Statistical Analysis Plan

[redacted]

ARIES HM3

Antiplatelet **R**emoval and Hemocompat**I**bility **E**vent**S** with the **H**eart**M**ate **3** Pump

Statistical Analysis Plan (SAP)

Version F

August 7, 2023

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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 intended to provide a detailed and comprehensive description of the planned methodology and analysis to be used for CIP 10305, the ARIES HM3 clinical investigation. Version F of the SAP is based on the Version C, March 13, 2020 Clinical Investigation Plan

1.2 Clinical Investigation Objectives

To study the safety and efficacy of an anti-platelet-free antithrombotic regimen in patients with advanced heart failure treated with the HM3 LVAS

1.3 Clinical Investigation Design

This is a prospective, randomized, double-blinded, placebo-controlled clinical investigation of advanced heart failure patients treated with the HM3 with two different antithrombotic regimens: vitamin K antagonist with aspirin vs vitamin K antagonist with placebo. [redacted]

The clinical investigation has been designed to involve as little pain, discomfort, fear, and any other foreseeable risk as possible for subjects.

The clinical investigation will be conducted at up to 50 centers worldwide. The primary, and secondary endpoints will be evaluated as described in this SAP. Outcomes for this study include death, transplant, withdrawal or pump exchange. All subjects, site, Clinical Events Committee (CEC), and sponsor personnel, will remain blinded to the randomization scheme until the last ongoing study subject completes follow-up (specifically, experiences an outcome or reaches 12-months of follow up) and all data have been collected and adjudicated, exceptions will be justified in the study blinding plan (eg. DSMB). After a patient reaches 12-months of follow up, they will continue to be followed every 6-months, as long as they remain on the treatment arm medication, until the last ongoing patient reaches 12-months of follow up. Beginning at the 12-month follow-up visit, patients should be requisitioned two bottles of the treatment arm medication to cover the 6 months until the next follow up visit.

1.4 Endpoints

1.4.1 Primary Endpoint

The primary endpoint for this study will be met if the placebo arm is non-inferior to the aspirin arm in the composite of survival free of any non-surgical[1] major hemocompatibility related adverse event[2] at 1-year post implant.

[1] - Non-surgical – any event occurring > 14-days post implant.
[2] - Major Hemocompatibility Related Adverse Event:

- Stroke
- Pump Thrombosis (suspected or confirmed)
- Bleeding (including intracranial bleeds that do not meet the stroke definition)
- Arterial Peripheral Thromboembolism

This study assesses the overall change in the overall incidence of major hemocompatibility related adverse events. Additional secondary endpoints will also be evaluated to monitor effects on other study outcome measures.

This composite primary endpoint reflects the interrelatedness of hemocompatibility related adverse events, providing an endpoint that will result in a clear answer to the study's primary question of whether or not anti-platelets are required to maintain the safety and efficacy profile of the HM3. Because post-implant clinical course can be widely variable due to clinical responses to adverse events, this composite endpoint focuses on the first major hemocompatibility related adverse event to ensure the effect of the treatment arm is reflected in the primary endpoint measure. Non-composite endpoints or endpoints that do not focus on the first event have the possibility of being rendered futile or distorted by treatment responses to prior adverse events.

1.4.2 Secondary Endpoint(s)

To assess the safety of removal of antiplatelets from the antithrombotic regimen, non-surgical major hemorrhagic events, non-surgical major thrombotic events, bleeding, stroke, pump thrombosis and survival will be compared between the two arms of the study.

1.4.3 Descriptive Endpoint(s)

This study will also assess changes in the Hemocompatibility Score, Rehospitalization, and Economic Cost Implications as a result of removal of antiplatelets from the antithrombotic regimen.

1.5 Randomization

[redacted]

1.6 Blinding

This is a double-blind study, neither patient nor investigator will know the subject's randomization throughout the study follow up. Additionally, sponsor personnel and the CEC will not have access to patient or population blinding information. The blind of the study will only be broken once the study follow-up is completed, and adverse event adjudication is completed. Questions related to unblinding should be directed to the Sponsor.

[redacted]

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

Subjects are considered enrolled at the time they sign informed consent. Subjects will be included in analysis populations when they have provided consent, have been implanted with the HeartMate 3 and have been randomized to a treatment arm. The reasons that enrolled subjects were not randomized will be summarized.

