**Statistical Analysis Plan**

ABT-CIP-10334
MitraClip Russia

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

## Statistical Analysis Plan (SAP)

Version A

February 10, 2020

Redacted Version A
November 19, 2021

[redacted]

# 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 Clinical Investigation Plan (CIP) CRD 1000, the MitraClip Russia clinical investigation. This plan is based on the Version 1.0, December 13, 2019 Clinical Investigation Plan.

## 1.2 Clinical Investigation Objectives

The objective of this study is to evaluate safety and effectiveness of the MitraClip NT procedure in the Russian population for treatment of Mitral Regurgitation.

## 1.3 Clinical Investigation Design

The MitraClip Russia trial is a prospective, single-center, single-arm clinical evaluation of the MitraClip System for the treatment of symptomatic chronic moderate-to-severe (3+) or severe (4+) Degenerative Mitral Regurgitation (DMR) or Functional Mitral Regurgitation (FMR) in Russia subjects deemed difficult for mitral valve surgery by the local site heart team. Follow-up of subjects enrolled in the MitraClip Russia study will occur at discharge, 10 days, and 30 days. Sixteen (16) subjects will be registered in this study.

## 1.4 Endpoints

### 1.4.1 Primary Endpoint

Successful implantation of the MitraClip NT device resulting in a decrease in the MR severity grade as assessed from the discharge echocardiogram (10-day echocardiogram will be used if discharge is unavailable or uninterpretable). Subjects who die or undergo mitral valve surgery before discharge will be considered a failure for the procedure.

### 1.4.2 Descriptive Endpoints

Clinical Endpoints

- Technical Success: Alive with successful access, delivery and retrieval of the device delivery system, and deployment and correct positioning of a Clip, and no need for additional unplanned or emergency surgery or re-intervention related to the device or access procedure.
- Device Success at 30-day post-procedure: Alive with original intended Clip(s) in place, and no additional surgical or interventional procedures related to access or device since completion of the original procedure, and intended performance of the Clip(s) with MR reduction to ≤ mild and freedom from device related Serious Adverse Events (SAE)s (i.e. embolization, mitral stenosis, single leaflet device attachment, Iatrogenic atrial septal defect, 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 NT device).
- Procedural Success at 30-day post-procedure: No procedure related SAEs (i.e. death, stroke, Myocardial Infarction (MI), renal failure, and non-elective cardiovascular surgery for device or procedure related adverse events occurring after the attempted MitraClip procedure (i.e. femoral vein puncture for trans-septal access).
- All-cause mortality

- Number of hospitalizations and reason for hospitalization (i.e. heart failure, cardiovascular, non-cardiovascular) through follow up
- Major bleeding requiring transfusion through follow up
- Six Minute Walk Test (6MWT) distance at baseline, 10 days and 30 days
- Average doses of concomitant cardiac medications at baseline, procedure, 10 days and 30 days.
- New York Heart Association (NYHA) Class at baseline, 10 days, 30 days

Device and Procedure-Related Endpoints

- Implant Rate: Defined as the rate of successful delivery and deployment of one or more MitraClip NT devices with echocardiographic evidence of leaflet approximation and retrieval of the delivery catheter.
- Device Procedure Time: Defined as the time elapsed from the puncture of the groin for the trans-septal procedure to the time the Steerable Guide Catheter is removed.
- Total Procedure Time: Defined as the time elapsed from the first of intravascular catheter placement, or transesophageal echocardiogram (TEE), to the removal of the last catheter and TEE.
- Device Time: Defined as the time the Steerable Guide Catheter is placed in the intra-atrial septum until the time the MitraClip NT Clip Delivery System (CDS) is retracted into the Steerable Guide Catheter.
- Fluoroscopy duration: Defined as the duration of exposure to fluoroscopy during the MitraClip NT procedure.
- Length of stay in Intensive Care Unit/Critical Care Unit/Post-Anesthesia Care Unit (ICU/CCU/PACU)
- Length of hospital stay excluding rehabilitation stay
- Length of rehabilitation stay
- Location to which subject was discharged (home or another facility)
- If subject discharged to another facility, length of stay at facility to which subject was discharged.
- Mitral valve surgery (including type of surgery), including reason for intervention
- Additional MitraClip NT device intervention, including reason for intervention

Echocardiographic Endpoints

The following echocardiographic endpoints will be reported at baseline, discharge, 10 days, 30 days. Echocardiographic endpoints will be assessed at baseline, discharge, 10 days, 30 days.

