Statistical Analysis Plan Cover Page

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RC-PMCF
Regent China Post-Market Clinical Follow-up Study
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Protocol #ABT-CIP-10412
RC-PMCF

Regent China Post-Market Clinical Follow-up Study

Statistical Analysis Plan (SAP)

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[redacted]

Abbott

Study Name: [redacted] Regent China PMCF

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 intended to provide a detailed and comprehensive description of the planned methodology and analysis to be used for ABT-CIP-10412, the Regent China PMCF clinical investigation. This plan is based on the Version C of Clinical Investigation Plan.

1.2 Clinical Investigation Objectives

The objective of this clinical investigation is to confirm the long-term safety and performance of Abbott Medical's Regent, model AGN-751 and AGFN-756, for replacement of native or prosthetic aortic valves in a Chinese population.

1.3 Clinical Investigation Design

The RC-PMCF is designed to meet the PMCF requirements of the NMPA. This is a prospective, observational, multi-center study of subjects clinically indicated for implantation of an Abbott Medical's Regent Valve. Two hundred subjects will be enrolled into the study, that undergo surgical aortic valve replacement using a commercially available Regent valve.

Study enrollment will occur at up to 10 centers in China. The study will enroll subjects expected to be implanted with an Abbott Regent Valve who meet all study eligibility requirements. Additionally, subjects who do enroll and do not undergo the Regent MHV implant within 60 days of enrollment will be withdrawn from the study and will not contribute to the study sample size.

Subjects will be followed for 5 years post-implant; the expected duration of enrollment is [redacted]. Study visits or data collection will occur at baseline, implant, discharge, 3 months, 6 months, and annually through 5 years post-implant.

1.4 Endpoints

1.4.1 Primary Safety Endpoint

The primary safety endpoint is freedom from valve-related mortality at 5 years.

1.4.2 Primary Performance Endpoint

The primary performance endpoint is freedom from valve-related reoperation at 5 years.

1.4.3 Descriptive Endpoints

The following outcomes will be assessed as descriptive endpoints for the study:

- Annualized rate from the following events from implant through five years post-implant:
  - All-cause mortality
  - Reintervention
  - Major bleeding

- Thromboembolism
- Valve thrombosis
- Endocarditis (Operated Valve)
- Major Paravalvular Leak

- NYHA (New York Heart Association) Functional Class at baseline and annually post-implant

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

2.1.1 Implant Population

[redacted]

2.2 Statistical Methods

2.2.1 Descriptive Statistics for Continuous Variables

For continuous variables (e.g., age, weight, height, etc.), results will be summarized with the numbers of observations, means, and standard deviations, with quartiles, minimums, maximums, and 95% confidence intervals, where specified.

2.2.2 Descriptive Statistics for Categorical Variables

For categorical variables (e.g. gender, diabetic status, etc.), results 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. Subjects without events will be censored at their last known event-free time point. [redacted]

2.2.4 Analysis in Response to COVID-19 Impact

As the Coronavirus Disease 2019 (COVID-19) pandemic has spread around the globe, the following analysis mechanism will be implemented to minimize the potential confounding effect from this emerging infectious disease for the trial primary and secondary endpoints set forth in assessing the trial success and labeling claims. In alignment with the EU guidance document "Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic" updated on 28-April-2020, additional consideration was given to the impact of the COVID-19 pandemic on the primary endpoint analyses for this study. As such, prespecified methods are included in the sections that follow to indicate the handling of any outcomes impacted by COVID-19 as well as efforts to minimize missing endpoint data during the COVID-19 pandemic. Specific analyses to address COVID-19 impacts are included in relevant

subsections in Section 2.10.

2.3 Endpoint Analysis

2.3.1 Primary Endpoint(s)

The primary safety endpoint is freedom from valve-related mortality [redacted]

The primary performance endpoint is freedom from valve-related reoperation. [redacted]

2.3.2 Secondary Endpoints

No secondary endpoints are specified for this study.

2.4 Sample Size Calculations

Two hundred implanted subjects will be enrolled. [redacted]

[redacted]

[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 reimbursement purposes.

2.6 Timing of Analysis

Data analyses will be performed when all subjects have either completed 5-year follow-up or have withdrawn from the study. In addition, study progress and data may be summarized and reported as needed.

2.7 Subgroups for Analysis

No subgroup analyses are planned for this clinical investigation.

2.8 Handling of Missing Data

There is no plan to impute missing data for this clinical study. All analyses will be performed on available data.

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 Sensitivity Analysis

If site-reported valve-related deaths include deaths that are also COVID-19 related, a sensitivity analysis of the primary safety endpoint will be performed with such deaths censored at the time of the event.

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: age, gender, height, weight, BMI, cardiac disease history, arrhythmia history, indication for aortic replacement, cardiac medication, implant procedural characteristics, etc.

3.2 Adverse Events

All of the adverse device effects, serious adverse device effects will be summarized for all subjects who enrolled in this trial in terms the number of events, the percentage of subjects with events.

3.3 Subject Early Termination

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

3.4 Protocol Deviation

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

3.5 Descriptive Endpoints or Additional Data

The following descriptive endpoints will be summarized as % events per valve-year. Major bleeding, thromboembolism, valve thrombosis, endocarditis and major paravalvular leak will be assessed at 5 years, and descriptively compared to 2 times the objective performance criteria as defined in ISO5840-2:2021 for mechanical heart valves. All-cause mortality and reintervention will be assessed at 5 years, and descriptively compared to acceptance criterion, as outlined below:

- Annualized rate of all-cause mortality (Acceptance criterion = 5% per valve-year)
- Annualized rate of reintervention (Acceptance criterion = 5% per valve-year)
- Annualized rate of major bleeding (OPC = 1.6% per valve-year)
- Annualized rate of thromboembolism (OPC = 1.6% per valve-year)
- Annualized rate of valve thrombosis (OPC = 0.1% per valve-year)
- Annualized rate of endocarditis (OPC = 0.3% per valve-year)
- Annualized rate of major paravalvular leak (PVL) (OPC = 0.3% per valve-year)

NYHA Classification will be assessed at baseline and annual visits.

4.0 DOCUMENTATION AND OHER CONSIDERATIONS

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

5.0 ACRONYMS AND ABBREVIATIONS

Acronym or Abbreviation	Complete Phrase or Definition
CIP	Clinical Investigation Plan
CRF	Case Report Form
AE	Adverse Event
SAE	Serious Adverse Event
SAP	Statical Analysis Plan

Acronym or Abbreviation	Complete Phrase or Definition
MHV	Mechanical Heart Valve
KM	Kaplan-Meier
PMCF	Post-market Clinical Follow-up
COVID-19	Coronavirus Disease 2019

6.0 REFERENCES

[redacted]

[redacted]

7.0 APPENDICE

Abbott

Study Name: [redacted] Regent China PMCF

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Study Name: [redacted] Regent China PMCF

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