[redacted]

[redacted]

2.2 Statistical Methods

2.2.1 Descriptive Statistics for Continuous Variables

Continuous variables will be summarized with the numbers of observations, means and standard deviations, with quartiles, minimum and maximum.

2.2.2 Descriptive Statistics for Categorical Variables

Categorical variables will be summarized with subject counts and percentages/rates, and with exact 95% Clopper-Pearson confidence intervals.

2.3 Endpoint Analysis

2.3.1 Primary Endpoint

The primary endpoint is a composite of survival free of any non-surgical[1] major hemocompatibility related adverse event[2] at 1-year post implant.

[1] - Non-surgical – any event occurring > 14-days post implant.
[2] - Major Hemocompatibility Related Adverse Event:

- Stroke
- Pump Thrombosis (suspected or confirmed)
- Bleeding (including intracranial bleeds that do not meet the stroke definition)
- Arterial Peripheral Thromboembolism

A subject will be considered a success if they survive to their 12 month visit and have not experienced a non-surgical hemocompatibility related adverse events. Subjects who have an outcome (e.g. transplanted or explanted due to recovery) prior to their 12 month visit that have not reported a non-surgical hemocompatibility related adverse event prior to censoring will also be considered a success.

A subject will be considered a failure if:

- the subject expires prior to their 12 month visit
- the subject experiences a non-surgical hemocompatibility related adverse event prior to their 12 month visit.

The primary analysis will be performed using the mITT population.

[redacted]

[redacted]

2.3.1.2 Sample Size

[redacted]

2.3.1.3 Analysis Methods

[redacted]

2.3.1.4 Justification of the Non-Inferiority Margin

[redacted]

[redacted]

2.3.1.5 Poolability Analysis

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.3.2 Secondary Endpoints

The secondary endpoints will be analyzed using the mITT population.

Non-surgical Major Hemorrhagic events: Hemorrhagic event rate per patient year will be calculated by dividing all non-surgical bleeding events and hemorrhagic stroke events by the cumulative years of study exposure. This rate will be compared between groups using Poisson regression.

Non-surgical Major Thrombotic events: The thrombotic event rate per patient year will be calculated by dividing the number of non-surgical ischemic strokes, pump thrombosis and arterial peripheral thromboembolic events by the cumulative years of study exposure. This rate will be compared between groups using Poisson regression.

Survival: The overall survival rate will be analyzed using a Kaplan-Meier analysis and the treatment groups compared using the log-rank test. Survival will be calculated starting at 14 days post implant.

Stroke Rate: The stroke rate will be calculated based on the number of strokes experienced by subjects, 14 days or more after device implant, and while on their treatment assignment, divided by the cumulative duration of study exposure (years of support). The treatment groups will be compared by using Poisson regression.

All strokes that occur 14 or more days after implant will be included, regardless of the treatment status of the subject (subjects who move off their randomized treatment will continue to be followed). Ischemic and hemorrhagic stroke rates and debilitating stroke rate (MRS > 3) will also be analyzed. The stroke rate and treatment comparison will be performed as described above.

Time to first non-surgical stroke event will also be analyzed using a Kaplan-Meier analysis. The treatment groups will be compared using a log-rank test.

[redacted]

Pump Thrombosis: The pump thrombosis rate will be calculated based on the number of suspected or confirmed pump thrombosis events experienced by the subject, 14 or more days post device implant, while on their treatment assignment divided by the cumulative duration of study exposure (years of support). The treatment groups will be compared by using Poisson regression.

All suspected pump thrombosis that occurs 14 or more days post implant will be included, regardless of the treatment status of the subject (subjects who move off their randomized treatment will continue to be followed). The pump thrombosis rate and treatment comparison will be performed as described above.

Bleeding: All bleeding events that occur will be captured. Subjects who terminate the study prematurely without experiencing any bleeding will have the time they were in the study counted in the analysis. For the mITT population, bleeding events will be included while the subject remains on their randomization assignment until the last randomized patient has been followed to one year. This will result in some subjects being followed for more than one year.

Bleeding rates will be differentiated based on severity and will include moderate bleeding, severe bleeding and fatal bleeding. Gastrointestinal (GI) bleeding and non-surgical bleeding will also be analyzed. The bleeding rate (events per patient year) will be calculated by dividing the number of bleeding events by the cumulative duration of study exposure (years of support). Bleeding rates will be compared between treatment groups using Poisson regression. In addition, a subgroup analysis will be performed according to subject aspirin responsive testing.

