Statistical Analysis Plan

ABT-CIP-10382

Hong Kong and Taiwan HM3 PMS

Post Market Surveillance of the HeartMate 3 Left Ventricular Assist System in Hong Kong and Taiwan

Statistical Analysis Plan (SAP)

Version A

February 15th 2021

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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 CIP 10382, the Post Market Surveillance (PMS) of the HeartMate 3 Left Ventricular Assist System in Hong Kong and Taiwan. This plan is based on the Version A, Dec 2, 2020 Clinical Investigation Plan (CIP).

1.2 Clinical Investigation Objectives

The primary objective of this PMS is to collect data on clinical and functional outcomes of the HeartMate 3™ (HM3) left ventricular assist system (LVAS) as a treatment for advanced heart failure, refractory to optimal medical management in Hong Kong and Taiwan.

1.3 Clinical Investigation Design

This is a prospective, single arm PMS which will enroll approximately 30 patients that meet the PMS Inclusion/Exclusion criteria, from approximately 4 sites in Hong Kong and Taiwan.

The surveillance period for this PMS is 24 months and follow-up visits will occur at Baseline/ Enrollment, HM3 Implant, 1, 3, 6, 12 and 24 months. All subjects will be followed from enrollment through the end of the 24 months surveillance period or occurrence of an outcome, whichever is earlier. Outcomes include Transplant, Explant, Exchange, Withdrawn or Death.

1.4 Endpoints

1.4.1 Primary Efficacy Endpoint

Primary efficacy endpoint is defined as the overall survival to transplant, myocardial recovery or on device support free of debilitating stroke (Day 60 Modified Rankin Score >3) or reoperation for pump replacement during the 24 months surveillance period. Subjects who are urgently transplanted due to a HM 3 malfunction prior to 24 months will be considered to have experienced a primary endpoint event, as will subjects who expire, suffer a debilitating stroke or have their HM3 exchanged due to a device failure prior to 24 months.

1.4.2 Primary Safety Endpoint

Primary safety endpoint is measured by the cumulative occurrence of all adverse events defined in Appendix II of the CIP.

1.4.3 Secondary Efficacy and Safety Endpoints

- Quality of Life: measured by the EuroQoL-5D-5L Quality of Life (EQ-5D-5L QoL)
- Functional Status: measured by the Six Minute Walk Test (6MWT) and New York Heart Association (NYHA) Classification
- Reoperations: Frequency and reasons of all reoperations
- Rehospitalizations: Frequency and reasons of all rehospitalizations
- Device Malfunction: Frequency and consequences of malfunction

NOTE: This is a PMS and all primary and secondary endpoints are not powered.

1.5 Randomization

This is a single arm PMS and no randomization will be implemented.

1.6 Blinding

This is a single arm PMS and no blinding will be implemented.

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

The analysis population is advanced heart failure patients of all genders with a HM3 implant. Patients must meet the PMS Inclusion/Exclusion criteria and provide written informed consent.

2.2 Statistical Methods

2.2.1 Descriptive Statistics for Continuous Variables

For continuous variables (e.g., age, weight, BMI, etc.), results will be summarized with the numbers of observations, means, standard deviations, quartiles, minimums, maximums, and the 95% confidence intervals for the means or median as appropriate. Comparison between subgroups of patient, when specified, will be summarized with the difference of the means or medians, p-values and 95% confidence intervals.

2.2.2 Descriptive Statistics for Categorical Variables

For categorical variables (e.g. gender, implant strategy, etc.), results will be summarized with counts, percentages and the exact 95% Clopper-Pearson or multinomial confidence intervals as appropriate. Comparison between subgroups of patient, when specified, will be summarized with the difference in percentage, p-values and 95% confidence interval.

2.2.3 Primary Efficacy Endpoint

The primary efficacy endpoint will be assessed using the Kaplan-Meier Product-Limit method. Subjects without an outcome, as defined in section 1.4.1, will be censored at the time of an elective transplant, explant for recovery, withdraw from the trial, lost to follow-up or the end of the 24 months surveillance period; whichever occurs first. A competing outcome graph will also be presented.

2.2.4 Primary Safety Endpoint

The primary safety endpoint is the occurrence of all adverse events defined in Appendix II of the CIP, which will be assessed by percent of subjects with the event and events per patient-year (EPPY). Comparison between subgroups of patient, when specified, will be presented as relative risk or relative rate, p-values and 95% confidence interval.

