ABT-CIP-10320
MitraClip EXPAND G4 Phase II

A Post-Approval Study Assessment of the Safety and Performance of MitraClip™ G4 System

Statistical Analysis Plan (SAP)

Version B

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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 MitraClip EXPAND G4 Post-market Study. This plan is based on the Version C, November 4, 2020 Clinical Investigation Plan (CIP).

1.2 Clinical Investigation Objectives

The primary objective of this study is to evaluate the safety and performance of the MitraClip G4 System in a post-market setting.

1.3 Clinical Investigation Design

This is a post-market, multi-center, single-arm, prospective study to assess the safety and performance of the next generation MitraClip G4 System in a contemporary, real-world setting. The current protocol describes two phases for targeting treatment of 1100 subjects at up to [redacted] sites in the Europe, the United States (US), Canada and Japan.

- *Phase I:* Included up to 100 patients at up to [redacted] sites in the US treated with a MitraClip G4 device and followed through 30 days (completed August 2020).
- *Phase II:* Includes 1,000 post-market, consented patients at up to [redacted] sites treated with a MitraClip G4 device according to local guidelines and IFU from the Europe, the United States, Canada and Japan followed through 5 years.

Follow-up echocardiograms for patients in Phase II will be collected at Discharge, 30 days and 1 year and 5 year at post-procedure visits. Additional clinical follow-up visits will be at 6 months (phone call), 2, 3, 4 year (office visits). Cardiovascular adverse events will be reported through 5 years to confirm safety of the MitraClip G4 System.

Additionally, the MitraClip G4 PMCF Study is a sub-analysis of the EXPAND G4 Post Market Study and will be conducted when 420 European subjects have completed 30-day follow-up with necessary data. An overall sample size of 1100 subjects will ensure at least 420 European subjects are treated with the MitraClip G4 System. Data from the MitraClip G4 PMCF Study will be used to fulfill the regulatory requirement for PMCF associated with the CE mark approval of the MitraClip G4 System.

1.4 Study Endpoints

The following study endpoints will be evaluated during the clinical trial for all Phase II subjects:

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.

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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

Procedural endpoints:

- 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 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.
- 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
- Use of Controlled Gripper Actuation (CGA)
- Use of Left Atrial Pressure (LAP) Monitoring
- Number of Attempted Grasps defined as the number of attempts to stabilize leaflets by the open Clip
- In-hospital Major Adverse Events (MAE) defined as the number of MAEs that occur prior to discharge from hospitalization in which MitraClip Procedure was performed
    - *MAE is defined as a composite of all-cause Death, Myocardial Infarction, Stroke, or non-elective Cardiovascular (CV) surgery for device related complications.*

Clinical endpoints evaluated at discharge, 30 days, 1, 6 and 12 months, and 2, 3, 4, 5 years are:

- All-cause Mortality
- Heart Failure Hospitalization
- Occurrence of AE
- 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
- MR Reduction to ≤1+ (evaluated at discharge, 30 day, 1 year, 5 year)
- MR Reduction to ≤2+ (evaluated at discharge, 30 day, 1 year, 5 year)

Functional improvement endpoints evaluated at baseline, 30 days, discharge, 12 months, and 2, 3, 4, 5 years are:

- New York Heart Association (NYHA) functional class improvement
- Quality of Life (QOL) assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ)
- 6 minute walk distance (6MWD)

The KCCQ and 6MWD are not required to be collected at discharge and will not be reported at discharge.

Echocardiographic endpoints evaluated at baseline, discharge, 30 days, 1 month, 12 months and 5 years are:

- MR Severity Grade
- Effective Regurgitant Orifice Area (EROA) as measured by measured by PISA method
- Coaptation Measures (depth/length) (Baseline only)
  - *Coaptation depth: Coaptation depth is defined as the distance from the plane of the mitral valve annulus to the first point of leaflet coaptation in the atrial-to-ventricular direction in the four-chamber view.*
  - *Coaptation length: Coaptation length is defined as the vertical length of leaflets that is in contact, or is available for contact, during systole in the atrial-to-ventricular direction in the four-chamber view.*
- Flail Measures (gap/width) (Baseline only)
  - *Flail Gap: Measured as the greatest distance between the ventricular side of the flail segment to the atrial side of the opposing leaflet. This distance is measured perpendicular to the plane of the annulus in two views and the largest measurement is used. The two views for measurement are the four-chamber long axis (LAX) view and the left ventricular outflow tract (LVOT) view.*
  - *Flail Width: Measured as the width of the leaflet segment that moves in and out of plane during systole in the short axis (SAX) view.*
- Grasping Area Anatomy (measure cleft or scallop if significant) (Baseline only)
- Assess chordal support (Baseline only)
- Regurgitant Jet(s) Position and Quantity (Baseline only)
- TR Severity: None, Mild, Moderate or Severe