In addition, all secondary endpoints will be analyzed to include non-surgical major hemocompatibility related adverse events beyond the time of transition to open label in the mITT population.

2.3.3 Descriptive Endpoints

Hemocompatibility Score: The Hemocompatibility Score (HCS) is a tiered hierarchal score that weighs each hemocompatibility related adverse event by its escalating clinical relevance (1, 2). The HCS will be calculated for each subject in the mITT population and summarized for the treatment group as a median score and range.

Rehospitalizations: The rehospitalization rate will be calculated based on the number of subjects who require a rehospitalization (excluding the hospitalization for the implant), for any cause, after randomization and initiation of the study treatment (14 or more days post implant), divided by the number of subjects. Patient year of support will be the cumulative patient duration from 14 days post implant to outcome (transplant, explant, withdrawal or death) or until the last subject reaches their 12-month follow-up, whichever occurs first.

2.3.4 Sensitivity Analyses to Evaluate Possible Impact of COVID-19

In order to evaluate the possible impact of COVID-19 on the primary and secondary endpoints, sensitivity analyses will be implemented. A COVID-19 subject is defined as any subject obtaining a positive COVID-19 test either prior to enrollment or during the 12-month follow-up or having an adjudicated COVID-19 related or possibly related adverse event during the 12-month follow-up. The following analyses will be included:

1) The primary endpoint will be analyzed excluding COVID-19 subjects from the denominator for the calculation of the composite success rate.

2) The primary endpoint will be analyzed excluding primary endpoint adverse events adjudicated as related or possibly related to COVID-19.

3) A subgroup analysis will be performed to examine the consistency of results for the primary endpoint between COVID-19 subjects and non-COVID-19 subjects.

4) All secondary endpoints will be evaluated excluding adverse events adjudicated as related or possibly related to COVID-19.

Other sensitivity analyses recommended based on available guidelines and modalities related to COVID-19 may also be performed as appropriate.

2.4 Interim Analysis

No formal interim analysis is planned for this study to stop the trial early due to futility or success.

2.5 Timing of Analysis

The primary endpoint analysis will be performed, and the clinical report prepared when all randomized subjects have reached a primary endpoint and the study has been unblinded.

2.6 Study/Trial Success

The trial will be considered successful if null hypothesis of the primary endpoint is rejected (i.e. the placebo group is non-inferior to the aspirin group).

2.7 Handling of Missing Data

[redacted]

[redacted].

2.8 Multiplicity Issues

This study includes a single primary endpoint. Thus, no Type I error adjustment is necessary.

2.9 Baseline and Demographic Characteristics

The following baseline characteristics will be descriptively presented according to treatment assignment: demographics, medical history, INTERMACS profile, vital signs, medications, laboratory assessments, coagulation assessments, hemodynamic assessments, and echocardiogram results. Continuous variables will be reported as a mean with standard deviation, and by quartiles, minimum and maximum values. Categorical variables will be reported as the number and percentage of subjects in each category.

[redacted]

2.10 Adverse Events

Adverse events are described in Section 6.8.1 of the ARIES HM3 Clinical Investigational Plan and defined in Appendix II of that document. Adverse events that occur within one year of implant will be reported per randomized treatment group. Adverse events in consented patients who are not reflected in the analysis populations (i.e. not randomized or who experience surgical events - ≤14 days post implant) will be summarized separately from the two treatment arms of the study. The data will be presented as the number and percentage of all subjects enrolled who experience the event and the total number of events.

Adverse events in the analysis populations will be presented as number and percentage of all subjects enrolled who experience the event, the total number of events and the events rate (events per patient year). Adverse events will also be analyzed according to their severity.

2.11 Operative Procedures

All operative procedures, regardless of cause, will be reported per randomized treatment arm. The report will include the number and percentage of subjects who receive an operative procedure after implant and the total number of procedures that occur within one year of the initial device implant. The reason for the operation will also be summarized.

2.12 Quality of Life and Functional Status

Quality of life and functional status will be measured at baseline, 6 months and 12 months. Results will be reported per randomized treatment group:

EQ-5D: The Visual Analog Score (VAS) will be summarized using descriptive statistics. A table will be created with the results of the EQ-5D questions

NYHA Class: Results will be categorically presented by time interval and treatment arm

6-Minute walk test (6MWT): Distance walked at each time interval will be descriptively presented. Subjects who are unable to walk due to heart failure will be imputed a score of 0. All other missing data will be ignored.

