This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes

Clinical Investigation Plan

CRD_971
ARIES HM3
Antiplatelet **R**emoval and Hemocompat**I**bility **E**vent**S** with the **H**eart**M**ate **3** Pump

Version	A
Date	AUG 22, 2019
Steering Committee	Mandeep Mehra MD, MSc, FRCP (Lon) - Chair Nir Uriel MD, MSc Francis Pagani MD, PhD Ulrich Jorde MD Jason Katz MD, MHS Finn Gustafsson MD, PhD Ivan Netuka MD, PhD
Planned Number of Sites	Up to 50 sites
Geographies	International
Clinical Investigation Type	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 versus vitamin K antagonist with placebo
Sponsor	Abbott 186 Middlesex Turnpike Burlington, MA 01803 USA
Randomization and Treatment Arm Medication Logistics	WebEZ (ALMAC Clinical Services)
Electronic Data Capture Software	Oracle Clinical
CIP Author (Current Version)	Daniel Crandall, PhD

Clinical Investigation Plan

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I have read and agree to adhere to the clinical investigation plan and all regulatory requirements applicable in conducting this clinical investigation.

Site Principal Investigator

Printed name:
Signature:
Date:

Clinical Investigation Plan

TABLE OF CONTENTS

Clinical Investigation Plan

Clinical Investigation Plan

Clinical Investigation Plan

Clinical Investigation Plan

Clinical Investigation Plan

COMPLIANCE STATEMENT:
This clinical investigation will be conducted in accordance with this Clinical Investigation Plan, the Declaration of Helsinki, applicable Good Clinical Practices and regulations (e.g., US 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 812, 45 CFR part 46, and OUS ISO14155:2011) and the appropriate local legislation(s). The most stringent requirements, guidelines or regulations must always be followed. The conduct of the clinical investigation will be approved by the appropriate Institutional Review Board (IRB)/Ethics Committee (EC) of the respective investigational site and by the applicable regulatory authorities.

Clinical Investigation Plan

1.0 INTRODUCTION

Heart failure (HF) is a growing epidemic, with 915,000 new cases diagnosed each year, resulting in over 1 million hospitalizations and costs the United States (US) healthcare system over $30 billion annually[1]. Left ventricular assist devices (LVAD) are increasingly being used for treating patients with advanced heart failure as they have demonstrated improved survival over optimal medical management[2]. Progressively improving outcomes with newer LVAD technology has led to LVAD therapy becoming a mainstay in the treatment of advanced heart failure[3], however, LVAD therapy has been beleaguered by hemocompatibility related adverse events – namely thrombosis, stroke and bleeding[4]. Within the prospective randomized multicenter MOMENTUM 3 clinical trial, the HeartMate 3 (HM3) Left Ventricular Assist System (LVAS; Abbott, Chicago, IL, Study Sponsor) showed a decrease in hemocompatibility related adverse events relative to the HeartMate II (HMII) LVAS (Abbott, Chicago, IL)[5]. This included decreases in pump thrombosis[6], stroke[7-9] ENREF 9, and bleeding[9] event rates ENREF 9. Despite these noted improvements a high residual risk of bleeding persists in patients treated with the HM3 LVAD[9]. Patients implanted with the HM3 pump are treated with a combination of antiplatelet and anticoagulation therapy but the role and implications of this regimen in determining the burden of hemocompatibility related adverse events have not been adequately investigated[9,10]. Whether antiplatelet therapy is essential in concert with anticoagulation in treating such patients remains unknown.

This clinical investigation is a prospective, randomized, double-blinded, placebo-controlled study of advanced heart failure patients treated with the HM3 with two different antithrombotic regimens: vitamin K antagonist with aspirin versus vitamin K antagonist with placebo. The objective of this investigation is to study the safety and efficacy of an anti-platelet-free antithrombotic regimen in patients with advanced heart failure treated with the HM3 LVAS.

This clinical investigation will be conducted in accordance with this clinical investigation plan (CIP). All investigators involved in the conduct of the clinical investigation will be qualified by education, training, or experience to perform their tasks and this training will be documented appropriately.

1.1 Background and Rationale

1.1.1 Background

The CE Mark trial (clinicaltrials.gov identifier: NCT02170363) for the HM3 LVAD was a prospective, multicenter, single arm trial that enrolled 50 subjects at 10 sites. Six-month outcomes from this trial demonstrated 92% (confidence interval 83-97%) survival and led to the CE Mark approval of the HM3. Analysis of longer term data demonstrated a 2-year survival of 74 ± 6%[11]. No instances of device thrombosis were observed in this cohort at 2 years[11]. Subjects will be followed through 5 years as a condition of CE Mark approval.

After approval, the ELEVATE (Evaluating the HeartMate 3 with Full MagLev Technology in a Post-Market Approval Setting; clinicaltrials.gov identifier: NCT02497950) registry was initiated to collect real-world data (i.e. there were no enrollment criteria) on consecutive HM3 patients at 26 total centers in Europe, Israel, Singapore, and Kazakhstan. The study enrolled 463 primary implant patients, 19 pump exchange patients, and collected only outcome data on an additional 58 patients who were unable to provide consent due to a study outcome (n=57 death, n=1 explant). The ELEVATE trial reported, for the primary implant cohort at

2-years, actuarial survival of 83.4%, and adverse events of stroke in 10%, suspected pump thrombosis in 1.5%, and bleeding in 34%[12].

The MOMENTUM 3 study (clinicaltrials.gov identifier: NCT02224755) was a prospective, randomized, multicenter, non-blinded, clinical trial that enrolled 1,028 patients at 69 sites in the US. The study randomized patients to receive either the HM3 or HMII LVAD. The study design incorporated an initial safety phase that evaluated 30 subjects at 5 sites prior to study expansion[13]. The primary objective of the trial was to evaluate the safety and efficacy of using the HM3 LVAD in indicated patients at two timepoints: 6 months (short-term n=294) and 2 years (long-term n=366)[13]. The primary endpoint was a composite of survival free of disabling stroke or survival free of reoperation to replace or remove the device (for reasons other than recovery)[14]. The secondary endpoint, which the study was powered to assess, was freedom from pump exchange through 2-years of follow-up in the full cohort of 1028 patients. All study endpoints were successfully met[6,8,9]. The MOMENTUM 3 trial reported the full cohort HM3 actuarial survival at 2-years as 79.0% and stroke rates of 9.9%, suspected pump thrombosis rates of 1.4%, and bleeding rates of 43.7%[9]. An analysis of the burden of hemocompatibility related adverse events showed improved survival free of hemocompatibility related adverse events with the HM3 over the HMII at 6 months[5] and 2 years[15]. Within the full cohort HM3 arm of MOMENTUM 3, at all time points, a cohort of patients were noted without aspirin as a part of their anti-thrombotic regimen, specifically at 6-months n=72/446 (16%), at 1-year n=78/371 (21%), at 18-months n=73/314 (23%), and at 2-years n=64/286 (22%)[9]. The MOMENTUM 3 study will continue to follow patients through 5-years post-implant as a condition of approval. After full enrollment in the MOMENTUM 3 study, a single arm (HM3 only) continued access protocol (CAP) was initiated while the MOMENTUM 3 IDE patients were being followed. This CAP study enrolled 1685 patients who will be followed for 2 years post implant.

A single center in Europe has investigated the use of the HM3 with low intensity anticoagulation (INR 1.5-1.9) in select patients, and reported positive outcomes[10]. These outcomes lead to the full removal of anticoagulation therapy in a subset of the low intensity anticoagulation patients, with favorable outcomes[16]. Additionally two reports from Europe have emerged on their initial experience with warfarin monotherapy with the HM3[17,18]. Both studies conclude it may be safe to remove aspirin therapy from HM3 patients and called for further evaluation of the effects of discontinuation of aspirin in HM3 patients. Specifically, in a multicenter, retrospective, observational study performed at the San Raffaele Scientific Institute in Milan and A.O. Brotzu in Cagliari, Italy, patients were stratified based on bleeding risk; patients with a HAS-BLED score ≥ 4 or who experienced a post-operative bleeding event were considered high risk[17]. Patients at high bleeding risk were discharged on warfarin monotherapy with INR targeted to 2.0-2.5 whereas the remaining patients were discharged with warfarin (INR 2.0-2.5) and aspirin (100mg/day) antithrombotic therapy[17]. In the other study at the University Hospital Birmingham, United Kingdom, a retrospective analysis of a prospective audit of a change in their institutional standard of care was conducted[18]. The center implemented as standard of care the discontinuation of aspirin therapy after >3 months or following a bleeding complication.

1.1.2 Rationale for Conducting this Clinical Investigation

Patients implanted with LVADs are typically treated with a combination of antiplatelet and anticoagulant therapy but the role and implications of this regimen in determining the burden of hemocompatibility related adverse events in patients implanted with the HM3 LVAS have not been adequately investigated[9,10]. Furthermore, a recent study showed that aspirin, in older, healthy adults without an LVAD, was associated with increased risk of major bleeding, including upper gastrointestinal bleeding, without a reduction in

thromboembolic events including ischemic stroke[19]. Whether antiplatelet therapy is essential in concert with anticoagulation in treating LVAD patients remains unknown.

Hemocompatibility related adverse events, both thrombotic and hemorrhagic, are highly interrelated. Frequently changes to a patient's antithrombotic therapy that occur in the setting of hemocompatibility related adverse events increase the propensity toward opposing events. Specifically, treatment of a thrombotic event with additional antithrombotic intensity may result in a hemorrhagic event or vise-versa. While these events may be commonly discussed discretely, decoupling them in the setting of a patient population predisposed to both events is not possible, which can lead to difficulty interpreting the results of clinical studies or, in the worst-case scenario, studies with little or no interpretive value. As such, this study focuses on de novo LVAD implants and the first events, prior to such modifications to the treatment arm antithrombotic regimen while encouraging investigators to maintain the randomized treatment arm therapy as long as clinically permissible, in an effort to avoid such confounding factors.

Bleeding events with the HM3, while decreased in comparison to a predicate device, remain burdensome[9]. All major prospective clinical trials conducted with the HM3 (MOMENTUM 3, CE Mark) have been in the context of a prescribed antithrombotic regimen of aspirin in concert with vitamin K antagonist. Within clinical studies[9,10,16], as institutional changes to their standard of care[18], or in response to increased bleeding risk[17], modifications to the HM3 anticoagulation regimen have been explored. Prior to the introduction of the HM3, which has a decreased thrombotic profile relative to the HMII, studies investigating the need for aspirin within the HMII antithrombotic regimen were conducted[20-23] ENREF 19 ENREF 20 ENREF 21. The experience with the HMII, the improved outcomes with the HM3 and the early experience of single centers exploring modification to the antithrombotic regimen in HM3 patients provide evidence for the clinical equipoise in HM3 antithrombotic therapy and forms the basis for randomization of patients to aspirin (100mg) vs placebo arms within this trial.

2.0 CLINICAL INVESTIGATION OVERVIEW

2.1 Clinical Investigation Objective

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

2.2 Hypothesis

Withdrawal of antiplatelet therapy from the antithrombotic regimen of HM3 pump patients will not adversely affect safety or efficacy of the HM3 and may reduce non-surgical bleeding.

2.3 Device(s) To Be Used in the Clinical Investigation

This Clinical Trial investigates the treatment of advanced heart failure with the HM3 and if the use of antiplatelet therapy is required as part of the antithrombotic regimen. Refer to the HM3 Instruction for Use (IFU) in your country for additional details.

Clinical Investigation Plan

Table 1 – Device Details

Device name	Model/Type	Serial/Lot Controlled	Manufacturer	Investigational or Market Released
HeartMate 3 (HM3) Left Ventricular Assist System (LVAS)	106523	Standard Commercial Controls	Abbott	The HM3 will be Market Released in all geographies included in this international study

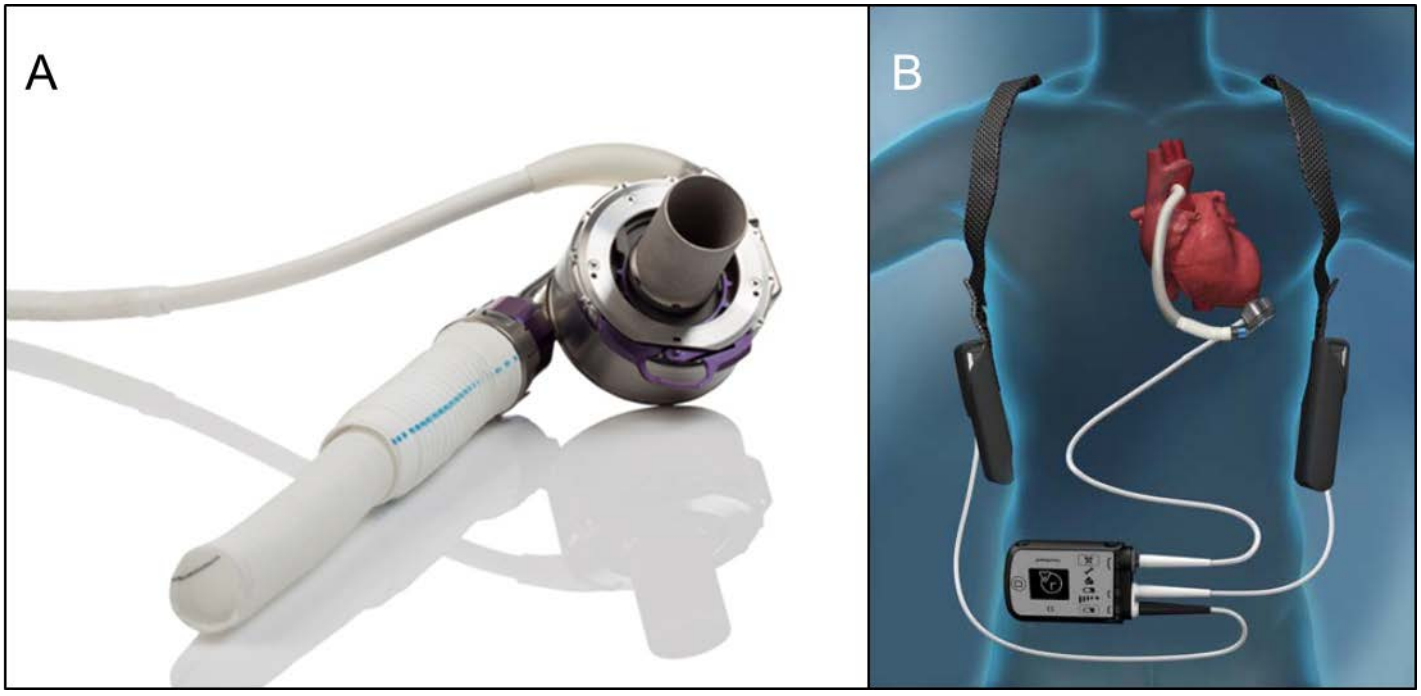


Figure 1 – HeartMate 3 LVAD (A) and System during Battery-powered Operation (B): The HM3 LVAS consists of an LVAD with an outflow graft and modular driveline cable, a pump controller and a power source (i.e. portable Batteries, Power Module, or Mobile Power Unit).

2.3.1 Indication for Use

The HM3 is market released in all geographies participating in this study, therefore refer to the local IFU for the local indication. In the US, the HM3 LVAS is indicated for providing mechanical circulatory support in patients with advanced refractory left ventricular heart failure (e.g. pending cardiac transplantation or myocardial recovery, or for permanent support). In Europe, the HM3 LVAS is intended to provide long term hemodynamic support in patients with advanced, refractory left ventricular heart failure. It is intended either for temporary support, such as a bridge to cardiac transplantation (BTT), or as permanent

destination therapy (DT) and it is intended for use inside or outside the hospital. In Canada, The HM3 LVAS is indicated for providing mechanical circulatory support in patients with advanced refractory left ventricular heart failure (e.g., pending cardiac transplantation or myocardial recovery, or for permanent support).