The following study endpoints will be evaluated during the clinical trial for all MitraClip G4 PMCF Study subjects:

- Acute Procedural Success (APS) as defined above
- Major Adverse Events (MAE): defined as a composite of All-cause Death, Myocardial Infarction, Stroke, or non-elective CV surgery for device related complications
- MR Severity (evaluated at discharge, 30 days, 1 year and 5 years)
- Device Related Adverse Events (including mitral valve stenosis, device embolization, single leaflet device attachment (SLDA), myocardial perforation, or the need for mitral valve replacement instead of repair due at least in part to the MitraClip procedure or the presence of the MitraClip device)

- All-cause mortality
- Recurrent heart failure hospitalization
- Quality of Life (QOL) assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ)
- New York Heart Association (NYHA) functional class improvement
- 6 minute walk distance (6MWD) (per standard of care)

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

2.1.1 Primary Analysis Population

A patient is considered enrolled upon signing and dating an informed consent form for participation. The primary analysis population will be defined as all enrolled subjects with a MitraClip G4 system implant procedure attempted.

2.1.2 MitraClip G4 PMCF Study Population

The MitraClip G4 PMCF population will be defined as enrolled subjects with a MitraClip G4 system implant procedure attempted and are in the first 420 subjects enrolled in Europe.

2.2 Statistical Methods

Descriptive analysis will be performed to summarize baseline, clinical and safety event data. Depending on the type of data (e.g., continuous or categorical), statistical methods described in the following sections will be used. Only subjects in the primary analysis population, as defined in Section 2.1.1., will be included in this analysis.

2.2.1 Descriptive Statistics for Continuous Variables

For continuous variables (e.g., age, etc.), results will be summarized with the numbers of observations, means, and standard deviations, with quartiles, minimums, maximums, and 95% confidence intervals for the means. Differences between subgroups, where specified, will be summarized with relative risks, 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 categorical variables (e.g. APS, etc.), results will be summarized with subject counts and percentages/rates, and where applicable, with exact 95% Clopper-Pearson[1] confidence intervals, and p-values may be presented for hypothesis generating purposes. 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.

2.2.3 Survival Analyses

Survival analysis will be conducted to analyze time-to-event variables, such as all-cause of mortality. Subjects without events will be censored at their last known event-free time point. Survival curves will be constructed using Kaplan-Meier[3] estimates. Summary tables for endpoints will include event (failure)

rates, Greenwood standard error and confidence interval for the event rates.

2.3 Primary Endpoint Analysis

For the EXPAND G4 Post Market study Phase II, there will be no hypothesis testing performed. This is a study with descriptive endpoint data in order to collect real world clinical experience of the MitraClip G4 System.

In the MitraClip G4 PMCF study, acute procedural success (APS) will be the only endpoint on which hypothesis testing will be performed. APS is defined as successful implantation of the MitraClip G4 Implant with resulting MR severity of 2+ or less on discharge Echocardiogram (30-day echocardiogram will be used if discharge information is unavailable or uninterpretable). Subjects who die or undergo mitral valve surgery before discharge are considered as an APS failure. This endpoint will be assessed as a proportion of subjects meeting the definition of APS and tested against a performance goal (PG) of 82.8%.

The null and alternative hypotheses are stated as:

H_0: APS rate ≤ PG

H_A: APS rate > PG

[redacted]

The null hypothesis will be rejected (i.e., successfully passing the PG) if the p-value is calculated to be less than 0.05. The analysis will be performed on the MitraClip G4 PMCF population defined above.

2.4 Sample Size Calculations

No sample size calculations were performed for the EXPAND G4 Post Market Phase II study.

