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MitraClip China Post-Market Study (PMS)
Study Document Name: MitraClip China PMS Statistical Analysis Plan
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[redacted]

MitraClip China PMS

A Prospective, Multi-Center, Single-Arm Clinical Evaluation of the MitraClip System for the Treatment of Symptomatic Chronic Severe Mitral Regurgitation

NCT Number: NCT04259411

Statistical Analysis Plan (SAP)

[redacted]

[redacted]

Statistical Analysis Plan

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Statistical Analysis Plan

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) [redacted], the MitraClip China post market study clinical investigation. This plan is based on [redacted] of the Clinical Investigation Plan.

1.2 Clinical Investigation Objectives

To confirm the evidence of safety and efficacy of MitraClip System in Chinese symptomatic MR subjects with a post market setting.

1.3 Clinical Investigation Design

The MitraClip China PMS is a prospective, multi-center, single-arm, post market study designed to collect data on use of the MitraClip System in Chinese subjects. A minimum of 50 subjects and a maximum of approximately 100 will be registered up to 10 sites in the MitraClip China PMS. Follow-up of subjects registered in the MitraClip China PMS will occur at discharge, 30 days and 1 year. [redacted]

1.4 Endpoints

1.4.1 Primary Endpoint(s)

Two primary endpoints are designed for the MitraClip China PMS.

- Acute procedural success (APS). APS is defined as successful implantation of the MitraClip device(s) with resulting MR severity of 2+ or less as determined by the ECL assessment of a discharge echocardiogram (30-day echocardiogram will be used if discharge echocardiogram is unavailable or uninterpretable). Patients who die or who undergo mitral valve surgery before discharge are an APS failure.
- Freedom from major adverse event (MAE) at 30 days. MAE is a composite of death, stroke, MI, renal failure, and non-elective cardiovascular surgery for device or procedure related adverse events occurring after the femoral vein puncture for transseptal access.

1.4.2 Descriptive Endpoint(s)

Clinical Endpoints

The following descriptive clinical endpoints will be assessed at all scheduled office visits:

- All-cause mortality
- Freedom from the components of MAE
- NYHA Functional Class
- Kansas City Cardiomyopathy Questionnaire (KCCQ) Quality of Life (QoL) scores
- Six Minute Walk Test (6MWT) distance
- Mitral valve surgery (including type of surgery), including reason for intervention
- Additional MitraClip System intervention, including reason for intervention
- Number of hospitalizations and reason for hospitalization (i.e., heart failure, cardiovascular, non-cardiovascular)

- Device-related complications: defined as a composite of single leaflet device attachment (SLDA), device embolization, clinically significant iatrogenic septal defect or mitral stenosis that requires intervention
- Major bleeding

Device and Procedure-Related Endpoints

- Total Procedure Time: defined as the time elapsed from the first of any of the following: intravascular catheter placement, anesthesia or sedation, or transesophageal echocardiogram (TEE), to the removal of the last catheter and TEE
- Device Procedure Time: Defined as the time elapsed from the start of the transseptal procedure to the time the Steerable Guide Catheter is removed
- Device Time: Defined as the time the Steerable Guide Catheter is placed in the intra-atrial septum until the time the MitraClip Delivery System is retracted into the Steerable Guide Catheter
- Fluoroscopy Time: defined as the total minutes of exposure to fluoroscopy during the MitraClip procedure
- Length of stay in Intensive Care Unit/Critical Care Unit/Post-Anesthesia Care Unit (ICU/CCU/PACU)
- Length of hospital stay for index MitraClip procedure

Echocardiographic Endpoints

The following descriptive echocardiographic endpoints will be assessed at all scheduled office visits.

- MR Severity Grade
- Effective Regurgitant Orifice Area
- Regurgitant Volume (RV)
- Regurgitant Fraction (RF)
- Left Ventricular End Diastolic Volume (LVEDV)
- Left Ventricular End Systolic Volume (LVESV)
- Left Ventricular End Diastolic Dimension (LVEDD)
- Left Ventricular End Systolic Dimension (LVESD)
- Left Ventricular Ejection Fraction (LVEF)
- Right Ventricular Systolic Pressure (RVSP)
- Mitral Valve Area (MVA)
- Mean Mitral Valve Pressure Gradient (MVG)
- Systolic Anterior Motion of the mitral valve (present or absent)
- Forward Stroke Volume (FSV)
- Cardiac Output (CO)
- Cardiac Index (CI)

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

2.1.1 Attempted Procedure Population (AP)

[redacted]

2.1.2 Implanted Population (IP)

[redacted]

2.2 Statistical Methods

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

2.2.1 Descriptive Statistics for Continuous Variables

For continuous variables (e.g., age, etc.), results within treatment arm will be summarized with the numbers of observations, means, and standard deviations, with 95% confidence intervals for the means as per the table mockups.