2.3.2 Description of the Device(s) Under Investigation

The HM3 LVAS consists of a centrifugal LVAD with an outflow graft and modular driveline cable, a pump controller and a power source (i.e. portable Batteries, Power Module, or Mobile Power Unit). The HM3 LVAD is comprised of an Inflow Cannula, a Pump Cover, a Lower Housing, a Screw Ring to attach the Pump Cover to the Lower Housing, a Motor, the Outflow Graft, the Outflow Graft Clip (if required), and a Pump Cable.

The HM3 LVAD has a displacement volume of 80 milliliters and weighs 200 grams. All blood contacting surfaces are composed of titanium (LVAD body and centrifugal rotor) or gelatin-impregnated woven polyester (outflow graft). The HM3 LVAD is designed to reduce adverse events associated with LVAD thrombosis. Primary design features include full magnetic levitation and large flow gaps, which minimize the shear stress imparted onto the blood elements.

The HM3 Controller is an extracorporeal interface device that receives power from the Power Module, Mobile Power Unit, or portable Batteries, and appropriately delivers that power to the HM3 LVAD. It is the primary user interface and has several important functions including:

- operating condition display,
- source of audible and visible alarms,
- communication link for transferring event/period log and alarm information, and
- battery backup in the case of full power disconnection.

The HM3 LVAD and Controller are sterilized using 100% ethylene oxide. Please refer to the local IFU for additional information regarding the device used in this clinical investigation.

2.3.3 Device Accountability

All devices used in this study will be commercial stock at each investigative site. The HM3 is commercially available and approved for the patient population enrolled in this study; therefore, study specific device accountability is not required. The standard commercial practices for device tracking, return and reporting to the Sponsor's Product Performance Group should be followed in accordance with local practices.

2.4 Treatment Arm Medication

2.4.1 Project Management

ALMAC Clinical Services will manufacture the blinded treatment arm medication at their facility at 25 Fretz Road, Souderton, PA 18964. The medication shall consist of 100mg aspirin blinded against a matching placebo. Distribution logistics, site inventory management, patient randomization and treatment arm medication bottle requisition will be coordinated by ALMAC Clinical Services' WebEZ system. Treatment arm medication will be stored in Souderton PA and may be stored in international depot sites administered by ALMAC including Craigavon, Northern Ireland and Singapore, prior to dispatch to sites. Medication accountability will be performed at their facility in Durham, NC or may be performed at depot sites in Craigavon, Northern Ireland or Singapore. Treatment arm medication accountability will include pill counts

of any bottle requisitioned to a patient and opened, as well as reconciliation of unused bottles that were not requisitioned to a patient or otherwise remain sealed, prior to destruction. All bottles should be returned to ALMAC or reported as lost within the Abbott electronic data capture system (EDC).

ALMAC Clinical Services is a part of ALMAC Group Limited headquartered at ALMAC House, 20 Seagoe Industrial Estate, Craigavon, BT63 5QD, Northern Ireland (Registration Number: NI 41905).

ALMAC Clinical Services responsibilities will be, but not limited to, the following:

- Treatment arm medication manufacture (blinded aspirin with placebo-to-match), including packaging and labelling (due to country-specific requirements treatment arm medication bottle labeling may vary)
- Patient randomization via the ALMAC WebEZ system
- Supplying treatment arm medication to sites including maintaining adequate site supply
- Providing support dispensing to study subjects via the ALMAC WebEZ system
- Treatment arm medication accountability, including both used and unused drug bottle returns

2.4.2 Treatment Arm Blinding

This study shall use 100mg aspirin, blinded against a placebo-to-match. Sites should reach out to the sponsor immediately regarding unblinding questions.

2.4.3 Treatment Arm Bottle Dispensing

Initial dispensing of the treatment arm bottle will occur upon randomization. Subjects will begin taking the treatment arm medication within 24 hours of randomization. Subjects will be resupplied 1 bottle at Month 3, Month 6, and Month 9 follow-up visits and 2 bottles at month 12 and every 6 months thereafter until study closure. Dispensing will be controlled at the sites with the use of ALMAC Clinical Services' WebEZ system. At each dispensing time point, the designated site personnel will log on to the WebEZ system, enter information required for randomization or resupply, and requisition a bottle to dispense to the subject from the on-site stock.

Each bottle will be tracked by individual bottle number. The WebEZ system will provide sites with the bottle number to be dispensed to a given subject. Bottle details should be tracked per patient by sites. Site supply and resupply shipments will be automatically controlled by ALMAC Clinical Services.

If a subject reports a lost or empty bottle of treatment arm medication or is unable to attend a resupply visit, the designated site personnel will log onto the WebEZ system to requisition a replacement bottle from the onsite supply. The replacement bottle may be shipped overnight to the subject, or the subject may choose to retrieve the replacement bottle from the site in person.

Subjects should always be sufficiently supplied with treatment arm medication until their next resupply visit. Each bottle will contain 120 capsules of the treatment arm medication, which is a sufficient supply for the period leading up to the subject's next visit, including the acceptable visit windows. Sites should carefully schedule follow up visits to ensure subjects are always sufficiently supplied.

2.4.4 Antithrombotic Therapy

Antithrombotic therapy throughout the study should consist of a vitamin K antagonist (e.g. warfarin, fluindione, phenprocoumon, etc.) and the treatment arm medication. No additional anti-platelet agents

will be added while patients are on the treatment arm medication. The treatment arm medication will be taken once daily by mouth. Vitamin K antagonist therapy will be per standard of care (SOC) with a target INR of 2.0-3.0. The use of aspirin and a vitamin K antagonist is normal clinical practice at many centers and is part of the HM3 IFU.

2.4.5 Treatment Arm Medication Accountability

To ensure treatment arm medication accountability, all bottles including (if applicable) all unused doses will be returned to ALMAC Clinical Services by the site. Subjects will be instructed to return the bottle and any unused doses of the treatment arm medication at each resupply visit.

The bottles and unused doses will be shipped (at the Sponsor's expense) per country- or region-specific Treatment Arm Medication Accountability Return Instructions.

In the event that a site has several bottles or unused portions to return to ALMAC Clinical Services, return shipments may be combined into a batch shipment. Empty research bottles and unused doses should not be stored on site and should be shipped to ALMAC Clinical Services within 14 days of receipt from the subject. Treatment Arm Medication Accountability Return Instructions will be provided during training.

2.4.6 Aspirin Response Testing

US-based patients receiving the treatment arm medication will have their response to aspirin assessed by serum thromboxane B2 testing. Testing will be performed by a core lab (Corgenix, Broomfield, Colorado). To retain the study blind, sites will not receive the results of the test. Samples will be collected and processed by the sites at baseline, 3, 6, and 12 months post-implant. Samples will be stored frozen at the sites until they are shipped (within 15 days of collection; overnight shipment Monday-Thursday with sufficient dry ice to retain frozen state) to Corgenix at:

Coregenix Clinical Laboratory
ATTN: General Supervisor
11575 Main Street
Suite 400
Broomfield CO 80020

Additional sample processing, storage, and shipment details will be provided in the ARIES HM3 Aspirin Response Instructions.

NOTE: Additional antiplatelet testing or platelet function testing, beyond the core lab test, should not be performed while patients are on the treatment arm medication, as it may result in un-blinding of the subject or the investigator.

3.0 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 versus vitamin K antagonist with placebo. Subjects will be randomized in a 1:1 ratio.

Clinical Investigation Plan

The clinical investigation has been designed to involve as little pain, discomfort, fear, and any other foreseeable risk as possible for subjects. Refer to the Risks Analysis section of this clinical investigation plan for details.

The clinical investigation will be conducted at up to 50 centers worldwide. Greater than 50% of the patients enrolled in this study will be from centers based in the United States. The primary, secondary, and safety endpoints will be evaluated according to the statistical section (Section 8 and in the study statistical analysis plan; SAP). Outcomes for this study include death, transplant, withdrawal or pump exchange. All subjects, site, Clinical Events Committee (CEC), and sponsor personnel (with exceptions noted in the study blinding plan) will remain blinded to the randomization scheme until the last ongoing study subject completes follow-up (specifically, experiences an outcome or has final study visit) and all data have been collected and adjudicated. Exceptions will be justified in the study blinding plan (e.g. data management, safety, biometrics). 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.

3.1 Clinical Investigation Procedures and Follow-up Schedule

The study flow chart (Figure 2) and the follow-up schedule of this clinical investigation are described below.

Clinical Investigation Plan

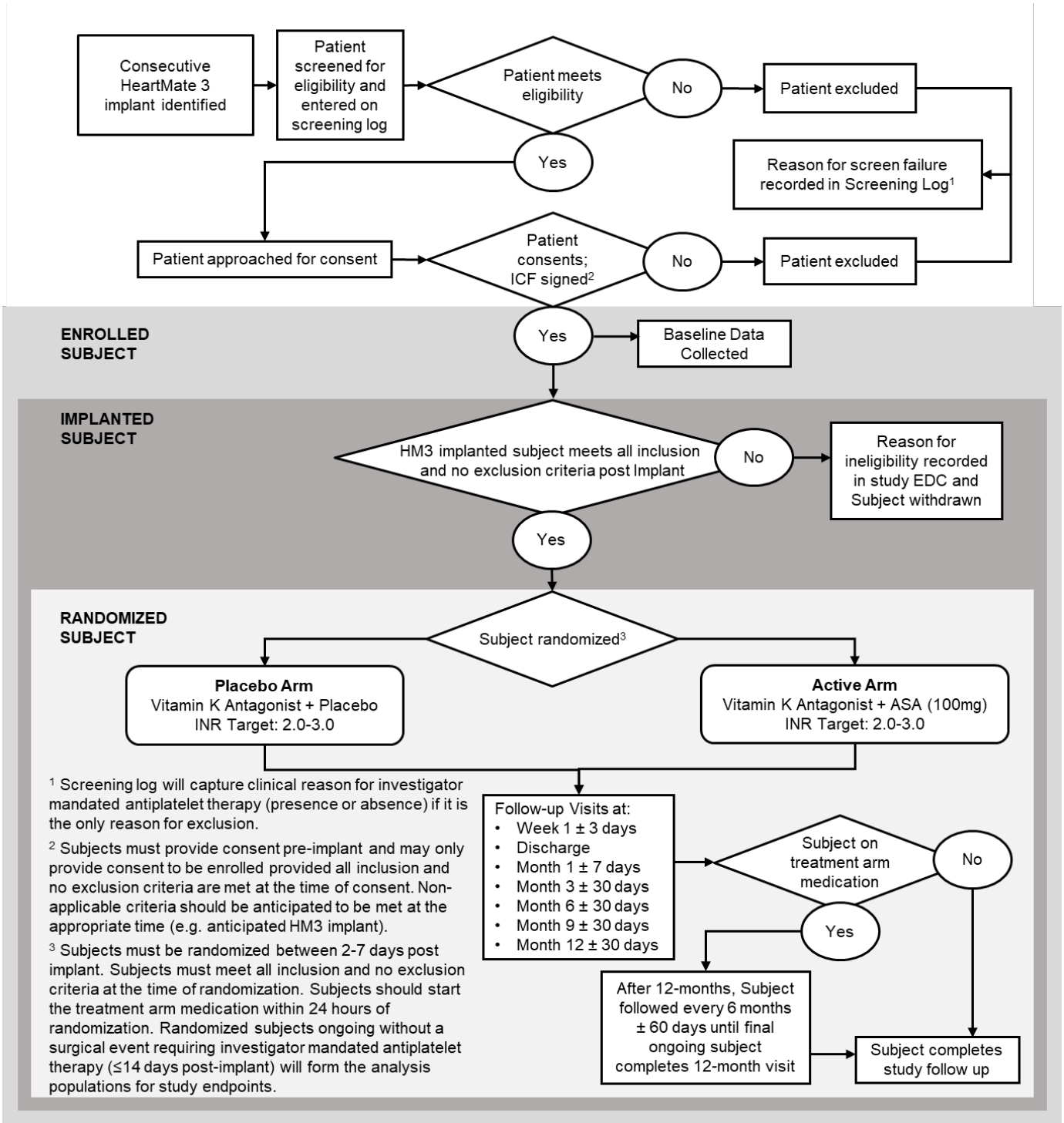


Figure 2 – Clinical Investigation Flow Chart

3.2 Measures Taken to Avoid and Minimize Bias

This study is designed to minimize bias by blinding all subjects, site personnel, sponsor personnel (with exceptions noted in the study blinding plan), and the CEC to the randomly assigned treatment regimen. Furthermore, screening logs will be captured including details on patients who are excluded from the study only because of investigator mandated antiplatelet therapy (presence or absence) prior to or after consent to understand any effect of selection bias on the generalizability of the study.

3.3 Suspension or Early Termination of the Clinical Investigation

While no formal statistical rule for early termination of the clinical investigation for insufficient effectiveness of the device under investigation is defined by the Sponsor or Steering Committee, the Sponsor reserves the right to discontinue the clinical investigation at any stage or reduce the follow-up period with suitable written notice to the investigator. Possible reason(s) may include, but are not limited to:

- Unanticipated adverse device effect (e.g., UADE) occurs and it presents an unreasonable risk to the participating subjects
- An oversight committee (e.g., Steering Committee, DSMB) makes a recommendation to stop or terminate the clinical investigation (such as in the event of higher frequency of anticipated adverse device effects)
    - The Data Safety Monitoring Board will create independent rules for study oversight including prespecified rules for recommending cessation of the study, which will be captured in the DSMB charter. In the event these rules are met, the sponsor will meet with the Steering Committee. The Sponsor will notify sites and, if agreed with the Steering Committee, enrollment in the study will be paused.
- Further study progress is cancelled.

Should the clinical investigation be discontinued by the Sponsor, subjects will be followed per routine hospital practice with device-related AEs reported to the Sponsor as per vigilance/commercial reporting requirements. The investigator shall return all clinical investigation materials (including both partially used and unused treatment arm medication bottles) to ALMAC or the Sponsor, as appropriate, and provide a written statement to the IRB/EC (if applicable). All applicable clinical investigation documents shall be subject to the same retention policy as detailed in Section 11.5 of the CIP.

A Principal Investigator, IRB/EC or regulatory authority may suspend or prematurely terminate participation in the clinical investigation at the investigational site(s) for which they are responsible. The investigators will follow the requirements specified in the Clinical Trial Agreement.

If the Sponsor suspends or prematurely terminates the clinical investigation at an individual site in the interest of safety, the Sponsor will inform all other Principal Investigators.

If suspension or premature termination occurs, the Sponsor will remain responsible for providing resources to fulfill the obligations from the CIP and existing agreements for following the subjects enrolled in the clinical investigation, and the Principal Investigator or authorized designee will promptly inform the enrolled subjects at his/her site, and return patients to their standard medical treatment.

Clinical Investigation Plan

4.0 ENDPOINTS

4.1 Primary Endpoint and Rationale

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 is defined as any event occurring > 14-days post implant.
[2] - Major Hemocompatibility Related Adverse Events include:

- 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 between the two groups. Additional safety and secondary endpoints will also be evaluated to monitor effects on other safety and efficacy 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 the 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. Refer to section 8 of this CIP and the SAP for details.

4.2 Secondary Endpoint

As a secondary endpoint, non-surgical bleeding rates will be compared between the two arms of the study using all patient follow up as detailed in section 8 of this CIP and the SAP.