- 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 (ATP)

FMR or DMR Russian patients who meet the eligibility criteria for the MitraClip NT System Instructions for Use (IFU) in Russia and registered into the study. [redacted]

## 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.

### 2.2.1 Descriptive Statistics for Continuous Variables

For continuous variables such as age, results will be summarized with the numbers of observations, means, standard deviations, and, if specified in the table mockups, with quartiles, minimums, and maximums.

### 2.2.2 Descriptive Statistics for Categorical Variables

For categorical variables such as sex, NYHA, results will be summarized with subject counts and percentages/rates, and where specified in the table mockups, with exact 95% Clopper-Pearson[1] confidence intervals. For binary variables such as adverse events, results will be summarized with patient counts, and percentages.

## 2.3 Endpoint Analysis

### 2.3.1 Primary Endpoint(s)

The primary endpoint is (the number of) successful implantation of the MitraClip NT device resulting in a decrease in the MR severity grade as assessed from the discharge echocardiogram (10-day echocardiogram will be used if discharge is unavailable or uninterpretable). Subjects who die or undergo mitral valve surgery before discharge will be considered a failure for the procedure. The primary analysis population is the ATP.

### 2.3.2 Descriptive Endpoints

The analyses for the descriptive endpoints will be performed using the methods described in Section 2.2 for ATP populations.

## 2.4 Sample Size Calculations

Sixteen (16) DMR or FMR patients will be registered in the study. This sample size is determined based on the primary endpoint of successful implantation of the MitraClip NT device resulting in a decrease in the MR severity grade as assessed from the discharge echocardiogram.

[redacted]

Therefore, a sample size of 16 subjects ensure an observed rate that is readily interpretable.

## 2.5 Timing of Analysis

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

## 2.6 Subgroups for Analysis

No subgroup analyses are planned for this clinical investigation.

## 2.7 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 DOCUMENTATION AND OHER CONSIDERATIONS

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

# 4.0 ACRONYMS AND ABBREVIATIONS

| Acronym or Abbreviation | Complete Phrase or Definition |
|---|---|
| 6MWT | 6-Minute Walk Test |
| ATP | Attempted Procedure Population |
| CCU | Critical Care Unit |
| CDS | Clip Delivery System |
| CI | Cardiac Index |
| CIP | Clinical Investigation Plan |
| CO | Cardiac Output |
| DMR | Degenerative Mitral Regurgitation |
| FMR | Functional Mitral Regurgitation |
| FSV | Forward Stroke Volume |
| HRR | High Risk Registry |
| ICU | Intensive Care Unit |
| IFU | Instructions For Use |
| LVEDD | Left Ventricular End Diastolic Dimension |
| LVEF | Left Ventricular Ejection Fraction |
| LVESD | Left Ventricular End Systolic Dimension |
| LVESV | Left Ventricular End Systolic Volume |
| MI | Myocardial Infarction |
| MR | Mitral Regurgitation |
| MVA | Mitral Valve Area |
| MVG | Mitral Valve Pressure Gradient |
| NYHA | New York Heart Association |
| PACU | Post-Anesthesia Care unit |
| RF | Regurgitation Fraction |

| Acronym or Abbreviation | Complete Phrase or Definition |
|---|---|
| RV | Regurgitation Volume |
| RVSP | Right Ventricular Systolic Pressure |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| TEE | Transesophageal Echocardiogram |

## 5.0 REFERENCES

1. Clopper C. J., Pearson E. S., The use of the confidence or fiducial limits illustrated in the case of the binomial. Biometrika, 1934, 26, 404-413.