Statistical Analysis Plan

AVJ 17-519

MitraClip NT System Post-marketing Surveillance

Statistical Analysis Plan (SAP)

Version A
CL1004808

25 June 2018

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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 to provide a detailed and comprehensive description of the planned methodology and analysis to be used for the AVJ 17-519 MitraClip NT System Post-marketing Surveillance (PMS) clinical investigation. This SAP is based on the Version 1.0, Jan 04, 2018 Clinical Investigation Plan (CIP).

1.2 Clinical Investigation Objectives

The purpose of this post-marketing clinical use surveillance (hereinafter referred to as "Surveillance") is to observe the frequency, type and degree of adverse device effects and adverse events in order to assure the safety of the new medical device, and to collect safety and efficacy information for evaluating the results of the clinical use.

1.3 Clinical Investigation Design

AVJ 17-519 is a prospective, multi-center, single-arm surveillance study of patients with moderate to severe and severe mitral regurgitation (3+ and 4+ MR) in whom a MitraClip implant was attempted (Marketing Approval No. 22900BZX00358000, October 31, 2017, hereinafter referred to as "MitraClip"). Information will be collected for up to 3 years post procedure.

- Approximate preparation period: 6 months
- Registration period: Approximately 2 years
- Follow-up period: 3 years
- Final re-examination report: 6 months
- Total PMS period: Approximately 6 years

1.4 Endpoints

1.4.1 Primary Endpoint(s)

The primary endpoints of this study are: a) the rate of single leaflet device attachment (SLDA) at 30 days; and b) acute procedural success (APS) assessed at discharge. The SLDA rate will be calculated based on site reported observations. APS is defined as successful implantation of the MitraClip device with resulting MR reduction to ≤ 2+ per echocardiographic assessment. If echocardiographic data at discharge is not available or unevaluable, echocardiographic data at 30 days will be used for evaluation. APS will not be achieved if a patient expired or received mitral valve surgery before discharge. Achievement of MR reduction to ≤ 2+ as result of additional MitraClip implantation during index procedure will be considered as an APS.

1.4.2 Other Endpoint(s)

Other endpoints will be evaluated at the specific follow-up time points may include, but not limited to, mitral regurgitation severity, New York Heart Association (NYHA) class, LV function and anatomy, cardiac medication, adverse events and device deficiency. Rate of heart failure hospitalizations in the 1-year post-procedure will be compared to the 1 year period prior to the index procedure.

1.4.3 Exploratory Endpoint(s)

The primary endpoints will be compared between the first 250 registered patients to the second 250 registered patients (or a 2-year registration period, whichever comes first), in order to evaluate the learning curve of the MitraClip procedure.

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

2.1.1 Intent-to-Treat Population (ITT)

All patients registered in the surveillance with MitraClip treatment attempted will be included.

2.2 Statistical Methods

Descriptive analysis will be performed to summarize baseline, procedural, clinical and safety event data. Depending on the type of data (e.g., continuous or categorical), statistical methods described in the section below will be used.

2.2.1 Descriptive Statistics for Continuous Variables

For continuous variables, such as age, 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 the two groups, where specified, will be summarized with the differences of the two means, and 95% confidence intervals for the difference between the means.

2.2.2 Descriptive Statistics for Categorical Variables

For binary variables (e.g. SLDA rate, gender, diabetic status, etc.), results will be summarized with patient counts and percentages/rates, and where applicable, with exact 95% Clopper-Pearson confidence intervals. Differences between the two groups, when specified, will be summarized with the difference in percent and the Newcombe[3] score 95% confidence interval for the difference of two percentages.

2.2.3 Survival Analyses

Survival analysis will be conducted using the Kaplan-Meier method. Patients without events will be censored at their last known event-free time point. Patients who withdraw will be censored at the date of withdrawal. Survival curves will be constructed using Kaplan-Meier estimates. Summary tables for endpoints will include event (failure) rates, Greenwood standard error and confidence interval for the event rates.

2.2.4 Recurrent Event Analysis

For recurrent event data such as recurrent heart failure hospitalization at 1-year pre- and 1-year post index procedure, data will be analyzed using a generalized estimating equation model (GEE), such as Poisson regression model.

To fit the GEE model, the input dataset will be prepared to include total hospital count and total follow-up time (in days) pre- and post-index procedure for each patient along with the indicator for the time cutoff. Summary tables for recurrent event endpoints will include number of patients with recurrent event, total number of events, event rate per patient-year, and confidence interval for the event rate.