4.3 Safety Endpoints

To assess the safety of removal of antiplatelet therapy from the antithrombotic regimen, survival, stroke rates, and pump thrombosis rates will be compared between the two arms of the study using all patient follow up as detailed in section 8 of this CIP and the SAP.

4.4 Descriptive Endpoints

This study will also assess changes in the Hemocompatibility Score, Rehospitalization, and Economic Cost Implications as a result of removal of antiplatelet therapy from the antithrombotic regimen. Refer to section 8 of this CIP and the SAP for details.

5.0 SUBJECT SELECTION AND WITHDRAWAL

5.1 Subject Population

This clinical investigation will enroll male and female subjects from the advanced heart failure population who, as part of their standard course of treatment, will receive a HM3 LVAD. Subjects are considered enrolled when they provide written informed consent. Subjects must meet all applicable eligibility criteria and provide written informed consent prior to the conduct of any investigation-specific procedures not considered standard of care. Furthermore, patients must meet all randomization eligibility requirements at randomization. Only randomized subjects will continue to be followed in this study. Subjects not meeting randomization eligibility requirements will be withdrawn from the study. Reason(s) for not meeting randomization eligibility requirements will be captured in the study EDC. Randomized subjects ongoing without a surgical adverse event, defined as ≤14 days post-implant, requiring investigator mandated antiplatelet therapy will form the analysis population for study endpoints. Details are available in section 8 of this CIP and the SAP.

5.2 Subject Screening and Informed Consent

5.2.1 Subject Screening

Patients receiving an LVAD at study sites should be considered for enrollment. All patients evaluated for inclusion in the clinical study, including those who provide informed consent and are enrolled, will be recorded on the site screening log. Rationale for exclusion from the trial will be recorded. Specifically, reasons may include refusal to consent, did not meet eligibility criteria or other specified reasons. To monitor for selection bias in enrollment, any patient excluded exclusively due to an investigator mandated antiplatelet therapy (either mandated antiplatelet presence or mandated absence of antiplatelets) will require specific clinical reasons recorded on the screening log.

Potential subjects presenting at the clinical sites will be fully informed about the clinical investigation, following the established informed consent process (described in Section 5.2.2). Once informed consent is obtained, subjects are considered enrolled. Thereafter, all subjects will have required baseline data beyond site standard of care captured and US-based patients will have blood drawn for baseline aspirin responsiveness testing (per section 2.4.6).

5.2.2 Informed Consent

The Investigator or his/her authorized designee will conduct the informed consent process, as required by applicable regulations and the center's IRB/EC. This process will include a verbal discussion with the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate, such as details of clinical investigation procedures, anticipated benefits, and potential risks of clinical investigation participation. Subjects must be informed about their right to withdraw from the clinical investigation at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled. Withdrawal from the clinical investigation will not jeopardize their future medical care or relationship with the investigator.

During the discussion, the Principal Investigator or his/her authorized designee will avoid any improper influence on the subject and will respect the subject's legal rights. Financial incentives will not be given to the subject. The subject shall be provided with the informed consent form written in a language that is

understandable to the subject and has been approved by the center's IRB/EC. The subject shall have adequate time to review, ask questions, and consider participation. The Principal Investigator or his/her authorized designee will make efforts to ensure that the subject understands the information provided. If the subject agrees to participate, the informed consent form must be signed and dated by the subject and thereafter by the person obtaining the consent prior to any clinical investigation-specific procedures beyond SOC. The signed original will be filed in the subject's hospital or research charts, and a copy will be provided to the subject.

Failure to obtain informed consent from a subject prior to clinical investigation enrollment should be reported to Sponsor within 5 working days and to the reviewing center's IRB/EC according to the IRB's/ EC's reporting requirements.

If, during the clinical investigation, new information becomes available that can significantly affect a subject's future health and medical care, the Principal Investigator or his/her authorized designee will provide this information to the subject. If relevant, the subject will be asked to confirm their continuing informed consent in writing.

In addition, an authorization for use and disclosure of the subject's protected health information, in accordance with the Health Insurance Portability and Accountability Act (HIPAA) or local equivalent, as applicable, must be obtained from the subject. This may be incorporated into the main ICF or captured as a standalone document.

This study will not permit informed consent via legally authorized representatives. Therefore, incapacitated individuals, including the mentally handicapped or individuals without legal authority or individuals under the age of 18 or local age of legal consent, are excluded from the study population. Furthermore, individuals unable to read or write are excluded from the study population.

5.3 Eligibility Criteria

Assessment for general eligibility criteria is based on the medical records of the site and an interview with a candidate patient. If some of the clinical and laboratory tests are not included in site standard tests, they must be done but after written informed consent is obtained. Patients must meet ALL of the inclusion criteria to be considered for the clinical investigation. If ANY of the exclusion criteria are met, the patient is excluded from the clinical investigation and cannot be enrolled. If the subject is found after the time of informed consent but prior to randomization to no longer meet any of the inclusion criteria, or to meet any of the exclusion criteria (randomization eligibility), the subject will not be randomized and will be withdrawn from the study.

5.3.1 Inclusion Criteria

1. Subject will receive the HeartMate 3 per standard of care (SOC) in accordance with the approved indications for use in the country of implant.
2. Subject will receive the HeartMate 3 as their first durable VAD.
3. Subject must provide written informed consent prior to any clinical investigation related procedure.
4. In female patients of child bearing capability, subject will not be currently pregnant or breastfeeding and on appropriate contraception.

5.3.2 Exclusion Criteria

1. Post-implant additional temporary or permanent mechanical circulatory support (MCS).
2. Investigator mandated antiplatelet therapy for other conditions (including mandated presence or absence of antiplatelet agent).
3. Patients who are nil per os (NPO) post-implant through day 7.
4. Subjects with a known allergy to acetylsalicylic acid (aspirin).
5. Participation in any other clinical investigation(s) involving an MCS device, or interventional investigation(s) likely to confound study results or affect study outcome.
6. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements, or impact the scientific soundness of the clinical investigation results.

5.4 Subject Enrollment

Once informed consent is obtained, subjects are considered enrolled. Subject data entry into the EDC will begin following enrollment into the clinical investigation. Subject data will be collected following enrollment to the clinical investigation until the subject is withdrawn, experiences an outcome (transplant, explant, exchange, or death), or completes study follow-up.

Subjects who provide informed consent and are subsequently found to not meet inclusion/exclusion criteria prior to randomization or otherwise do not proceed to randomization will be withdrawn in accordance with section 5.5 of this CIP. Subjects who experience a surgical adverse event prior to day 14 that requires investigator mandated antiplatelet therapy (either presence or absence) will be withdrawn and not included in the analysis population. Subjects who expire prior to day 14 will not be included in the analysis population. All patients considered for this study, including enrolled subjects not included in the analysis population, will be reported in the study consort diagram.

5.4.1 Enrollment of Medicare Beneficiaries

This clinical investigation will enroll both Medicare beneficiaries and private payors in the US. Because this study enrolls Medicare beneficiaries, it conforms to all standards of Medicare coverage requirements. The Risks and Benefits in section 15 of this CIP describe how all enrolled subjects, including Medicare beneficiaries, may be affected by the hypothesis under investigation. The demographics representative of LVAD therapy reflect primarily a CMS population. Common complications associated with LVADs are frequently associated with hemocompatibility-related adverse events such as pump thrombosis, stroke and bleeding events. Improvements in contemporary LVAD technology with the HeartMate 3 LVAD have shown significant improvement in reduction of pump thrombosis, stroke and bleeding, but bleeding events persist at a high incidence. If bleeding events could be reduced with the withdrawal of antiplatelet therapy from the antithrombotic regiment with HM3, this could improve clinical outcomes for Medicare beneficiaries and have added relevancy to their treatment plan. For this purpose, it is important that Medicare beneficiaries are studied in this trial so that relevant outcomes may be translated more broadly.

To further characterize the portion of the subjects enrolled in the clinical investigation that display characteristics consistent with the Medicare population based on age, the clinical investigation results will

be analyzed by age (< 65 years and ≥ 65 years) to ensure that the outcomes are similar between the Medicare and non-Medicare populations. Additional subgroup analyses are detailed in section 8.5.

5.4.2 Historically Under-Represented Demographic Subgroups

The Sponsor intends to implement the FDA's guidance on sex-specific data in medical device clinical investigations to ensure adequate representation of women and other traditionally under-represented demographic subgroups in this clinical investigation. As noted in the guidance, some barriers to participation of women and ethnic minorities in clinical investigations have traditionally been:

- Lack of understanding about main obstacles to participation of such subgroups in clinical research
- Inclusion/exclusion criteria potentially not needed to define the clinical investigation population may unintentionally exclude specific subgroups
- Under diagnosis of disease etiologies and pathophysiology leading to under referral of demographic subgroups
- Sex differences in disease etiology, which predispose one sex to LVAD therapy
- Avoidance of specific subgroups by investigators and Sponsors due to the perception that it takes more time and resources to recruit them
- Family responsibilities limiting women's ability to commit time for follow-up requirements

The Sponsor will take the following steps to ensure adequate representation of women and racial or ethnic minorities in this clinical investigation:

- All patients receiving an LVAD at enrolling sites will be considered for this study and this data will be reviewed regularly
- The Sponsor will provide training to investigational site personnel to ensure adequate representation of these demographic subgroups
- As appropriate and necessary, the Sponsor will retrain sites on the importance of recruiting and retaining subjects in the clinical investigation if trends in withdrawal or selection bias are noted
- The Sponsor will approach sites without bias or consideration for specific demographic subgroups
- The Sponsor will have informed consent materials in alternative languages and will work with sites and IRBs/ECs on recruitment materials

5.5 Subject Withdrawal

If a subject does not meet all inclusion criteria, or meets at least one exclusion criteria after the subject is enrolled (consented), but prior to randomization, the subject will be withdrawn and will not be included in the analysis populations.

Those enrolled (consented) subjects that meet all inclusion criteria and no exclusion criteria post implant will be randomized within 2-7 days post-implant (the day of implant is day 0). However, if these subjects do not meet the randomization eligibility criteria, are not randomized, never start the treatment arm

regimen, experience a surgical event (≤ 14 days post implant) that requires investigator mandated anti-platelet therapy or experience an outcome ≤ 14 days post implant then they will be withdrawn.

Each randomized subject shall remain in the clinical investigation until completion of the required follow-up period; however, a subject's participation in any clinical investigation is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit. Conceivable reasons for discontinuation may include, but not be limited to, the following:

- Subject outcome including death, transplant, or device explant or exchange
- Physician or subject voluntary withdrawal
- Subject lost-to follow-up as described below.

The Sponsor must be notified of the reason(s) for subject discontinuation. The site will provide this information to the Sponsor. Investigators must also report this to their respective IRB/EC as defined by their institution's procedure(s).

No additional follow–up will be required or data recorded from subjects once withdrawn from the clinical investigation, except for the status at the time of withdrawal (deceased/alive).

In case of subject withdrawal of consent, the site should make attempts to schedule the subject for a final clinical investigation visit. At this final follow-up visit, the following will be recorded, with the subject's permission:

- Subject status (deceased/alive)
- Any adverse event details prior to withdrawal of consent

Lost-to-Follow-up

If all attempts at contacting the subject have been exhausted, then the subject is considered lost-to-follow-up Site personnel shall make all reasonable efforts to locate and communicate with the subject (and document these efforts in the source documents), including the following, at each contact time point:

- A minimum of two telephone calls on different days over the specified follow-up windows to contact the subject should be recorded in the source documentation, including date, time and initials of site personnel trying to make contact.
- If these attempts are unsuccessful, a letter (certified, if applicable) should be sent to the subject.
- If a subject misses one or more non-consecutive follow-up contact time points, it will be considered a missed visit. The subject may then return for subsequent visits.

Note: Telephone contact with General Practitioner, non-clinical investigation cardiologist or relative without the presence of the subject or indirect documentation obtained via discharge letters will not be considered as subject contact.

5.5.1 Incidental Use of Aspirin Containing Products

At baseline and at each scheduled visit, subjects should be provided with the Sponsor provided list of aspirin containing products. At each visit post-implant, subjects should be asked if they have taken or

been prescribed any of the medications on the list and, if so for what duration. Responses will be captured in the EDC. If a subject reports or other evidence of incidental aspirin use is obtained (i.e. a prescription which the patient confirms from a non-investigator healthcare provider) lasting for a duration of > 7 days, the subject will be withdrawn from the study.

5.6 Transition to Open Label

During a subject's clinical course, post-randomization events may result in the investigator mandating antiplatelet therapy. The mandate may consist of the presence of an antiplatelet or the absence of all antiplatelets from the patient's antithrombotic regimen in response to clinical events. These subjects should remain in the study for the full 12-month study follow up whenever possible. In these instances, the treatment arm medication is no-longer administered, and investigator initiates their mandated therapy. These subjects are considered to have transitioned to open label. Clinical events which resulted in the transition to open label will be documented in the EDC. Subjects who transition to open label after 12 months will be considered to have completed the study required follow up at12 months post implant. Subjects who transition to open label after 12-months of study follow up will be considered to have completed study follow up at that time except if a subject has experienced a stroke or potential stroke neurologic adverse event prior to transitioning to open label, then they will be followed for an additional 60-days post event for MRS score evaluation. In this case, the subject is considered to have reached end of study follow up upon completion of the MRS evaluation.

5.7 Number of Subjects

This study will enroll enough subjects to randomize 628 subjects in the clinical investigation. No site may randomize more than 15% of the total number of randomized subjects without Sponsor authorization.

5.8 Total Expected Duration of the Clinical Investigation

The expected duration of each subject's participation is at least 12 months and up to 36 months post-implant. Scheduled visits and data collection for this clinical investigation will occur at Baseline, Implant, Randomization, Week 1 ± 3 days, Discharge, Month 1 ± 7 days, Month 3 ± 30, Month 6 ± 30 days, Month 9 ± 30 days, Month 12 ± 30 days and, in patients still on the treatment arm medication, follow up will continue every 6 months ± 60 days until the final ongoing patient completes their month 12 follow up visit. Subjects not on the treatment arm medication will be exited from the trial at the conclusion of their month 12 follow-up visit. The expected duration of enrollment is 24 months. Therefore, the total duration of the clinical investigation is expected to be 36 months.

6.0 TREATMENT AND EVALUATION OF ENDPOINTS

6.1 Avoidance of Additional Antiplatelet Medications

Subjects on the treatment arm medication will not be prescribed or administered additional antiplatelet medications.

6.2 Avoidance of Platelet Function Testing

Antiplatelet testing or platelet function testing should not be performed while patients are on the treatment arm medication, except for Aspirin Response Testing per Section 2.4.6. The results of protocol specified Aspirin Response Testing will not be provided the physician or patient through the follow up period. Performing additional antiplatelet testing or platelet function testing may result in un-blinding of the subject or the investigator. Un-blinding of a subject or investigator will be considered a protocol deviation. Sites should address any questions related to potential unblinding to the Sponsor.

6.3 Study Activities and Procedures

The assessments in table 2 will occur throughout the study.

