviation	Complete Phrase or Definition
AE	Adverse Event
APS	Acute Procedural Success
CEC	Clinical Events Committee
CI	Confidence Interval
CIP	Clinical Investigation Plan
DMR	Degenerative Mitral Regurgitation
FMR	Functional Mitral Regurgitation
KCCQ	Kansas City Cardiomyopathy Questionnaire
IP	Implanted Population
MAE	Major Adverse Event
MitraClip NTR	MitraClip NTR System (new delivery system)
MitraClip XTR	MitraClip XTR System (new delivery system and longer clip arms)
MR	MR Mitral Regurgitation
N	Sample Size
NYHA	NYHA New York Heart Association
QOL	Quality of Life
SAE	Serious Adverse Event
SAP	Statically Analysis Plan
SLDA	Single leaflet device attachment
TEE	Transcatheter Esophageal Echocardiogram

6.0 REFERENCES

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