Statistical Analysis Plan

[redacted]

Trifecta GT PMCF

Trifecta™ GT Post Market Clinical Follow-up

Statistical Analysis Plan (SAP)

[redacted]

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[redacted]

CL1024229

[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 intended to provide a detailed and comprehensive description of the planned methodology and analysis to be used for [redacted], the Trifecta GT PMCF clinical investigation. [redacted]

1.2 Clinical Investigation Objectives

The objective of this study is to evaluate the safety and performance of the Trifecta™ GT valve through 5-year follow-up in a prospective, multi-center, real-world setting. This study is intended to satisfy post-market clinical follow-up requirements of CE Mark in Europe. This study is sponsored by Abbott.

1.3 Clinical Investigation Design

This study is a multi-center, prospective 5-year study of approximately 350 subjects intended to be implanted with a SJM Trifecta GT valve. It will be conducted in approximately 35 sites worldwide. [redacted]

To ensure an adequate number of subjects at each site, no individual site may enroll more than 10% of the maximum sample size (n=35 subjects) without prior approval from the sponsor.

1.4 Endpoints

There is one primary endpoint and five descriptive endpoints in this clinical study.

1.4.1 Primary Endpoint

The primary safety endpoint is freedom from surgical valve replacement or transcatheter valve-in-valve implantation at 5 years post implant.

1.4.2 Descriptive Endpoints

This section lists descriptive endpoints that will be summarized using descriptive statistics:

- Freedom from all-cause mortality at 5 years post implant
- Freedom from valve related mortality at 5 years post implant
- Freedom from Structural Valve Deterioration (SVD) at 5 years post implant
- Freedom from surgical valve replacement or transcatheter valve Implantation due to SVD at 5 years post implant
- Valve hemodynamic performance (e.g., left ventricular ejection fraction, mean and peak gradients, aortic insufficiency, and effective orifice area via any available/performed echocardiograms) at pre-discharge, 6 months, 3 years, and 5 years post implant.

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Population

[redacted]

2.2 Statistical Methods

2.2.1 Descriptive Statistics for Continuous Variables

Continuous variables will be summarized with the numbers of observations, mean, standard deviation and range.

2.2.2 Descriptive Statistics for Categorical Variables

Categorical variables will be summarized with subject counts and percentages/rates.

2.2.3 Survival Analyses

Survival analysis will be conducted to analyze all time-to-event variables. Subjects without events will be censored at their last known event-free time point. Survival curves will be constructed using Kaplan-Meier estimates.

2.2.4 Annualized Rates

The annualized event rate will be estimated using the number of late events (those occurring > 30 days post implant) divided by the total patient time in years, expressed as a percentage.

For each subject, Patient time will be the time from implant to last contact date (date of death, explant, withdrawal, or last known visit).

Total patient time will be calculated as the sum of late post-operative follow up time in years.

2.3 Endpoint Analysis

There will be no hypothesis testing in this clinical investigation. Results will be analyzed and presented descriptively.

2.3.1 Primary Endpoint

The primary endpoint, freedom from surgical valve replacement or transcatheter valve-in-valve implantation at 5 years post implant, will be summarized using Kaplan-Meier methods and annualized rate as described in Section 2.2.3 and 2.2.4.

2.3.2 Descriptive Endpoints

The following describes the additional endpoints that will be analyzed descriptively at 5-years post procedure:

- Freedom from all-cause mortality at 5 years post implant
- Freedom from valve related mortality at 5 years post implant

[redacted]

- Freedom from Structural Valve Deterioration (SVD) at 5 years post implant
- Freedom from surgical valve replacement or transcatheter valve Implantation due to SVD at 5 years post implant
- Valve hemodynamic performance (e.g., left ventricular ejection fraction, mean and peak gradients, aortic insufficiency and effective orifice area via any available/performed echocardiograms) at pre-discharge, 6 months, 3 years and 5 years post implant.

All time-to-event endpoints will be summarized using survival estimates as described in Section 2.2.3.

Valve hemodynamic performance endpoint variables will be analyzed by valve size for each specified follow up visit using appropriate summary statistics as discussed in sections 2.2.1 and 2.2.2.

2.4 Sample Size Calculations

[redacted]

2.5 Interim Analysis

No formal interim analyses are planned for this trial. 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.

2.6 Timing of Analysis

Study endpoints will be analyzed after the completion of the 5-years post procedure follow up.

2.7 Study/Trial Success

The study has one primary endpoint without formal hypothesis. The primary endpoint result will be compared with data reported in the literature.

2.8 Subgroups Analysis

No subgroup analyses is planned.

2.9 Handling of Missing Data

All analysis will be based on available data. No missing data imputation is planned for this trial.

2.10 Multiplicity Issues

No hypothesis testing will be performed; therefore, there will be no adjustments to multiplicity.

[redacted]

2.11 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 Baseline and Demographic Characteristics

Baseline and medical characteristics such as age, gender, Euroscore, STS mortality risk score, cardiovascular history, etc. will be summarized using appropriate summary statistics.

3.2 Adverse Events

All adverse events (AEs) reported will be summarized by seriousness (serious AE vs. nonserious AE), primary relationship (device, procedure, and unrelated).
The follow definitions will apply:

- AE: Adverse Events (Non-serious and non-device or procedure related)
- ADE: Adverse Device Effects (Non-serious and device or procedure related)
- SAE: Serious Adverse Events (Serious and non-device or procedure related)
- SADE: Serious Adverse Device Effects (Serious and device or procedure related)

Summaries will be presented in terms the number of events and number and percentage of subjects with events. Categories will be non-overlapping.
All events adjudicated as related or possibly related to COVID-19 will also be summarized.
All CEC adjudicated adverse events will also be summarized in terms of the number of events, number and percentage of subjects with events.

3.3 Subject Early Termination

Reasons for early termination including deaths, withdrawals, lost to follow-up, unsuccessful implant, etc. will be summarized.

3.4 Protocol Deviation

Protocol deviations will be by deviation category (Inclusion/Exclusion criteria not met, Informed consent, visit not done etc.) using number of events.

All protocol deviations related or possibly related to COVID-19 will be summarized as above.

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 Events
ADE	Adverse Device Effects
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
PMCF	Post-Market Clinical Follow-up
SAE	Serious Adverse Events
SADE	Serious Adverse Device Effects
SAP	Statistical Analysis Plan
SVD	Structural Valve Deterioration