Table 2 – Schedule of Assessments

Assessment	Baseline	Implant	Randomization	Discharge	Week 1 (± 3 days)	Month 1[1] (± 7 days)	Month 3[1] (± 30 days)	Month 6[1] (± 30 days)	Month 9[1] (± 30 Days)	Month 12[1] (± 30 days)	Every 6 months ± 60 days thereafter	As Occurs/ Unscheduled
Inclusion/ Exclusion	X		X									
Informed Consent	X											
Demographics	X											
General and Cardiac Medical History	X											
Coagulation Assessment	X[4]											
Right Heart Catheterization	X[2]											X[4]
Modified Rankin Score (MRS)	X											X
Incidental Use of Aspirin Containing Products	X			X	X	X	X	X	X	X	X	
Vital Signs	X			X	X	X	X	X	X	X		
Laboratory Assessments	X[3]				X	X	X	X	X	X		X[4]
Anticoagulation/Antiplatelet Medications Log	X	X		X	X	X	X	X	X	X		X
Echocardiogram	X[2]				X[4]	X[4]	X[4]	X[4]	X[4]	X[4]		X[5]
Other Medications	X					X	X	X	X	X		
Sample for Core Lab (ASA response, US only)	X						X	X		X		
QOL and Functional Capacity	X						X	X		X		
Implant Data		X										X[6]
Enrollment	X[7]											
Randomization			X									
Pump Parameters		X			X	X	X	X	X	X		X[5]
Bottle Requisition via WebEZ			X				X	X	X		X[8]	X
Bottle Dispensing/Return Log			X				X	X	X	X	X[8]	X
Return Used Bottle to for Accountability							X	X	X	X	X[8]	
Initial Discharge Data				X								
Cardiac Arrhythmias Assessment (e.g. EGM, EKG)	X				X	X	X	X	X	X		X
Subject Status				X	X	X	X	X	X	X	X[8]	
INR & LDH Log	X			X	X	X	X	X	X	X		X
Death												X
Withdrawal (early termination)												X
Transition to Open Label												X
Hospitalizations												X
Adverse Events												X

Clinical Investigation Plan

Assessment	Baseline	Implant	Randomization	Discharge	Week 1 (± 3 days)	Month 1[1] (± 7 days)	Month 3[1] (± 30 days)	Month 6[1] (± 30 days)	Month 9[1] (± 30 Days)	Month 12[1] (± 30 days)	Every 6 months ± 60 days thereafter	As Occurs/ Unscheduled
Device Deficiencies												X
Operative Procedures (excluding primary implant)												X

[1] *For follow-up visit scheduling, one month = 30 days.*
[2] *Most recent results within 30 days prior to implant, if collected as SOC.*
[3] *Most recent results obtained within 30 days prior to implant will be permitted as baseline data.*
[4] *If performed as SOC.*
[5] *At time of suspected thrombotic adverse event or pump exchange, if performed as SOC.*
[6] *Pump exchange data collection includes all required implant data for HM3 to HM3 exchanges and all relevant data for HM3 to other LVAD exchanges.*
[7] *Subject is considered enrolled upon signing of the informed consent form.*
[8] *Subjects on the treatment arm medication will be followed every six months after the 12-month visit. Safety monitoring including adverse events, outcomes and device deficiencies and other associated "as occurs" procedures will be collected*

The clinical study will be conducted in accordance with the CIP. All parties participating in the implementation of the study will be qualified to perform their designated tasks by education, training, and experience. Applicable documentation will be maintained.

No study activities may begin until the site has received written Sponsor approval. Copies of written approval from the IRB and/or the relevant regulatory authorities, as well as all required regulatory documents must be received by the Sponsor before approval will be given.

6.4 Baseline

The baseline assessments in table 3 will be performed.

Table 3 – Baseline Data Collection

Study Activity	**Data Collection**
Informed Consent	Informed consent details
Inclusion/Exclusion	Subject's eligibility details
Demographics	Age, height, gender, ethnicity, race, blood type, INTERMACS profile, and NYHA class

Clinical Investigation Plan

Study Activity	Data Collection
General and Cardiac Medical History	Etiology of HF, duration of HF, therapeutic intent (BTT/BTC/DT), arrhythmias, prosthetic valve(s), history of stroke, diabetes, smoking, history of bleeding (diverticular disease, diagnosed arteriovenous malformations (AVMs), GI ulcer(s), anemia and/or erythropoietin treatment), aortic stenosis, hypertension, history of MI, peripheral thromboembolism, coronary stents, CABG, substance abuse (drug/alcohol), drug/radiation toxicity, peripheral vascular disease, carotid artery disease, cardiac rhythm management device, intra-aortic balloon pump, other pre-implant circulatory support, CardioMEMS, and HIV status
Modified Rankin Score	Modified Rankin Score (MRS)
Vital Signs	Weight, blood pressure, and heart rate
Anticoagulation/Antiplatelet Medications	Vitamin K antagonist (e.g. warfarin, fluindione, phenprocoumon, etc.), clopidogrel, dipyridamole, other anticoagulation agents, other vitamin K antagonists, direct thrombin inhibitors, etc. (including treatment arm medication) *All new medications started, or current medications stopped during the follow-up period must be recorded. All dose changes (including IV titrations as total daily dose) during the follow-up period must be recorded with the exclusion of vitamin K antagonist. Only the type, start and stop dates, and target INR will be collected for vitamin K antagonist.*
Other Medications	ACE inhibitors, inotropes, ARBs, beta blockers, antiarrhythmics, statins, nitrates, allopurinol, aldosterone blockers, antibiotics, diuretics, insulin and antidiabetic medications, and other cardiovascular medications
Laboratory Assessments[1]	Hemoglobin (Hgb), Hematocrit (Hct), White Blood Cell Count (WBC), Platelets (PLT), Creatinine (Cr), Estimated Glomerular Filtration Rate (eGFR), LDH and INR, liver function tests (AST, ALT, total bilirubin, albumin, pre-albumin), blood urea nitrogen (BUN) Collected only if SOC: Activated Partial Thromboplastin Time (aPTT), Partial Thromboplastin Time (PTT), Plasma free Hgb (PHgb), D-Dimers, P Selectin, and fibrinogen. For diabetic patients: HbA1c, and fasting glucose
Coagulation Assessment[2]	Collected only if prior testing performed or SOC: Tests may include but are not limited to HIT, protein C deficiency, protein S deficiency, antithrombin deficiency, plasminogen deficiency, lupus anticoagulant, factor V Leiden, prothrombin G20210A mutation, and primary antiphospholipid syndrome
Right Heart Catheterization[2]	Central venous pressure (CVP) or right atrial pressure (RAP), systolic, diastolic and mean pulmonary artery pressure (PAS, PAD, PAM), pulmonary capillary wedge pressure (PCWP), cardiac output (CO), and cardiac index (CI)
Echocardiogram[2]	Type of assessment, LVEF, LVEDD, LVESD, AI, MR, TR, PR, including severity and/or grade, and presence of LV or LA thrombus, and aortic valve opening ratio

Study Activity	Data Collection
QOL and Functional Capacity	EQ-5D-5L, 6-minute Walk Test (if subject is able, reason must be provided if not performed), NYHA Class, INTERMACS Profile

[1] *Most recent results obtained within 30 days prior to implant will be permitted as baseline data.*
[2] *If collected per standard of care, most recent results within 30 days prior to implant.*

6.5 Implant Procedure

The data in table 4 will be collected for each subject's HM3 implant procedure.

Table 4 – Implant Procedure Data Collection

Study Activity	Data Collection
HM3 System Information	VAD serial number, reference number and date of implant of entire implanted system
Implant Data	Presence of intracardiac (LA or LV) thrombus, concurrent procedures, Factor VII administration, vitamin K administration, anti-fibrinolytic administration, pump position, transfusions (whole blood, packed red blood cells [PRBC], fresh frozen plasma [FFP], platelets, cryoprecipitate, Cell Saver), cardiopulmonary bypass (CPB) time, and total implant time, procedure initiation/completion time, additional post-implant MCS
Pump Parameters	Pump Speed, Pump Flow, Pulsatility Index, and Pump Power

6.6 Randomization

Only subjects who have provided informed consent, been enrolled, been implanted with the HM3 and subsequently met all inclusion and no exclusion criteria (randomization eligibility) will be randomized in the study. Randomization will be performed through ALMAC Clinical's WebEZ system. Subjects will be randomized 1:1, by site, and in permuted blocks of 4. Prior to randomizing a patient in WebEZ, patients will have been initialized in the Sponsor's EDC portal upon enrollment and obtained a subject ID number, which will also be used as the patient identifier in the WebEZ system. Subjects should begin taking the treatment arm medication within 24 hours of randomization.

6.7 Initial Discharge Data

Upon discharge from the initial hospitalization for the implant procedure, the days hospitalized, including the days in the Intensive Care Unit, will be collected. Vital signs and subject status will be recorded along with anticoagulation/antiplatelet medications, LDH, and INR logs.

6.8 Scheduled Follow-up for All Subjects

The required assessments (detailed in tables 2 and 6), follow-up schedule, and associated visit windows (table 5) are generally aligned with SOC LVAD patient follow up and MCS registry data collection. All follow-up visits are based on the initial implant date. The windows for each follow-up visit are as follows:

Clinical Investigation Plan

Table 5 – Follow-up Visit Windows

Randomization	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7+
2-7 days	Week 1 ± 3 days	Month 1 ± 7 days	Month 3 ± 30 days	Month 6 ± 30 days	Month 9 ± 30 days	Month 12 ± 30 days	Every 6 Months ± 60 days

The follow-up visit must occur within the designated window. Follow-up assessments for a single visit do not have to occur on the same date, but must occur within the designated window, or will be considered a protocol deviation. The Sponsor understands that some lab results may be received several days after the visit has occurred, in these instances the date the lab occurred is considered as the date the blood draw occurred. All subjects should be asked, at each follow up visit after discharge, if they were seen at an outside facility. If so, medical records from any facility that has seen the patient must, with the subject's consent, be requested and reviewed for potential adverse events.

For subjects not on the treatment arm medication, the completion of the Month 12 visit will signify completion of the study, with the exception of some lab results that may be received after the visit has occurred, no other assessments or study related activities may be performed after the final visit has occurred, even if later assessments are performed within the acceptable window. Month 12 assessments (including required laboratory assessments blood draws) not collected by the date of the final visit will be considered protocol deviations.

Subjects on the treatment arm medication will continue to be followed every 6 months after their month 12 visit until the final ongoing patient completes their month 12 visit. Upon close of enrollment, the sponsor will notify sites of the anticipated date of study conclusion which will be 12 months after the last patient enrolls. All required visit data must be collected by the final visit, as outlined above.

Table 6 – Scheduled Follow-Up Visit Data Collection through 12-months

Study Activity	Definition
Subject Status	Whether the subject is ongoing on HM3 LVAD support, if not, what was the outcome the patient experienced
Vital Signs	Weight, blood pressure and method of blood pressure measurement
Pump Parameters	Pump Speed, Pump Flow, Pulsatility Index, and Pump Power
Cardiac Arrhythmias	Atrial (fibrillation/flutter), ventricular (fibrillation/VT), and treatment
Anticoagulation / Antiplatelet Medications	All changes made during the follow-up period *All new medications started, or current medications stopped during the follow-up period must be recorded. All dose changes (including IV titrations) during the follow-up period must be recorded with the exclusion of* vitamin K antagonist*. Only the type, start and stop dates, and target INR will be collected for* vitamin K antagonist*.*
Other Medications	ACE inhibitors, inotropes, ARBs, beta blockers, antiarrhythmics, statins, nitrates, allopurinol, aldosterone blockers, antibiotics, diuretics, insulin and antidiabetic medications, and other cardiovascular medications
Treatment Arm Bottle Dispensing/Return Log	All bottles dispensed during the follow-up period (Month 3, 6 and 9 follow-up visits only), including replacement bottles that are dispensed outside of the follow-up

Study Activity	Definition
	schedule, bottle status (lost by patient, returned to ALMAC) and shipping information. All bottles and unused doses must be returned to ALMAC Clinical within 14 days of receipt from subject.
Laboratory Assessments	Hemoglobin (Hgb), Hematocrit (Hct), White Blood Cell Count (WBC), Platelets (PLT), Creatinine (Cr), Estimated Glomerular Filtration Rate (eGFR), liver function tests (AST, ALT, total bilirubin, albumin, pre-albumin), blood urea nitrogen (BUN), Log Data (all measurements during the follow up period will be collected with, at a minimum, 1 reading within each follow up window): LDH and INR. Collected only if SOC: Activated Partial Thromboplastin Time (aPTT), Partial Thromboplastin Time (PTT), Plasma free Hgb (PHgb), D-Dimers, P Selectin, and fibrinogen. For diabetic patients: HbA1c, and fasting glucose *Note: To protect blinding of the study, platelet function testing (including ASA resistance testing) will not be performed while patient is on the treatment arm medication, except as outlined in section 2.4.6.*
[1] Echocardiogram	LVEF, LVEDD, LVESD, AI, MR, TR, PR, including severity and/or grade, and presence of LV or LA thrombus, and aortic valve opening ratio
QOL and Functional Capacity	EQ-5D-5L, 6-minute Walk Test, NYHA Class, INTERMACS Profile

[1] *If collected per SOC.*

6.8.1 Continued follow up beyond 12-months post implant

Subjects on the treatment arm medication will be followed every six months after the 12-month follow up visit. Only treatment arm medication bottle details, subject status (including death, withdrawal, or transplant) along with adverse events and device deficiencies will be collected along with additional supportive data should adverse events or device deficiencies occur. If a patient's clinical course after 12 months of follow up requires transition to open-label, the patient will be considered to have reached the end of study follow up unless the transition to open label is due to a stroke, in which case the patient should be followed for an additional 60-days to capture the MRS score . The clinical reason for transition to open-label will be captured. Subjects transitioned to open label prior to 12 months of follow up should be followed to their 12-month follow up.

6.9 Unscheduled Visits

6.9.1 Adverse Events

For additional details regarding adverse events, refer to section 7. Data related to adverse events will be collected as they occur. Depending on the type of adverse event, relevant data will be collected.

6.9.1.1 Neurologic Adverse Events

Modified Rankin Scores (MRS) scores will be captured at:

- Baseline,

- The time of any stroke or potential stroke events, and
- 60-days after any stroke or potential stroke events to adjudicate the severity of the event.

MRS will be determined by an independent assessor, defined as an independent, trained, and certified clinician. Event severity will be determined based on MRS, specifically MRS > 3 as disabling versus MRS ≤ 3 as nondisabling. Strokes will be characterized as ischemic or hemorrhagic in etiology with ischemic-hemorrhagic conversion considered an ischemic stroke.

6.9.2 Operative Procedures

Data related to any cardiac or non-cardiac operative procedures, excluding the primary HM3 LVAD implant, occurring after enrollment will be collected. Operative procedures must be reported to the Sponsor through the EDC system within three days of awareness of the event or, at the latest, if the operation is unknown to the implanting site (i.e. occurring at another facility), during the next follow-up visit. For pump exchanges, additional implant data will be collected, including exchange status and pump exchange type.

6.9.3 Hospitalizations

All hospitalizations, excluding the primary implant hospitalization, with associated reasons will be captured during the follow-up period for all subjects. While hospitalized, the follow-up visit assessments will continue to be performed according to the follow-up schedule. Hospitalizations must be reported to the Sponsor through the EDC system within three days of awareness or discovery of the event or, at the latest, if the hospitalization is unknown to the implanting site (i.e. occurring at another facility), during the next follow-up visit.

6.9.4 Outcomes

Subjects will be followed for at least 12 months and until the final ongoing subject reaches their 12 month visit or an outcome is reached, whichever occurs first. Outcomes include death, heart transplantation, device explant, and withdrawal from the study. Outcomes must be reported to the Sponsor through the EDC system immediately upon discovery of the event. Subjects should continue follow up through 12-months whenever possible, even in the instance the subject has transitioned to open-label (e.g. due to pump thrombosis the investigator believes the patient should remain on open-label aspirin therapy).