The incidence of important adverse events such as Stroke or Gastrointestinal (GI) Bleeding, relative to the time it occurred will be presented as freedom from event by using the Kaplan-Meier Product-Limit method if required.

2.2.5 Secondary Endpoints

2.2.5.1 Six-minute Walk Test

Subjects may not be able to walk due to heart failure, especially at baseline. Subjects unable to walk due to heart failure will receive a score of 0 meters. The 6-minute Walk test will be conducted at all follow-up visits and the overall mean, median, standard deviation, minimum and maximum by visits will be presented. Differences in walking distance between each visit and baseline will be calculated and assessed for improvements using Wilcoxon signed-rank test. In addition, box plots will be used to show changes in walking distance over time.

2.2.5.2 NYHA

Subjects' NYHA Functional Status will be assessed and percent of subjects in each class will be presented for all follow-up visits. For comparison, patients will be grouped into NYHA Class I/II (No limitation and Slight limitation of physical activity) vs. NYHA Class III/IV (Marked limitation and Inability to carry out physical activities). McNemar's test will then be used to assess if there is an increase in proportion of Class I and II subjects at each visit comparing to the baseline. In addition, bar charts will be used to show changes in NYHA classification over time.

2.2.5.3 EQ-5D-5L QoL questionnaire

Subject's quality of life will be measured by the EQ-5D-5L QoL questionnaire at baseline and all visits after HM3 implant until the end of surveillance period. EQ-5D-5L QoL Visual Analog Scale (VAS) score at each visit will be presented as mean, median, standard deviation, minimum and maximum. Comparison to baseline by visits will be performed using Wilcoxon signed-rank test.

2.2.5.4 Rehospitalization and Reoperation

Percent of patients with events and frequency of events will be reported by reasons of rehospitalization and reoperation. Freedom from rehospitalization and reoperation will be assessed using the Kaplan-Meier Product-Limit method when specified.

2.2.5.5 Device Malfunction

Percent of patients with suspected HM3 device malfunctions and frequency of all suspected malfunctions will be reported by components of HM3 involved. Additionally, days to the malfunction, reoperations or death due to malfunction and actions taken in response to malfunction will be reported.

2.3 Sample Size Calculations

No formal sample size calculation is required. Sample size is based on the estimated number of consecutive patients likely to be implanted with a HM3 at the participating sites during the study period.

2.4 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.

2.5 Timing of Analysis

All endpoints will be analyzed at the end of the 2-year surveillance period.

2.6 Study/Trial Success

There is no formal definition of success in this PMS.

2.7 Subgroups for Analysis

No subgroup analyses are planned for this PMS.

2.8 Handling of Missing Data

Data collected outside of the study visit window will be excluded from the analysis. Except for 6-minute Walk Test stated above, missing data will not be imputed.

2.9 Poolability Issue

The objective of this PMS is to assess real-world clinical and functional outcomes under Hong Kong and Taiwan standard of care for advanced heart failure patients implanted with the HM3 LVAS. Therefore, data from all sites will be used in the analysis.

2.10 Multiplicity Issues

No adjustments for multiplicity will be made.

2.11 Adjustments for Covariates

Unless otherwise specified, no adjustments for covariates will be made for any of the variables in the analyses.

2.12 Exploratory Analysis

No exploratory analysis is planned for this study.

3.0 DESCRIPTIVE ENDPOINTS AND ADDITIONAL DATA

3.1 Baseline and Demographic Characteristics

Baseline demographic variable will be summarized for subjects enrolled, including but not limited to age, gender, ethnicity, cardiovascular disease history, medical history, vital signs, echocardiogram, medications and laboratory assessments.

3.2 Protocol Deviation

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

3.3 COVID-19

Any primary and secondary endpoints or additional data affected by or related to COVID-19 will be reported.

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
BMI	Body Mass Index
CIP	Clinical Investigation Plan
EPPY	Event Per Patient-Year
EQ-5D-5L QoL	EuroQoL-5D-5L Quality of Life
GI	Gastrointestinal
HM3	HeartMate 3™
LVAS	Left Ventricular Assist System
NYHA	New York Heart Association
PMS	Post-Market Surveillance
AE	Adverse Event
SAP	Statistical Analysis Plan
VAS	Visual Analog Scale
6MWT	Six Minute Walk Test

6.0 REFERENCES

ABT-CIP-10382 Post Market Surveillance of the HeartMate 3 Left Ventricular Assist System in Hong Kong and Taiwan

7.0 APPENDICES

N/A