However, the sample size for the MitraClip G4 PMCF study were derived using APS. The expected APS rate for MitraClip G4 is assumed to be 88%. For a performance goal of 82.8%, an effective sample size of 400 subjects will provide 90% power using the exact test to reject the null hypothesis in Section 2.3 at

a one-sided 5% significance level. Assuming a 5% attrition rate account for missing echocardiographic assessment or non-evaluable MR assessment at discharge, a sample size of 420 subjects is determined based on the primary endpoint of APS.

[redacted]

[redacted]

A meta-analysis with weights of inverse-variance method is used to analyze the APS in these MitraClip studies. The estimated APS rate from the meta-analysis is 87.8%, with 95% confidence interval of [82.8%, 92.7%]. Hence, the PG of the APS is set as the lower limit of 95% CI for APS from the meta-analysis, i.e. 82.8%. As MitraClip G4 system is expected to perform as good as or better than the first and secondary generation of MitraClip system, thus the expected APS of MitraClip G4 is assumed to be 88%.

[redacted]

2.5 Interim Analysis

No formal interim analyses are planned for this study. Interim study reports with descriptive analysis may be produced for regulatory or reimbursement purposes.

2.6 Timing of Analysis

For the MitraClip G4 PMCF study, the analysis of the primary endpoint will be performed when the last subject completes the 30 days visit.

For the remaining endpoints in both the EXPAND G4 Post Market Study and MitraClip G4 PMCF study, the analysis will be performed after all subjects in the PMCF populations have completed 5-year follow-up visit, are discontinued from the trial or have passed the end of their 5-year visit window.

2.7 Subgroups for Analysis

The following subgroups will be performed for primary analysis to evaluate the safety and efficacy of MitraClip G4 system.

MitraClip usage:

- G4NT
- G4XT
- G4NTW
- G4XTW

Etiology:

- DMR
- FMR
- Mixed

Anatomical Measurements such as Shorter Leaflet, Primary Jet A2-P2, Large Flail, Smaller MV Area (MVA < 4 cm2), Mitral valve commissures will be analyzed by the following subgroups:

SLDA events:

- Subjects with SLDA
- Subjects without SLDA

Clip usage:

- G4NT
- G4XT
- G4NTW
- G4XTW

Use of the CGP feature and left atrium pressure monitoring will also be analyzed.

2.8 Handling of Missing Data

If Echocardiography assessed MR severity at discharge is unavailable or cannot be assessed, the 30-day value will be used to assess APS. All analyses will be based on available data with missing data excluded. Any unused or spurious data will be noted as appropriate.

2.9 Multiplicity Issues

No multiplicity adjustment is needed for this EXPAND G4 Post Market Phase II study, because there is no pre-specified hypothesis test.

For the MitraClip G4 PMCF study, there is a single primary endpoint and hence no multiplicity adjustment is needed.

2.10 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 Endpoints

For the EXPAND G4 Post Market Phase II study, the study endpoints as listed in section 1.4 will be evaluated descriptively in the primary analysis population. For the MitraClip G4 PMCF study, all study endpoints will be evaluated descriptively in the PMCF population.

3.2 Baseline and Demographic Characteristics

The following baseline and demographic variables will be summarized based on the primary analysis and MitraClip G4 PMCF populations: demographics, baseline comorbidities, medical history, echo data, MR severity, NYHA functional class, KCCQ, etc.

3.3 Adverse Events

Endpoint adverse events reported during this study include: all cardiovascular events, device-related adverse events, and events classified as MAEs (as defined in section 1.4). These endpoint adverse events, serious adverse events, adverse device effects and serious adverse device effects will be summarized based on the primary analysis and the MitraClip G4 PMCF populations in terms of the number of events and the percentage of subjects with events per MedDRA coding.

3.4 Subject Early Termination

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

3.5 Protocol Deviations

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

3.6 Device Deficiencies

Device deficiencies will be summarized based on the primary analysis and MitraClip G4 PMCF populations in terms of the number of device deficiencies and the percentage of subjects with device deficiencies.

4.0 DOCUMENTATION AND OTHER 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
CV	Cardiovascular
EP	Enrolled Population
MAE	Major Adverse Event
MitraClip G4	MitraClip G4
MR	Mitral Regurgitation
N	Sample Size
NYHA	New York Heart Association
SAE	Serious Adverse Event
SAP	Statically Analysis Plan
SLDA	Single leaflet device attachment
TEE	Transcatheter Esophageal Echocardiogram
6MWD	6 minute walk distance

6.0 REFERENCES

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3. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457-481.