If a subject receives a pump exchange during the follow-up period, this event will be considered a device explant outcome and data will be collected on the pump exchange procedure but not after. If a subject has a device explanted for suspected or confirmed pump thrombosis, the pump will be returned to the Sponsor for analysis. Standard commercial processes will be used for pump return.

6.10 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 (with exceptions noted in the study blinding plan), 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, all data have been received, and all adverse events have been adjudicated. Questions related to unblinding should be directed to the Sponsor.

6.11 Patient Reported Outcome (PRO) Measure

The Coordinator or designee will administer patient-reported outcome questionnaires. It is important the subject understands the meaning of all words and instructions in the questionnaires. The subject should be instructed to ask any questions about the questionnaires if further explanation is needed. Once the questionnaires are completed, the Coordinator or designee will review for completeness to verify that all questions have been answered according to the directions provided.

The following PRO measures will be collected according to the requirements of the questionnaire and this CIP.

- EQ-5D-5L - EuroQOL

The EQ-5D-5L is a standardized measure of health status developed by the EuroQOL Group in order to provide a simple, generic measure of health for clinical and economic appraisal. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of healthcare as well as in population health surveys. The questionnaire will take approximately two minutes to complete.

The EQ-5D-5L consists of two components – the EQ-5D-5L descriptive system and the EQ Visual Analogue scale (VAS). For the descriptive system, five dimensions are measured (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension has five levels: 1=none, 2=slight, 3=moderate, 4=severe, and 5=extreme. The respondent indicates his or her health state by ticking in the box against the most appropriate statement in each of the five dimensions. The VAS is scored from 0 (worst health) to 100 (best health).

7.0 ADVERSE EVENTS

To comply with worldwide standards and guidelines on clinical investigation adverse event reporting, the Sponsor has adopted uniform and worldwide applicable standard definitions and reporting timelines to be used and adhered to by the investigators.

7.1 Definition

7.1.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects.

7.1.2 Serious Adverse Event

If the AE meets any of the criteria below, it is regarded as a serious adverse event (SAE).

a) Led to a death,

b) Led to a serious deterioration in health of the subject, that either resulted in

   1. a life-threatening illness or injury, or
   2. a permanent impairment of a body structure or a body function, or

3. in-patient hospitalization or prolongation of existing hospitalization, or
4. medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
5. chronic disease

c) Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note: A planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a serious deterioration in health, is not considered to be an SAE.

7.1.3 Device Deficiency

Device deficiency is defined as an inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling. This includes the failure of the device to meet its performance specifications or otherwise perform as intended. Note: Performance specifications include all claims made in the labeling of the device.

7.2 Device Relationship

Determination of whether there is a reasonable possibility that the HM3 LVAS caused or contributed to an AE is to be determined by the Investigator and recorded on the appropriate CRF form. Determination should be based on assessment of temporal relationships, evidence of alternative etiology, medical/biologic plausibility, and patient condition (pre-existing condition).

7.2.1 Unanticipated Adverse Device Effect (UADE)

Unanticipated adverse device effect (UADE) refers to any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

7.3 Adverse Event and Device Deficiency/Device Malfunction Reporting

7.3.1 Adverse Event Reporting

Safety surveillance and reporting details will be in the study SAP and Safety Plan. Adverse events occurring prior to randomization which disqualify a patient for randomization, but occur after consent, will be captured in the EDC and, if necessary, should be reported to the sponsor through standard commercial practices. Safety surveillance and reporting will continue until the last follow-up visit has been performed, the subject is deceased, the subject concludes participation in the clinical investigation or the subject withdraws from the clinical investigation. All adverse event, deaths, and device deficiency data will be collected throughout the time period defined above and will be reported to the Sponsor on a CRF. Additional information about an adverse event should be updated within the appropriate CRF. An offline form will be made available to allow the investigator to report SAEs in the event the entry cannot be made in the EDC. This offline form can be submitted by email to AdverseEvent@Abbott.com. This

does not replace the EDC reporting system. All information must still be entered in the EDC system as soon as feasible.

Unchanged, chronic, non-worsening or pre-existing conditions are not AEs and should not be reported.

Abnormal laboratory values will not be considered AEs unless:

1. the investigator determined that the value is clinically significant,
2. the abnormal lab value required intervention, or
3. the abnormal lab value required subject withdrawal from the clinical investigation, or
4. the abnormal lab value meets the definition of an adverse event.

All adverse events will be collected on each subject throughout the follow up period – until the subject reaches an outcome or withdraws or until the study ends. Causes of death will be captured for all subjects who expire during follow up.

SAE Reporting

The investigator should report all SAEs to the Sponsor as soon as possible but no later than outlined below.

Clinical Site	Reporting timelines
All Sites	SAEs must be reported to the Sponsor no later than 3 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

The date the site staff became aware the event met the criteria of an SAE must be recorded in the source document. The Investigator will further report the SAE to the local IRB/EC according to the institution's IRB/EC reporting requirements.

7.3.2 Unanticipated Adverse Device Effect Reporting to Sponsor and IRB/EC

The Sponsor requires the Investigator to report any UADE to the Sponsor within 3 calendar days of the investigator's knowledge of the event, unless local requirements are more stringent, and to the IRB/EC per IRB/EC requirements.

7.3.3 Device Deficiency Reporting

All device deficiencies/malfunctions should be reported on the appropriate CRF form.

The investigator should report all device deficiencies/malfunctions to the Sponsor as soon as possible but no later than outlined below.

Clinical Sites	Reporting timelines
All Sites	Device deficiencies/malfunctions must be reported to the Sponsor no later than 3 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

Device deficiencies/malfunctions should be reported to the IRB/EC per the investigative site's local requirements.

An offline form will be made available to allow the investigator to report device deficiencies/malfunctions in the event that the entry cannot be made in the EDC system. This offline form can be submitted by email to AdverseEvent@Abbott.com. This does not replace the EDC reporting system. All information must still be entered in the EDC system as soon as feasible.

7.3.4 Adverse Event Reporting to Country Regulatory Authorities by the Sponsor

The Sponsor will report SAEs and reportable device deficiencies/malfunctions to the country regulatory authority, per local requirements.

Note: Reportable device deficiencies/malfunctions include device deficiencies/malfunctions that might have led to an SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

Clinical investigation SAEs and device deficiencies/malfunctions reportable per MedDEV 2.7/3 regulations will be submitted to European Competent Authorities by the Sponsor's Clinical Safety Group. The Sponsor's Clinical Safety Group's contact details can be found in Appendix III.

8.0 STATISTICAL CONSIDERATIONS

The following section describes the statistical methods for the clinical investigation. Additional details on statistical analyses, including justification of clinical investigation design, sensitivity analyses, poolability analyses, subgroup analyses and analysis of descriptive endpoints, will be maintained in a separate Statistical Analysis Plan (SAP).

8.1 Analysis Populations

8.1.1 Primary Endpoint Analysis Population:

The primary endpoint analysis population will include all randomized subjects with the following exception:

1. Subjects who experience a surgical adverse event, defined as ≤14 days post-implant, requiring investigator mandated antiplatelet therapy
2. Subjects who expire, are transplanted, or withdrawn within 14 days of implant

Subjects will be withdrawn at the time of an outcome (i.e. transplant, explant, exchange, or study withdrawal) or censored at the time of open label. Subjects will be analyzed according to the treatment arm assigned at randomization.

8.1.2 As-Treated Population:

All randomized subjects with the following exception:

1. Subjects who experience a surgical adverse event, defined as ≤14 days post-implant, requiring investigator mandated antiplatelet therapy
2. Subjects who expire, are transplanted, or withdraw within 14 days of implant.

Subjects will only be withdrawn at the time of a patient outcome (i.e. transplant, explant, exchange, or study withdrawal). Non-surgically related hemocompatibility related adverse events will continue to be analyzed beyond the time of open label.

8.2 Statistical Analyses

8.2.1 Primary Endpoint Hypothesis

The primary endpoint hypothesis is formally expressed as:

$$H_0: \pi_{placebo} \leq \pi_{aspirin} - \Delta$$
$$H_a: \pi_{placebo} > \pi_{aspirin} - \Delta$$

where $\pi_{placebo}$ and $\pi_{aspirin}$ are the percentage of subjects who successfully achieve the composite endpoint in the placebo and aspirin groups and where Δ is the non-inferiority margin fixed at 10%. Justification of the non-inferiority margin is included in the SAP.

8.2.2 Primary Endpoint Analyses Methodology

The primary endpoint composite success rate will be calculated for each treatment arm based on the number of subjects who successfully meet the primary endpoint divided by the total number of subjects in the primary endpoint analysis population. The placebo arm will be considered non-inferior to the aspirin arm if the lower boundary of the two-sided 95% confidence limit of the risk difference in the composite success between treatment arms (Placebo-arm minus Aspirin-arm) is greater than the non-inferiority margin (10%). If non-inferiority is met, the primary endpoint will be assessed for superiority. Details of the superiority analysis are included in the SAP.

8.2.3 Secondary and Safety Endpoint Analyses

8.2.3.1 Secondary Endpoint

Non-surgical bleeding rate: The non-surgical bleeding rate per patient year will be compared between treatment groups in the Primary Endpoint Population using Poisson regression. The details of the analysis are included in the SAP.

8.2.3.2 Safety Endpoints

Details of the safety endpoint analysis are provided in the SAP.

Stroke Rate: The stroke rate will be calculated based on the number of strokes experienced by subjects, 14 days or more after device implant, divided by the cumulative duration of study exposure (events / patient-year). Data will be analyzed in the Primary Endpoint Analysis Population and As-Treated using Poisson regression.

Pump Thrombosis: The pump thrombosis rate will be calculated based on the number of suspected pump thrombosis events occurring 14 days or more post implant, divided by the cumulative duration of study exposure (events / patient-year). Data will be analyzed in the Primary Endpoint Analysis Population and As-Treated using Poisson regression.

Survival: The survival rate will be analyzed using the Kaplan-Meier method. Treatment groups will be compared in the Primary Endpoint Analysis Population and As-Treated using a log-rank test.

8.2.3.3 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[4]. The HCS will be calculated for each subject in the Primary Endpoint Analysis 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, for any cause, after randomization and initiation of the study treatment, divided by the number of subjects in the Primary Endpoint Analysis and As-Treated Populations. The number of rehospitalizations per treatment arm will also be presented as rehospitalizations per patient year of support using the As Randomized population. Details of the analysis are presented in the SAP.

Economic Cost: This analysis will only be performed if superiority in the primary endpoint is met. Health resource utilization will be assessed by comparing days hospitalized (categorized by intensive care vs general ward) between groups in the Primary Endpoint Analysis Population with cost implications compared based on cost of hospitalization, per day
hospitalized.

8.3 Sample Size Calculation and Assumptions

Results from the MOMENTUM 3 trial were used to derive a point estimate of 71% survival to 1 year free of any major hemocompatibility related adverse events in the aspirin treated arm. It is assumed that in the absence of aspirin a 2% improvement in the composite endpoint will be noted, mainly due to the reduction of bleeding complications without a change in thromboembolic complications. Based on these assumptions 220 patients will need to be randomized in each arm (440 total) to achieve 80% power to prove that the placebo group is non-inferior to the aspirin group using a non-inferiority margin of 10% with the Farrington-Manning risk difference approach to non-inferiority at a one-sided alpha = 0.025. To account for an expected 30% dropout rate associated with events occurring 2-14 days post implant, up to 628 patients will be randomized in the trial. Sample size calculations were performed using PASS 15 software.

8.4 Timing of Analysis

The primary endpoint analysis will be performed, and the clinical report prepared when 440 subjects have data available to assess the primary endpoint.

8.5 Subgroup Analysis

A subgroup analysis will be performed to examine the consistency of results for the primary endpoint across specific populations. Analysis will be performed using Fisher's exact test. No subgroup specific labeling claims are intended for the primary endpoint and no adjustment will be made for multiplicity. Subgroups to be examined include, but are not limited to, gender, age (stratified by median age), age (less than 65 vs 65 and greater), race, INTERMACS profile (INTERMACS 1-2 vs INTERMACS 3+) and surgical implant method.

8.6 Multiplicity

This study includes a single primary endpoint and a non-powered secondary endpoint. Safety and descriptive endpoints are not intended to support labeling claims. Thus, multiplicity adjustment is not applicable.

8.7 Pooling Strategy

An analysis will be performed to assess if data can be pooled among study sites and geographic regions. A detailed description of the pooling analysis is included in the SAP.

8.8 Procedures for Accounting for Missing Data

Primary endpoint data is unambiguous. Missing primary endpoint data is not expected due to monitoring activities. No imputation is planned for primary endpoint data.

8.9 Planned Interim Analysis

No interim analyses to stop the trial early for futility or success are planned for this study.

8.10 Statistical Criteria for Termination

There are no statistical criteria for termination of this clinical investigation.

8.11 Success Criteria

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).

Clinical Investigation Plan

8.12 Deviations from Statistical Plan

Any major changes to the statistical plan will be documented in an amendment to the statistical plan. Less significant changes to the planned analyses will be documented in the final report.

9.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/institution will permit direct access to source data/documents for the purpose of performing clinical investigation-related monitoring, audits, IRB/EC review and regulatory inspections.

Subjects providing informed consent are agreeing to allow clinical investigation monitors or regulatory authorities including foreign countries to review, in confidence, any records identifying the subjects in this clinical investigation. This information may be shared with regulatory agencies; however the Sponsor undertakes not to release the subject's personal and private information otherwise.

10.0 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Selection of Clinical Sites and Investigators

The Sponsor will select investigators qualified by training and experience to participate in the clinical investigation. Sites will be selected based upon review of a recent site assessment, if applicable, and the qualifications of the investigators who will participate in the clinical investigation.

10.2 Clinical Investigation Finances and Agreements

The clinical investigation will be financed by Abbott. Investigational sites will be compensated by Abbott for participation in the clinical investigation per the conditions of agreement between the Sponsor and the Investigational site.

10.3 CIP Amendments

Approved CIP amendments will be provided to the Investigators by the Sponsor prior to implementing the amendment. The Principal Investigator is responsible for notifying the IRB/EC or equivalent committee of the CIP amendment (administrative changes) or obtaining IRB's/EC's approval of the CIP amendment (changes in subject care or safety), according to the instructions provided by the Sponsor with the CIP amendment.

Acknowledgement/approval by the IRB/EC of the CIP amendment must be documented in writing prior to implementation of the CIP amendment. Copies of this documentation must also be provided to the Sponsor.

Clinical Investigation Plan

10.4 Training

10.4.1 Site Training

All Investigators and clinical investigation personnel are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, a site initiation visit, or other appropriate training sessions. Over-the-phone or self-training may take place as required. Training of Investigators and clinical investigation personnel will include, but is not limited to, the CIP requirements, electronic case report form completion, WebEZ functionality, and clinical investigation personnel responsibilities. All Investigators and clinical investigation personnel that are trained must sign a training log (or an equivalent) upon completion of the training. Prior to signing the training log, Investigators and clinical investigation personnel must not perform any CIP-related activities that are not considered standard of care at the site.

10.5 Monitoring

Sponsor and/or designee will monitor the clinical investigation over its duration according to the CIP-specific monitoring plan which will include the planned extent of source data verification.

Prior to initiating any procedure, the Sponsor monitor (or delegate) will ensure that the following criteria are met:

- The investigator understands and accepts the obligation to conduct the clinical investigation according to the CIP and applicable regulations and has signed the Investigator Agreement or the Clinical Trial Agreement, as applicable.
- The Investigator and his/her staff should have sufficient time and facilities to conduct the clinical investigation and should have access to an adequate number of appropriate subjects to conduct the clinical investigation.
- Source documentation (including original medical records) must be available to substantiate proper informed consent procedures, adherence to CIP procedures, adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, and device information.
- The Investigator/site will permit access to such records. A monitoring visit sign-in log will be maintained at the site. The Investigator will agree to dedicate an adequate amount of time to the monitoring process. The Investigator and/or research coordinator will be available for monitoring visits. It is expected that the Investigator will provide the monitor with a suitable working environment for review of clinical investigation-related documents.