2.13 Stratification by Pre-implant Aspirin Use

The primary endpoint will be analyzed by stratifying subjects that are on aspirin pre-implant of the HM3 versus subject who are not using aspirin pre-implant.

2.14 Subject Early Termination

The reason for early termination will be summarized for each randomized treatment group. Causes of death will also be summarized by treatment group.

2.15 Protocol Deviation

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

- withdrawal of the treatment arm antithrombotic regimen without clinical reasons
- additional antiplatelet medications added to the treatment arm antithrombotic regimen
- enrollment or randomization of patients who do not meet eligibility requirements
- informed consent deviations, except inadvertent incorrect dating.

3.0 DOCUMENTATION AND OTHER CONSIDERATIONS

[redacted]

4.0 ACRONYMS AND ABBREVIATIONS

Acronym or Abbreviation	Complete Phrase or Definition
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
HCS	Hemocompatibility Score
HM3	HeartMate 3
ITT	Intent To Treat
LVAS	Left Ventricular Assist System
MRS	Modified Rankin Score
NIM	Non-Inferiority Margin
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TTR	Time in Therapeutic Range

5.0 REFERENCES

1. Mehra, M. R. The burden of haemocompatibility with left ventricular assist systems: a complex weave. *European Heart Journal*. 2019, 40, 673-677.

2.Uriel N. Colombo PC. Cleveland JC et al. Hemocompatibility-related outcomes in the MOMENTUM 3 trial at 6 months. A randomized controlled study of a fully magnetically levitated pump in advanced heart failure. *Circulation* 2017; 135:2003-2012.

3. Com-Nougue C, Rodary C, Patte C. How to establish equivalence when data are censored: a randomized trial of treatments for B non-Hodgkin lymphoma. *Statist Med* 1993; 12:1353-1364.

6.0 APPENDICES

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APPENDIX B: Device Position Substudy

A substudy is proposed to develop and validate the use of a radiopaque surgical marker placed on the anterior surface of the aortic root below the sino-tubular ridge of the aorta just above the ostia of the right coronary artery to be used as a surrogate anatomical reference or landmark to more optimally assess HeartMate 3 inflow cannula position. The substudy will include subjects enrolled in the ARIES HM3 study who also meet eligibility requirements for this substudy at participating centers. Validation will be performed by assessing:

1. Safety and feasibility assessment of the radiopaque surgical marker will be made using anteroposterior (AP) and lateral radiographs captured prior to discharge (but within 30 days of implant) and at the 3-month follow up visit. The following assessments will be descriptively presented as the number and percentage of subjects for each category: successful placements, successful visualizations, and gross migrations. Adverse events related to the clip or placement procedure will be presented as the number and percentage of subjects enrolled in the substudy and total number of events.

2. The angular position of the canula relative to the marker will be measured from the AP view, and the distance of the marker to the axial alignment of the canula will be measured from the lateral view. The cannula position relative to the radiopaque marker and cannula positional changes over time will be descriptively and graphically summarized from both the AP and lateral radiographs. These measurements will be summarized as mean with standard deviation, and by quartiles, minimum and maximum values.

   The radiographs recorded at both pre-discharge and 3 months will be reviewed by an independent evaluator and assessed visually for cannula position at both time points along with potential significant change in position from pre-discharge to 3 months. Visual assessments will be categorized and summarized as count and percentage of subjects enrolled in the substudy.

3. Patients may also be grouped into clusters with each cluster representing different levels of change in cannula position. Comparisons of adverse clinical outcomes and functional capacity including the following will be made between clusters:

   - Adverse Events: Mortality, Stroke, Pump Thrombosis, Bleeding, Major HRAE, HRAE, Right Heart Failure, Cardiac Arrhythmia
   - Major thrombotic and major hemorrhagic events
   - Hospitalizations
     - Index Hospitalization and ICU Length of Stay; All Cause readmission; Number of readmissions; Days out of the hospital vs in-hospital
     - RHF Caused Hospitalizations
   - 6 Minute Walk Test Distance as a surrogate for LV unloading
     - Change over time, cumulative 6MWT distance (post implant only)
   - EQ-5D-5L
   - NYHA Classification
   - Effect of Treatment Arm designation on AEs as Sensitivity Analysis

   Clinical significance can then be interpreted with the results of comparison.