2.2.2 Descriptive Statistics for Categorical Variables

For categorical variables (e.g., gender, etc.), results within treatment arm will be summarized with subject counts and percentages/rates[redacted]

2.2.3 Survival Analyses

Survival analysis will be conducted to analyze time-to-event variables (e.g., all-cause mortality, etc.). Subjects without events will be censored at their last known event-free time point. [redacted]

2.3 Endpoint Analysis

2.3.1 Primary Endpoint(s)

The primary endpoints APS and MAE at 30 days. The primary endpoints analysis will be performance on AP population, and IP population (if applicable). [redacted]

2.3.2 Descriptive Endpoints

The analyses for the descriptive endpoints will be performed using the methods described in Section 2.2 for on the AP and IP populations (if applicable).

2.4 Sample Size Calculations

A minimum of 50 subjects and a maximum approximately 100 subjects will be registered at up to 10 sites. [redacted]

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 publication purposes.

2.6 Timing of Analysis

The primary endpoint analyses will be performed when all registered subjects complete their 30-day follow-up.

2.7 Subgroups for Analysis

Descriptive or exploratory analyses may be performed for specific subgroups.

2.8 Handling of Missing Data

All analyses will be based on available data with missing data excluded. Any unused or spurious data will be noted as appropriate in the final report.

3.0 DESCRIPTIVE ENDPOINTS AND ADDITIONAL DATA

3.1 Baseline and Demographic Characteristics

The following baseline and demographic variables will be summarized for the subjects enrolled: gender, age, medical history, baseline echocardiographic measurements, etc.

3.2 Adverse Events

All the adverse device effects, serious adverse device effects, UADEs, USADEs will be summarized for all subjects who enrolled in this trial in terms the number of events, the percentage of subjects with events and event rate as # event/patient-month per MedDRA coding. Moreover, COVID-19 related AEs with be summarized in terms of number of events, the percentage of subjects with events per AE terms.

3.3 Subject Early Termination

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

3.4 Protocol Deviation

Protocol deviations will be summarized for subjects in whom a protocol deviation was reported. COVID-19 related protocol deviations will also be summarized.

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
6MWD	Acute procedural success
AP	Attempted Procedure Population
APS	Acute Procedure Success
CCU	Critical Care Unit
CI	Cardiac Index
CO	Cardiac Output
DMR	Degenerative Mitral Regurgitation
ECL	Echocardiographic Core Laboratory
FMR	Functional Mitral Regurgitation
FSV	Forward Stroke Volume
GEE	Generalized Estimating Equation
HRR	High Risk Registry
ICU	Intensive Care Unit
IP	Implanted Population
FAS	Full Analysis Set
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEDD	Left Ventricular End Diastolic Dimension
LVEDV	Left Ventricular End Diastolic Volume
LVEF	Left Ventricular Ejection Fraction
LVESD	Left Ventricular End Systolic Dimension
LVESV	Left Ventricular End Systolic Volume
LVIDs	Left Ventricular Internal Dimension Systole
MAE	Major Adverse Event
MR	Mitral Regurgitation
MVA	Mitral Valve Area
MVG	Mitral Valve Pressure Gradient
NYHA	New York Heart Association
NMPA	National Medical Products Administration
QoL	Quality of Life
RF	Regurgitation Fraction
RR	Ratio of Rate
RV	Regurgitation Volume
RVSP	Right Ventricular Systolic Pressure

Acronym or Abbreviation	Complete Phrase or Definition
SAP	Statistical Analysis Plan
SLDA	Single Leaflet Device Attachment
TEE	Transesophageal Echocardiogram

6.0 REFERENCES

N.A.

7.0 APPENDICES

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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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