10.6 Deviations from the CIP

The Investigator should not deviate from the CIP for any reason except in cases of medical emergencies when the deviation is necessary to protect the rights, safety and well-being of the subject or eliminate an apparent immediate hazard to the subject. In that event, the Investigator will notify Sponsor immediately by phone or in writing and will also file required protocol deviation documentation.

Clinical Investigation Plan

No waivers for CIP deviations will be granted by the Sponsor. All deviations must be reported to the Sponsor using the Deviation CRF. The occurrence of protocol deviations will be monitored by the Sponsor for evaluation of investigator compliance to the CIP and regulatory requirements and dealt with according to written procedures. Investigators will inform their IRB/EC or equivalent committee of all CIP deviations in accordance with their specific IRB/EC or equivalent committee reporting policies and procedures.

In the event of repeated non-compliance, as determined by the Sponsor, a Sponsor's monitor or company representative will attempt to secure compliance by one or more of the following (and not limited to):

- Visiting the investigator and/or delegate
- Telephoning the investigator and/or delegate
- Corresponding with the investigator and/or delegate

Repeated non-compliance with the signed agreement, the CIP or any other conditions of the clinical investigation may result in further escalation in accordance with the Sponsor's written procedures, including securing compliance or, at its sole discretion, Sponsor may terminate the investigator's participation in the clinical investigation.

Deviations from the protocol include, but are not limited to:

- 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.

10.7 Quality Assurance Audit

A Sponsor representative or designee may request access to all clinical investigation records, including source documentation, for inspection during a Quality Assurance audit.

1. The Sponsor shall prepare an audit plan as well as the operating procedures for the related duties, and conduct audits in accordance with the audit plan and the operating procedures.
2. Individual engaged in auditing (hereinafter referred to as "auditor") shall be different than those in charge of medical device development or monitoring.
3. The auditor shall prepare an audit report documenting the matters confirmed in the audit to certify and verify that the audit has been conducted, and submit them to the Sponsor.

In the event that an investigator is contacted by a Regulatory Agency in relation to this clinical investigation, the Investigator will notify Sponsor immediately. The Investigator and Research Coordinator must be available to respond to reasonable requests and audit queries made during the audit process. The Investigator must provide Sponsor with copies of all correspondence that may affect the review of the current clinical investigation (e.g., Form FDA 483, Inspectional Observations, Warning Letters, Inspection Reports, etc.). Sponsor may provide any needed assistance in responding to regulatory audits.

Clinical Investigation Plan

10.8 Committees

10.8.1 Steering Committee

The Steering Committee is assigned by the Sponsor and consists of investigators. The Steering Committee will remain blinded to the treatment group assignments throughout the study. The Sponsor will also be represented on the committee. The Steering Committee is responsible for overseeing the scientific and operational aspects of the clinical investigation. This committee will meet regularly to monitor subject enrollment, general data collection and non-compliance with the CIP at individual centers, to review and act upon recommendations of the Data Safety Monitoring Board (DSMB), to review operational issues that may arise and warrant a CIP amendment or other corrective action and to determine policy regarding any publications arising from data generated from the performance of the clinical investigation. The Steering Committee or designee will determine policy and strategies regarding individual presentations and/or publications arising from clinical investigation generated data. The committee will also review all external requests for accessing clinical investigation-related data and strategies aligning with the Sponsor's presentation and publication team expectations. The Sponsor will align with the committee to ensure the Sponsor's applicable policies and Standard Operating Procedures are followed.

10.8.2 Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board (DSMB) is an independent multidisciplinary group restricted to individuals free of apparent significant conflicts of interest. The source of these conflicts may be financial, scientific, or regulatory in nature. The DSMB is typically composed of at least two physicians with experience relevant to the clinical investigation and a biostatistician. The DSMB will meet within 3 months of study initiation for protocol/study training and to discuss oversight rules including first data review point, recurring data review points, and formal rules for recommending study cessation. Formal rules for recommending study cessation will be determined by the DSMB prior to review of safety data. The DSMB will be blinded to the study treatment groups (aspirin vs placebo), unless and until the DSMB makes a formal unblinding request, the rules for which will be pre-defined within the DSMB charter.

The DSMB will serve in an advisory role to the Sponsor to ensure safety by reviewing cumulative data from the clinical investigation at prescribed intervals for the purpose of safeguarding the interests of enrolled subjects and those patients yet to be enrolled, as well as the continuing validity and scientific merit of the clinical investigation. The composition, frequency of the meetings and the statistical monitoring guidelines will be described in detail in the DSMB charter.

The DSMB may consider a recommendation for modifications or termination of the clinical investigation based on any perceived safety concerns regardless of statistical significance. The recommendations of the DSMB are not binding, and all final decisions related to clinical investigations modifications rest with the Sponsor in consultation with the study Steering Committee.

10.8.3 Clinical Events Committee (CEC)

The Clinical Events Committee (CEC) is an independent adjudication body comprised of qualified physicians who are not participants in the clinical investigation. The CEC will remain blinded to the subjects' treatment arm assignments. The CEC will review and adjudicate pre-specified events reported by investigators or identified by Safety personnel for the clinical investigation as defined in the CEC charter and according to definitions provided in this CIP. The CEC will adjudicate all deaths, neurologic

dysfunction, pump thrombosis events, bleeding events, and arterial peripheral thromboembolism events including events that could be adjudicated to one of these categories.

11.0 DATA HANDLING AND RECORD KEEPING

Sponsor and/or its affiliates will maintain documentation of the systems and procedures used in data collection for the duration of the clinical investigation.

CRF data collection will be performed through a secure web portal and only authorized personnel will access the Electronic Data Capture (EDC) system using a unique username and password to enter, review or correct data. Passwords and electronic signatures will be strictly confidential.

The data will be subjected to consistency and validation checks within the EDC system and supplemental review by the Sponsor.

At the conclusion of the clinical investigation, completed CRF images with the date-and-time stamped electronic audit trail indicating the user, the data entered, and any reason for change (if applicable) will be provided to the investigational sites, if requested.

For the duration of the clinical investigation, the Investigator will maintain complete and accurate documentation including, but not limited to, medical records, clinical investigation progress records, laboratory reports, CRFs, signed ICFs, correspondence with the IRB/EC and clinical investigation monitor/Sponsor, adverse event reports, and information regarding subject discontinuation or completion of the clinical investigation.

11.1 Protection of Personally Identifiable Information

The Sponsor respects and protects personally identifiable information collected or maintained for this clinical investigation.

The Sponsor implements technical and physical access controls to ensure that Personal Information is accessible only to and processed only on a ‘need to know’ basis, including periodic review of access rights, and revocation of access when an individual’s employment is terminated or the individual transitions to a role that does not require access to Personal Information, and appropriate restrictions on physical access to premises, facilities, equipment, and records containing Personal Information.

The Sponsor requires the investigational sites to transfer into Sponsor’s data management systems only pseudonymous Personal Information (key-coded) necessary to conduct the Clinical Investigation, such as the patient’s medical condition, treatment, dates of treatment, etc. The Sponsor discloses as part of the clinical investigation informed consent process that some Sponsor representatives still may see Personal Information at the participating sites for technical support of the participating physicians on the device implant or procedures, monitoring and quality control purposes. Confidentiality of Personal Information will be observed by all parties involved at all times throughout the clinical investigation. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data.

Clinical Investigation Plan

The Sponsor data management systems and processes were designed, developed, and tested according to industry standards to appropriately safeguard Confidential Information (including any Personal Information) against unauthorized access and/or interference by third parties, intrusion, theft, destruction, loss or alteration. Clinical Investigation data are encrypted in transit and at rest.

The Sponsor maintains a Privacy Incident procedure that complies in all respects with Applicable Law and industry best practices.

11.2 Data Management Plan

A Data Management Plan (DMP) will describe procedures used for data review, data cleaning, and issuing and resolving data discrepancies. If appropriate, the DMP may be updated throughout the duration of the clinical investigation. All revisions will be tracked and document-controlled.

11.3 Source Documentation

Regulations and GCP require the Investigator to maintain information in the subject's original medical records that corroborates data collected on the CRFs. In order to comply with these regulatory requirements/GCP, the following information should be included in the subject record at a minimum and if applicable to the clinical investigation:

- Medical history/physical condition of the subject before involvement in the clinical investigation sufficient to verify CIP entry criteria
- Dated and signed notes on the day of entry into the clinical investigation referencing the Sponsor, CIP number, subject ID number and a statement that informed consent was obtained
- Dated and signed notes from each subject visit (for specific results of procedures and exams)
- Adverse events reported and their resolution, including supporting documents, such as discharge summaries, catheterization laboratory reports, ECGs, and lab results including documentation of site awareness of SAEs and of investigator assessment of device relationship for SAEs.
- CIP-required laboratory reports and other tests, reviewed and annotated for clinical significance of out of range results (if applicable).
- Notes regarding CIP-required and prescription medications taken during the clinical investigation (including start and stop dates)
- Subject's condition upon completion of or withdrawal from the clinical investigation
- Any other data required to substantiate data entered into the CRF
- Patient reported outcome measures may be completed using CRF worksheets. These serve as the source documentation.

11.4 Case Report Form Completion

Primary data collection based on source-documented hospital and/or clinic chart reviews will be performed clearly and accurately by site personnel trained on the CIP and CRF completion. The investigator will ensure accuracy, completeness, legibility and timeliness of the data reported to the Sponsor on the CRFs and in all required reports.

Data on CRFs will be collected for all subjects that are enrolled into the clinical investigation.

Only authorized site personnel will be permitted to enter the CRF data through the EDC system deployed by the Sponsor. An electronic audit trail will be used to track any subsequent changes of the entered data.

11.5 Record Retention

The Sponsor and Investigator/Site will archive and retain all documents pertaining to the clinical investigation as per the applicable regulatory record retention requirements. The Investigator must obtain permission from Sponsor in writing before destroying or transferring control of any clinical investigation records.

12.0 ETHICAL CONSIDERATION

12.1 Institutional Review Board/Medical Ethics Committee Review and Approval

Institutional Review Board (IRB)/ Ethics Committee (EC) approval for the CIP and ICF/other written information provided to the patient will be obtained by the Principal Investigator at each investigational site prior to consenting and enrolling patients in this clinical investigation. The approval letter must be received prior to the start of this clinical investigation and a copy must be provided to the Sponsor.

Any amendments to the CIP as well as associated ICF changes will be submitted to the IRB/EC and written approval obtained prior to implementation, according to each institution's IRB/EC requirements.

No changes will be made to the CIP or ICF or other written information provided to the patient without appropriate approvals, including IRB/EC, the Sponsor, and the regulatory agencies (if applicable).

Until the clinical investigation is completed, the Investigator will advise his/her IRB/EC of the progress of this clinical investigation, per IRB/EC requirements. Written approval must be obtained from the IRB/EC yearly to continue the clinical investigation, or according to each institution's IRB/EC requirements.

No investigative procedures other than those defined in this CIP will be undertaken on the enrolled subjects without the written agreement of the IRB/EC and the Sponsor.

13.0 CLINICAL INVESTIGATION CONCLUSION

The clinical investigation will be concluded when:

- All sites are closed AND
- The final report has been provided to investigators (within one year of the end of the investigation) or the Sponsor has provided formal documentation of clinical investigation closure.

Upon conclusion of the study (when the last subject completes their 12 month follow up), investigators will return patients to their standard of care aspirin use.

Clinical Investigation Plan

14.0 REPORTS AND PUBLICATIONS

14.1 Sponsor Reports

The Sponsor will submit study progress reports to all principle investigators for submission to reviewing IRBs/ECs at least yearly. The sponsor will submit a final report to appropriate regulatory bodies and to all principle investigators for submission to all reviewing IRBs/ECs and participating investigators within one year after completion or termination. The Sponsor will comply with all other reporting requirements.

14.2 Publication Policy

The data and results from the clinical investigation are the sole property of the Sponsor. The Sponsor shall have the right to access and use all data and results generated during the clinical investigation. The Investigators will not use clinical investigation-related data without the written consent of the Sponsor for any purpose other than for clinical investigation completion or for generation of publication materials, as referenced in the Clinical Trial Agreement. Single-center results are not allowed to be published or presented before the multi-center results. Any proposals for publications or presentations by the investigators must be reviewed and approved by the Sponsor in a timely manner to enable Sponsor review in compliance with the Sponsor's publication policy set forth in the Clinical Trial Agreement.

14.3 Trial Registration

The Sponsor will register the clinical trial on www.clinicaltrials.gov, in accordance with the International Committee of Medical Journal Editors guidelines, or any other applicable guidelines. The Sponsor shall be responsible for any such registration and results posting as required by ClinicalTrials.gov. Investigational sites shall not take any action to register the trial. A full report of the pre-specified outcomes, including any negative outcomes, will be made public through the ClinicalTrials.gov website according to the requirements of Section 801 of the FDA Amendments Act. If this clinical investigation is terminated early, the Sponsor will make every effort to hasten the release of the pre-specified outcomes through ClinicalTrials.gov website.

15.0 RISK ANALYSIS

15.1 Anticipated Clinical Benefits

Withdrawal of aspirin from the antithrombotic regimen of HM3 pump patients will not adversely affect safety and efficacy and may reduce non-surgical bleeding.

15.2 Foreseeable Adverse Events and Anticipated Adverse Device Effects

Risks associated with the specified device and aspirin treatment arm are available in the local IFU and expected to be similar to those reported in the Short-Term (6 months post-implant)[6] and Full Cohort (24 months post-implant)[9] cohort of the MOMENTUM 3 Clinical Trial, which are described in Table 7. There may be risks related to the device that are unknown at present. Likewise, the exact frequency of the risk associated with the placebo treatment arm are not known, but are hypothesized to be similar to the aspirin arm.

Table 7 – Expected Incidence Rate of Adverse Events

Adverse Event	Short-Term (6-month) MOMENTUM 3 Results[6] n=151:	Full Cohort (24-month) MOMENTUM 3 Results[9] n=515
Death	11%	19%
Bleeding	33%	44%
Cardiac Arrhythmia	31%	36%
Hepatic Dysfunction	5%	5%
Driveline Infection	12%	23%
Blood Infection	9%	15%
Localized Infection (not associated with LVAS)	31%	41%
Stroke	8%	10%
Other Neurological Dysfunction	6%	12%
Renal Dysfunction	11%	14%
Respiratory Failure	22%	22%
Moderate or Severe Right Heart Failure	30%	34%
Suspected Device Thrombosis	0%	1.4%

15.3 Residual Risks Associated with the Clinical Investigation, as Identified in the Risk Analysis Report

No additional Residual Risks associated exclusively with the withdrawal of aspirin from the antithrombotic regimen have been identified at this time. Refer to the local IFU for warning and caution statements associated with the HM3.

15.4 Risks Associated with Participation in this Clinical Investigation

There are no known additional risks for the clinical population and hypothesis under investigation.

15.5 Possible Interactions with Protocol-Required Concomitant Medications

Anti-platelet medications, which in this study are replaced by the treatment arm medication which may be active aspirin or a placebo, are typically required as standard of care for LVAD patients along with vitamin K antagonists and as such no new possible interactions are expected. No new medications are introduced in this study. For further detail, refer to the prescribing information for the anticoagulants in use – specifically vitamin K antagonists (e.g. warfarin, fluindione, phenprocoumon, etc.) or aspirin.