2.3 Endpoint Analysis

2.3.1 Primary Endpoint(s)

The primary analysis population is the Intent-to-treat (ITT) population. The primary endpoints of SLDA rate at 30 days and APS at discharge will be summarized with patient counts and percentages/rates, and exact 95% Clopper-Pearson confidence intervals as described in Section 2.2. Registered patients who do not have MitraClip procedure attempted will be excluded from the ITT population.

2.3.2 Other Endpoints

The analyses for the other endpoints will be performed using the methods described in Section 2.2 for the ITT population.

2.4 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.

2.5 Timing of Analysis

Analyses for the primary endpoints will be performed when the last registered patient completes 30-day follow-up. Annual progress reports (up to 3 years) will be submitted to the regulatory authority at each time point accordingly.

Data will be collected at the following time points:

- Baseline (pre-procedure)
- Procedure
- Discharge
- 30 days （30 days+14 days）(by visit)
- 1 year （365 days±28 days）(by visit)
- 2 years （730 days±28 days） (by visit)

- 3 years （1095 days±28 days）(by visit)

2.6 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 final report. For the primary endpoint of APS, a 30-day echocardiogram will be used if discharge echocardiogram is unavailable or uninterpretable.

2.7 Subgroups for Analysis

Subgroup analysis may be performed as required to evaluate the safety and efficacy of MitraClip.

2.8 Poolability Analysis

Poolability analysis will be performed as required to evaluate the primary endpoints of MitraClip across different sites. Center effect on the primary endpoint may be investigated based on Fisher's exact test. For the analysis of center effect, data from smaller sites may be combined for the analysis. If there is evidence of inconsistency in the primary endpoints across sites, patient's demographics, baseline clinical and echocardiogram characteristics may be examined.

2.9 Adjustments for Covariates

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

2.10 Exploratory Analysis

The safety and efficacy outcomes in the first 250 registered patients will be compared to that of the second 250 registered patients (or end of the 2-year enrollment period, whichever occurs first) to evaluate the learning curve of the MitraClip procedure. The analyses will be performed using the methods described in Section 2.2 for the ITT population.

3.0 DESCRIPTIVE ENDPOINTS AND ADDITIONAL DATA

3.1 Baseline and Demographic Characteristics

The following baseline and demographic variables will be summarized for the ITT population: gender, age, height, weight, etiology of mitral regurgitation (MR), Society of Thoracic Surgeons (STS) score, prior HF hospitalization within 1 year, NYHA functional class, cardiac disease history, arrhythmia history, history of smoking, prior history

of cerebrovascular accident (CVA), prior history of transient ischemic attack (TIA), hypertension, dyslipidemia, diabetes, prior history of percutaneous coronary intervention (PCI), prior aortic valve (AV) intervention, history of prior myocardial infarction, history of renal failure, history of chronic lung disease, history of peripheral arterial disease, history of prior major bleeding, history of cirrhosis, history of cancer, use of cardiac resynchronization therapy/device (CRT/CRT-D), implant procedural characteristics, HF medications, and echocardiogram characteristics.

3.2 Adverse Events

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

3.3 Patient Early Termination

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

4.0 DOCUMENTATION AND OHER CONSIDERATIONS

All analyses will be performed using SAS® for Windows, version 9.2 or higher or R software.

5.0 ACRONYMS AND ABBREVIATIONS

Acronym or Abbreviation	Complete Phrase or Definition
APS	Acute procedure success
AV	Aortic valve
CIP	Clinical Investigation Plan
CRF	case report form
CABG	Coronary artery bypass grafting
CRT/CRT-D	Cardiac resynchronization therapy/device
CVA	Cerebrovascular accident
DMR	Degenerative mitral regurgitation
FMR	Functional mitral regurgitation
GEE	Generalized estimating equation
HF	Heart Failure

Acronym or Abbreviation	Complete Phrase or Definition
ITT	Intent-to-treat
MHLW	Minister of Health, Labour and Welfare
MR	Mitral regurgitation
NYHA	New York Heart Association
PCI	Percutaneous coronary intervention
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statically analysis plan
SLDA	Single leaflet device attachment
STS	Society of Thoracic Surgeons
TIA	Transient ischemic attack

6.0 REFERENCES

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