15.6 Steps Taken to Control or Mitigate Risks

Mitigations and treatment for all adverse events should be per the current practice standards/standards of care as determined by the investigator, except for the antithrombotic therapy for mitigation of thrombotic risk in enrolled patients, which is the subject of this study.

Subject risk from study participation will be mitigated by ensuring that only experienced LVAD personnel will be involved in the care of research subjects. In addition to providing local product specific IFU, study staff will have undergone product, implant and study training prior to initiating study activities, and all subjects will be closely monitored throughout the study duration at pre-specified time points to assess their clinical status.

Specific information applicable to this study are listed below.

- Inclusion/Exclusion criteria avoid patients who are at an inordinately elevated risk for complications including, but not limited to, women who are or may become pregnant, patients with a known allergy to aspirin, and patients who require aspirin therapy or lack of aspirin therapy post-implant in the opinion of the investigator.
- It is suggested that patients possess a minimum 5th grade educational level and shall be versed in basic computer literacy (i.e., Microsoft Windows® and Office software).
- All users, including clinicians, patients, and caregivers, must be trained on system operation and safety before use.
- All implanting surgeons must be trained on HeartMate 3 surgical implant technique.
- Clinical procedures (including LVAS settings) should be conducted under the direction of the prescribing physician (Authorized Personnel) only.
- A data safety monitoring board (DSMB) will be monitoring adverse event data at regular intervals independently specified to assure safety is maintained throughout the study. In the event of an unacceptable safety profile, the DSMB will make a recommendation to pause or stop study enrollment while the DSMB, Sponsor, and steering committee determine if additional actions are necessary. Formal rules for making a recommendation to stop the study will be independently determined by the DSMB prior to data review. Rules will be contained within the DSMB Charter.

15.7 Risk to Benefit Rationale

The HM3 is a safe and effective treatment for advanced, refractory heart failure, and the medical benefits outweigh the risks of harm to the patient. MCS therapy is proven to be an effective treatment for advanced, refractory heart failure. The HM3 is an advancement in MCS technology and complies with all relevant international standards.

There have been no additional risks identified with the HM3 beyond what has been established with other VAD devices in clinical trials that have not been effectively mitigated within this trial; the risks are comparable or superior to the HMII.

All identified risks were managed through the risk management process and reduced as much as possible. The overall residual risks have been deemed acceptable, per the risk management process, and in consideration of the benefits provided by the therapy. The risk benefit analysis “basis for acceptance” for each of the residual risks are documented in the HeartMate 3 Risk Management Report.

Removal of antiplatelet agents from the antithrombotic therapy of HM3 patients may reduce bleeding This study hypothesizes that there will be no additional thrombotic risk based on the growing body of

scientific evidence that shows the HM3 has a low thromboembolic profile[5,9,24]. However, bleeding events, while decreased in comparison to a predicate device, remain burdensome[9]. All major prospective clinical trials conducted with the HM3 (MOMENTUM 3, CE Mark) have been in the context of a prescribed antithrombotic regimen of aspirin in concert with vitamin K antagonist. Within clinical studies[9,10,16], as institutional changes to their standard of care[18], or in response to increased bleeding risk[17], modifications to the HM3 anticoagulation regimen have been explored. Prior to the introduction of the HM3, which has a decreased thrombotic profile relative to the HMII, studies investigating the need for aspirin within the HMII antithrombotic regimen were conducted[20-23]_ENREF_19_ENREF_20_ENREF_21.

In conclusion, for the intended patient population, the probable medical benefits of the HM3 outweigh the overall residual risk and may be improved in the absence of antiplatelet agents as part of the antithrombotic regimen. This study aims to conclusively determine if antiplatelet agents are required as part of the HM3 antithrombotic regimen.

Clinical Investigation Plan

APPENDIX I: ABBREVIATIONS AND ACRONYMS

Abbreviation	Term
ACE	Angiotensin Converting Enzyme
AE	Adverse Event
AI	Aortic Insufficiency
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
ARB	Angiotensin II Receptor Blockers
AST	Aspartate Aminotransferase
AVM	Arterio-venous malformation
BTC	Bridge-to-Candidacy
BTT	Bridge-to-Transplant
BUN	Blood Urea Nitrogen
CABG	Coronary Artery Bypass Graft
CEC	Clinical Events Committee
CI	Cardiac Index
CIP	Clinical Investigation Plan
CK	Creatinine Kinase
CK-MB	Creatinine Kinase Muscle/Brain
CMS	Centers for Medicare and Medicaid SERVICES
CNS	Central Nervous System
CO	Cardiac Output
CPB	Cardiopulmonary Bypass
Cr	Creatinine
CRF	Case Report Form
CT	Computed Tomography
CVP	Central Venous Pressure
DMP	Data Management Plan
DSMB	Data Safety Monitoring Board
DT	Destination Therapy
EC	Ethics Committee
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EGM	Intracardiac electrogram
EKG	Electrocardiogram
ELEVATE	Evaluating the HeartMate 3 with Full MagLev Technology in a Post-Market Approval Setting
EQ-5D-5L	EuroQOL 5 Dimension 5 Level questionnaire
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GI	Gastrointestinal
HAS-BLED	Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs or Alcohol

Clinical Investigation Plan

Abbreviation	Term
HbA1c	Glycated Hemoglobin
HCS	Hemocompatibility Score
Hct	Hematocrit
HF	Heart Failure
HgB	Hemoglobin
HIE	Hypoxic-ischemic injury
HIPAA	Health Insurance Portability and Accountability Act
HIT	Heparin Induced Thrombocytopenia
HM3	HeartMate 3
HMII	HeartMate II
ICF	Informed Consent Form
ICH	Intracranial Hemorrhage
IFU	Instructions for Use
INR	International Normalized Ratio
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
IRB	Institutional Review Board
LA	Left Atrium
LAAO	Left Atrial Appendage Occlusion
LDH	Lactate dehydrogenase
LV	Left Ventricle
LVAD	Left Ventricular Assist Device
LVAS	Left Ventricular Assist System
LVEDD	Left Ventricular End Diastolic Diameter
LVEF	Left Ventricular Ejection Fraction
LVESD	Left Ventricular End Systolic Diameter
MCS	Mechanical Circulatory Support
MedDEV	Medical Device Directives
MI	Myocardial Infarction
MOMENTUM3	Multi-center Study of MagLev Technology in Patients Undergoing MCS Therapy With HeartMate 3™ IDE Study
MR	Mitral Regurgitation
MRI	Magnetic Resonance Imaging
MRS	Modified Rankin Score
NPO	Nil per os. Latin for “Nothing through the Mouth”.
NYHA	New York Heart Association
OUS	Outside the United States
PAD	Diastolic Pulmonary Artery Pressure
PAM	Mean Pulmonary Artery Pressure
PAS	Systolic Pulmonary Artery Pressure
PCWP	Pulmonary Capillary Wedge Pressure
PHgB	Plasma Free Hemoglobin
PLT	Platelets
PR	Pulmonary Regurgitation

Clinical Investigation Plan

Abbreviation	Term
PRBC	Packed Red Blood Cells
PRO	Patient Reported Outcome
PTFE	Polytetrafluoroethylene
PTT	Partial Thromboplastin Time
QOL	Quality of Life
RAP	Right Atrial Pressure
RHF	Right Heart Failure
RVAD	Right Ventricular Assist Device
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	Standard of Care
tPA	Tissue Plasminogen Activator
TR	Tricuspid Regurgitation
UADE	Unanticipated Adverse Device Effect
UNOS	United Network for Organ Sharing
UADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analogue Scale
VT	Ventricular Tachycardia
WBC	White Blood Cells

Clinical Investigation Plan

APPENDIX II: DEFINITIONS

ADVERSE EVENT DEFINITIONS:

1. Bleeding

VAD-IMPLANT-RELATED BLEEDING:
VAD-implantation-related bleeding (includes concomitant cardiac or non-cardiac surgical procedures) that requires:

- Reoperation after closure of incision or incisions used to implant the VAD for the purpose of controlling bleeding
- If ≥ 50 kg, ≥ 4U packed red blood cells (PRBC) within any 48-hour period during first 7 days post implant.
- If < 50 kg, ≥ 20 cc/kg packed red blood cells (PRBC) within any 24-hour period during first 7 days post implant.
- Or any transfusion from 8-14 days

or exhibits:

- Chest tube output > 2L within a 24-h period

MODERATE:
Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for a Severe or Surgical Bleeding Definitions but does meet at least one of the following criteria:

- requiring nonsurgical, medical intervention by a healthcare professional;
- leading to hospitalization or increased level of care; or
- prompting evaluation.

SEVERE:

- Type A: (Meets any of the below)
  - Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL (provided hemoglobin drop is related to bleed)
  - Any transfusion with overt bleeding
- Type B: (Meets any of the below)
  - Overt bleeding plus hemoglobin drop 5 g/dL or greater (provided hemoglobin drop is related to bleed)
  - Cardiac tamponade
  - Bleeding requiring surgical intervention for control (excluding dental, nasal, skin, or hemorrhoid)
  - Hypotension attributable to bleeding and requiring intravenous vasoactive agents for hemodynamic support
  - Intracranial Hemorrhage that does not meet the definition of hemorrhagic stroke
- Type C1: Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

- Type C2: Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

2. Cardiac Arrhythmias

Any documented arrhythmia that results in clinical compromise (e.g., diminished VAD flow, oliguria, pre-syncope or syncope) that requires hospitalization or occurs during a hospital stay. Cardiac arrhythmias are classified as 1 of 2 types:

- Sustained ventricular arrhythmia requiring defibrillation or cardioversion.
- Sustained supraventricular arrhythmia requiring drug treatment or cardioversion.

3. Device Thrombosis

Device thrombosis is an event in which the pump or its conduits contain a thrombus that results in or could potentially induce circulatory failure. Suspected device thrombus is an event in which clinical or pump parameters suggest thrombus on the blood contacting components of the pump, cannula, or grafts. Signs and symptoms should include at least 2 of the 3 following criteria:

- Presence of hemolysis
- Worsening heart failure or inability to decompress the left ventricle
- Abnormal pump parameters

Suspected pump thrombus should be accompanied by 1 or more of the following events or interventions:

- Treatment with intravenous anticoagulation (e.g., heparin), intravenous thrombolytics (e.g., tPA), or intravenous antiplatelet therapy (e.g., eptifibatide, tirofiban)
- Pump replacement
- Pump explantation
- Urgent transplantation (UNOS status 1A)
- Stroke
- Arterial non-CNS thromboembolism
- Death

Confirmed device thrombus is an event in which thrombus is confirmed by the Sponsor's returned product analysis to be found within the blood contacting surfaces of device inflow cannula or outflow conduit or grafts. This can also be reported via direct visual inspection or by incontrovertible contrast radiographic evidence or by the absence of an appropriate Doppler flow signal that results in or could potentially induce circulatory failure or result in thromboembolism.

4. Hemolysis*

A plasma-free hemoglobin value that is greater than 40 mg/dl, concomitant with a rise in serum LDH above three times the upper limit of normal, in association with clinical signs

associated with hemolysis (e.g., anemia, low hematocrit, hyperbilirubinemia) occurring after the first 72 hours post-implant.
*Hemolysis in the presence of worsening heart failure or inability to decompress the left ventricle or abnormal pump parameters should be reported as suspected device thrombosis, not as hemolysis

5. Hepatic Dysfunction

An increase in any two of the following hepatic laboratory values (total bilirubin, aspartate aminotransferase/AST and alanine aminotransferase/ALT) to a level greater than three times the upper limit of normal for the hospital, beyond 14 days post-implant (or if hepatic dysfunction is the primary cause of death).

6. Hypertension

Blood pressure elevation of a mean arterial pressure greater than 110 mm Hg, despite anti-hypertensive therapy.

7. Major Infection

A clinical infection accompanied by pain, fever, drainage and/or leukocytosis that is treated by anti-microbial agents (non-prophylactic). A positive culture from the infected site or organ should be present unless strong clinical evidence indicates the need for treatment despite negative cultures. The general categories of infection are listed below:

Localized Non-Device Infection

Infection localized to any organ system or region (e.g. mediastinitis) without evidence of systemic involvement (see sepsis definition), ascertained by standard clinical methods and either associated with evidence of bacterial, viral, fungal or protozoal infection, and/or requiring empirical treatment.

Percutaneous Site and/or Pump Infection

A positive culture from the skin and/or tissue surrounding the drive line or from the tissue surrounding the external housing of a pump implanted within the body, coupled with the need to treat with antimicrobial therapy, when there is clinical evidence of infection such as pain, fever, drainage, or leukocytosis.

Internal Pump Component, Inflow or Outflow Tract Infection

Infection of blood-contacting surfaces of the LVAD documented by positive site culture.

Sepsis

Evidence of systemic involvement by infection, manifested by positive blood cultures and/or hypotension.

8. Myocardial Infarction

Two categories of myocardial infarction will be identified:

Peri-Operative Myocardial Infarction

The clinical suspicion of myocardial infarction together with CK-MB or Troponin > 10 times the local hospital upper limits of normal, found within 7 days following VAD implant

together with ECG findings consistent with acute myocardial infarction. (This definition uses the higher suggested limit for serum markers due to apical coring at the time of VAD placement and does not use wall motion changes because the apical sewing ring inherently creates new wall motion abnormalities.)

Non-Perioperative Myocardial Infarction
The presence at > 7 days post-implant of two of the following three criteria:

- Chest pain which is characteristic of myocardial ischemia,
- ECG with a pattern or changes consistent with a myocardial infarction, and
- Troponin or CK (measured by standard clinical pathology/laboratory medicine methods) greater than the normal range for the local hospital with positive MB fraction (≥ 3% total CK). This should be accompanied by a new regional LV or RV wall motion abnormality on a myocardial imaging study.

9. Neurologic Dysfunction

Any new, temporary or permanent, focal or global neurological deficit, ascertained by a standard neurological history and examination administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests and consultation note; or an abnormality identified by surveillance neuroimaging. The examining physician will classify the event as defined below:

- Transient ischemic attack*, defined as an acute transient neurological deficit conforming anatomically to arterial distribution cerebral ischemia, which resolves in < 24 hours and is associated with no infarction on brain imaging (head CT performed >24 hours after symptom onset; or MRI)
- Ischemic Stroke*: a new acute neurologic deficit of any duration associated with acute infarction on imaging corresponding anatomically to the clinical deficit, or a clinically covert ischemic stroke seen by surveillance imaging, without clinical findings of stroke or at the time of event recognition.
- Hemorrhagic Stroke*: a new acute neurologic deficit attributable to intracranial hemorrhage (ICH), or a clinically covert ICH seen by surveillance imaging, without clinical findings of ICH at the time of event recognition.
- Encephalopathy: Acute new encephalopathy** due to hypoxic-ischemic injury (HIE), or other causes, manifest as clinically evident signs or symptoms, or subclinical electrographic seizures found by complete neurological diagnostic evaluation to be attributable to acute global or focal hypoxic, or ischemic brain injury not meeting one of ischemic stroke or ICH events as defined above.
- Seizure of any kind
- Other neurological event (non-CNS event): examples include neuro muscular dysfunction or critical care neuropathy

*Modified Rankin Score (MRS) will be used to classify the severity of all strokes. MRS will be captured at baseline, the time of stroke, and at 60 days post-stroke. MRS will be determined by an independent assessor, defined as an independent, trained, and certified clinician. Severity will be defined as disabling (MRS > 3) or nondisabling (MRS ≤ 3). MRS is defined below.
**Acute encephalopathy is a sign or symptom of some underlying cerebral disorder, and is manifest as depressed consciousness with or without any associated new global or multifocal neurologic deficits in cranial nerve, motor, sensory, reflexes and cerebellar function.

10. Renal Dysfunction

Two categories of renal dysfunction will be identified:

Acute Renal Dysfunction

Abnormal kidney function requiring dialysis (including hemofiltration) in Subjects who did not require this procedure prior to implant, or a rise in serum creatinine of greater than 3 times baseline or greater than 5 mg/dL sustained for over 48 hours.

Chronic Renal Dysfunction

An increase in serum creatinine of 2 mg/dl or greater above baseline, or requirement for hemodialysis sustained for at least 90 days.

11. Respiratory Failure

Impairment of respiratory function requiring reintubation, tracheostomy or the inability to discontinue ventilatory support within six days (144 hours) post-VAD implant. This excludes intubation for reoperation or temporary intubation for diagnostic or therapeutic procedures.

12. Right Heart Failure

Symptoms and signs of persistent right ventricular dysfunction requiring RVAD implantation, or requiring inhaled nitric oxide or inotropic therapy for a duration of more than 14 days at any time after LVAD implantation. To compare to prior studies, this study will begin collecting details of events involving nitric oxide or inotropic therapy for a duration of more than 7 days, whereas reportable right heart failure will begin at 14 days of therapy.

To further stratify right heart failure (RHF) events, the following criteria will be used to identify a sub-category of persistent, clinically significant RHF events:

- Death due to right heart failure or
- RVAD or
- Hospitalization with primary diagnosis of decompensated heart failure with evidence of right heart support or
- Post-discharge inotropes or

- > 30 consecutive days on inotropes.

13. Arterial Peripheral Thromboembolism

An acute systemic arterial perfusion deficit in any non-cerebrovascular organ system due to thromboembolism confirmed by one or more of the following:

1) Standard clinical and laboratory testing
2) Operative findings
3) Autopsy findings

This definition excludes neurological events.

14. Venous Thromboembolism Event

Evidence of venous thromboembolic event (e.g. deep vein thrombosis, pulmonary embolism) by standard clinical and laboratory testing.

Clinical Investigation Plan

NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION

NYHA Classification	Definition
I	Cardiac disease without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea or anginal pain.
II	Cardiac disease resulting in slight limitation of physical activity. Subjects are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
IIIA	Cardiac disease resulting in marked limitations of physical activity. Subjects are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IIIB	Cardiac disease resulting in marked limitations of physical activity. Subjects are comfortable at rest. Mild physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV*	Cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Clinical Investigation Plan

INTERMACS PROFILE

INTERMACS Profile*	Definition
1	Critical cardiogenic shock describes a patient who is “crashing and burning”, in which a patient has life-threatening hypotension and rapidly escalating inotropic pressor support, with critical organ hypoperfusion often confirmed by worsening acidosis and lactate levels.
2	Progressive decline describes a patient who has been demonstrated “dependent” on inotropic support but nonetheless shows signs of continuing deterioration in nutrition, renal function, fluid retention, or other major status indicator. Patient profile 2 can also describe a patient with refractory volume overload, perhaps with evidence of impaired perfusion, in whom inotropic infusions *cannot be maintained* due to tachyarrhythmias, clinical ischemia, or other intolerance.
3	Stable but inotrope dependent describes a patient who is clinically stable on mild-moderate doses of intravenous inotropes (or has a temporary circulatory support device) after repeated documentation of failure to wean without symptomatic hypotension, worsening symptoms, or progressive organ dysfunction (usually renal). It is critical to monitor nutrition, renal function, fluid balance, and overall status carefully in order to distinguish between a patient who is truly stable at Patient Profile 3 and a patient who has unappreciated decline rendering this person a Patient Profile 2. This patient may be either at home or in the hospital.
4	Resting symptoms describes a patient who is at home on oral therapy but frequently has symptoms of congestion at rest or with ADL. He or she may have orthopnea, shortness of breath during ADL such as dressing or bathing, gastrointestinal symptoms (abdominal discomfort, nausea, poor appetite), disabling ascites or severe lower extremity edema. This patient should be carefully considered for more intensive management and surveillance programs, by which some may be recognized to have poor compliance that would compromise outcomes with any therapy.
5	Exertion Intolerant describes a patient who is comfortable at rest but unable to engage in any activity, living predominantly within the house or housebound. This patient has no congestive symptoms, but may have chronically elevated volume status, frequently with renal dysfunction, and may be characterized as exercise intolerant.
6	Exertion Limited also describes a patient who is comfortable at rest without evidence of fluid overload, but who is able to do some mild activity. Activities of daily living are comfortable and minor activities outside the home such as visiting friends or going to a restaurant can be performed, but fatigue results within a few minutes of any meaningful physical exertion. This patient has occasional episodes of worsening symptoms and is likely to have had a hospitalization for heart failure within the past year.
7	Advanced NYHA Class 3 describes a patient who is clinically stable with a reasonable level of comfortable activity, despite history of previous decompensation that is not recent. This patient is usually able to walk more than a block. Any decompensation requiring intravenous diuretics or hospitalization within the previous month should make this person a Patient Profile 6 or lower.

Clinical Investigation Plan

MODIFIED RANKIN SCORE (MRS)

MRS	Definition[1]
0	No observed neurological symptoms
1	No significant neurological disability despite symptoms; able to carry out all usual duties and activities
2	Slight neurological disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate neurological disability; requiring some help, but able to walk without assistance
4	Moderate severe neurological disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe neurological disability; bedridden, incontinent and requiring constant nursing care and attention as a result of a neurological deficit
6	Dead

NON-SURGICAL

Greater than 14 days post implant.

[1] van Swieten J, Koudstaal P, Visser M, Schouten H, *et al* (1988). “Interobserver agreement for the assessment of handicap in stroke Subjects”. *Stroke* **19** (5): 604-607

Clinical Investigation Plan

APPENDIX III: STUDY CONTACT INFORMATION

Contact information for each participating clinical site is available under separate cover by contacting the Project Management.

Project Management Contact

Binh Ngo
Abbott
15900 Valley View Court
Sylmar, CA, 91342
USA
Phone: +1 818 493 2060
E-mail: binh.ngo1@abbott.com

Clinical Safety Contact

Mallik Pinnamaneni
Sr. Manager - Clinical Safety
3200 Lakeside Drive
Santa Clara, CA 95054
USA
E-mail: AdverseEvent@Abbott.com

Requests for further clarifications on submitted reports can be sent to AdverseEvent@Abbott.com.

Clinical Investigation Plan

APPENDIX IV: INFORMED CONSENT FORM

The study template informed consent form is available under a separate cover.

Clinical Investigation Plan

APPENDIX V: MONITORING PLAN

A copy of the Monitoring Plan can be obtained upon request from the Sponsor Clinical Project Manager.

Clinical Investigation Plan

APPENDIX VI: REVISION HISTORY

This CIP may be amended as appropriate by the Sponsor. Rationale will be included with each amended version in the revision history table below. The version number and date of amendments will be documented.

IRB/EC and relevant Regulatory Authorities, if applicable, will be notified of amendments to the CIP.

Amendment Number	Version	Date	Details	Rationale
Not Applicable	A	22AUG2019	First release of CIP	NA

Clinical Investigation Plan

APPENDIX VII: CIP SUMMARY

Clinical Investigation Name and Number	ARIES HM3 CRD_971
Title	**A**ntiplatelet **R**emoval and Hemocompat**I**bility **E**vent**S** with the **H**eart**M**ate **3** Pump
Background	Heart failure (HF) is a growing epidemic, with 915,000 new cases diagnosed each year, resulting in over 1 million hospitalizations and costs the United States (US) healthcare system over $30 billion annually[1]. Left ventricular assist devices (LVAD) are increasingly being used for treating patients with advanced heart failure as they have demonstrated improved survival over optimal medical management[2]. Progressively improving outcomes with newer LVAD technology has led to LVAD therapy becoming a mainstay in the treatment of advanced heart failure[3], however, LVAD therapy has been beleaguered by hemocompatibility related adverse events – namely thrombosis, stroke and bleeding[4]. Within the prospective randomized multicenter MOMENTUM 3 clinical trial, the HeartMate 3 (HM3) Left Ventricular Assist System (LVAS; Abbott, Chicago, IL, Study Sponsor) showed a decrease in hemocompatibility related adverse events relative to the HeartMate II (HMII) LVAS (Abbott, Chicago, IL)[5]. This included decreases in pump thrombosis[6], stroke[7-9] ENREF 9, and bleeding[9] event rates ENREF 9. Despite these noted improvements a high residual risk of bleeding persists in patients treated with the HM3 LVAD[9]. Patients implanted with the HM3 pump are treated with a combination of antiplatelet and anticoagulation therapy but the role and implications of this regimen in determining the burden of hemocompatibility related adverse events have not been adequately investigated[9,10]. Whether antiplatelet therapy is essential in concert with anticoagulation in treating such patients remains unknown.
Objective	To study the safety and efficacy of an anti-platelet-free antithrombotic regimen in patients with advanced heart failure treated with the HM 3 LVAS
Hypothesis	Withdrawal of aspirin from the antithrombotic regimen of HM3 pump patients will not adversely affect safety and efficacy and may reduce non-surgical bleeding

Clinical Investigation Plan

Clinical Investigation Design	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 versus vitamin K antagonist with placebo
Device Under Investigation and Indications	HeartMate 3 Left Ventricular Assist System (LVAS) In the US, the HM3 LVAS is indicated for providing mechanical circulatory support in patients with advanced refractory left ventricular heart failure (e.g. pending cardiac transplantation or myocardial recovery, or for permanent support). In Europe, the HM3 LVAS is intended to provide long term hemodynamic support in patients with advanced, refractory left ventricular heart failure. It is intended either for temporary support, such as a bridge to cardiac transplantation (BTT), or as permanent destination therapy (DT) and it is intended for use inside or outside the hospital. In Canada, The HM3 LVAS is indicated for providing mechanical circulatory support in patients with advanced refractory left ventricular heart failure (e.g., pending cardiac transplantation or myocardial recovery, or for permanent support).
Treatment Arm Medication	Aspirin (100 mg– active ingredient: Acetylsalicylic acid) OR Placebo (ALMAC Group, Craigavon, UK)
Study Sites	Up to 50 US and international sites
Patient Protection Procedures	This study will employ an independent clinical events committee (CEC), which will remain blinded to subject randomization, to adjudicate primary endpoint related adverse events. Study monitoring will be performed by an independent data safety monitoring board (DSMB), which will be blinded to subject and population randomization and determine independent rules for safety oversight.
Primary Endpoint	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

Clinical Investigation Plan

Primary Endpoint Evaluation	The primary endpoint composite success rate will be calculated for each treatment arm based on the number of subjects who survive to 12 months with no primary endpoint events divided by the total number of subjects in the primary endpoint analysis population. The placebo arm will be considered non-inferior to the aspirin arm if the lower boundary of the two-sided 95% confidence limit of the risk difference in the composite success between treatment arms (Placebo-arm minus Aspirin-arm) is greater than the non-inferiority margin (10%). If the lower 95% confidence limit is also greater than 0, then the placebo will be superior to the aspirin treatment. Superiority will also be confirmed at a 1-sided 0.025 level of significance using the z-test of proportions using the normal approximation to the binomial distribution.
Number of Subjects Required for Inclusion in Clinical Investigation	Results from the MOMENTUM 3 trial were used to derive a point estimate of 71% survival to 1 year free of any major hemocompatibility related adverse events in the aspirin treated arm. It is assumed that in the absence of aspirin a 2% improvement in the composite endpoint will be noted, mainly due to the reduction of bleeding complications without a change in thromboembolic complications. Based on these assumptions 220 patients will need to be enrolled in each arm (440 total) to achieve 80% power to prove that the placebo group is non-inferior to the aspirin group using a non-inferiority margin of 10% with the Farrington-Manning risk difference approach to non-inferiority at a one-sided alpha = 0.025. To account for an expected 30% dropout rate associated with events occurring 2-14 days post implant, up to 628 patients will be randomized in the trial. Sample size calculations were performed using PASS 15 software.
Secondary Endpoint	Non-surgical Bleeding Rates
Safety Endpoints	Stroke Rates, Survival, Pump Thrombosis Rates
Descriptive Endpoints	Hemocompatibility Score, Rehospitalizations, Economic Cost Implications
Subject Follow-up	– Baseline – Implant – Randomization – Discharge – Week 1 ± 3 days – Month 1 ± 7 days – Month 3 ± 30 days – Month 6 ± 30 days – Month 9 ± 30 days – Month 12 ± 30 days – Every 6 month ± 60 days until last subject has completed the 12-month follow-up.

Clinical Investigation Plan

Inclusion Criteria	• Subject will receive the HeartMate 3 per standard of care (SOC) in accordance with the approved indications for use in the country of implant. • Subject will receive the HeartMate 3 as their first durable VAD. • Subject must provide written informed consent prior to any clinical investigation related procedure. • In female patients of child bearing capability, not currently pregnant and on appropriate contraception.
Exclusion Criteria	• Post-implant additional temporary or permanent mechanical circulatory support (MCS) post-implant (other than the HM3 LVAD). • Investigator mandated antiplatelet therapy for other conditions (including mandated presence or absence of antiplatelet agent). • Patients who are nil per os (NPO) post-implant through day 7. • Subjects with a known allergy to acetylsalicylic acid. • Participation in any other clinical investigation(s) involving an MCS device, or interventional investigation(s) likely to confound study results or affect study outcome. • Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements, or impact the scientific soundness of the clinical investigation results.

Clinical Investigation Plan

APPENDIX VIII: REFERENCES

1 Mozaffarian, D. *et al.* Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation* **133**, e38-360, doi:10.1161/CIR.0000000000000350 (2016).

2 Rose, E. A. *et al.* Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med* **345**, 1435-1443, doi:10.1056/NEJMoa012175 (2001).

3 Cook, J. L. *et al.* Recommendations for the Use of Mechanical Circulatory Support: Ambulatory and Community Patient Care: A Scientific Statement From the American Heart Association. *Circulation* **135**, e1145-e1158, doi:10.1161/CIR.0000000000000507 (2017).

4 Mehra, M. R. The burden of haemocompatibility with left ventricular assist systems: a complex weave. *Eur Heart J* **40**, 673-677, doi:10.1093/eurheartj/ehx036 (2019).

5 Uriel, N. *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* **135**, 2003-2012, doi:10.1161/CIRCULATIONAHA.117.028303 (2017).

6 Mehra, M. R. *et al.* A Fully Magnetically Levitated Circulatory Pump for Advanced Heart Failure. *N Engl J Med* **376**, 440-450, doi:10.1056/NEJMoa1610426 (2017).

7 Colombo Paolo, C. *et al.* Comprehensive Analysis of Stroke in the Long-Term Cohort of the MOMENTUM 3 Study. *Circulation* **139**, 155-168, doi:10.1161/CIRCULATIONAHA.118.037231 (2019).

8 Mehra, M. R. *et al.* Two-Year Outcomes with a Magnetically Levitated Cardiac Pump in Heart Failure. *N Engl J Med* **378**, 1386-1395, doi:10.1056/NEJMoa1800866 (2018).

9 Mehra, M. R. *et al.* A Fully Magnetically Levitated Left Ventricular Assist Device - Final Report. *N Engl J Med* **0**, null, doi:10.1056/NEJMoa1900486 (2019).

10 Netuka, I. *et al.* Evaluation of low-intensity anti-coagulation with a fully magnetically levitated centrifugal-flow circulatory pump-the MAGENTUM 1 study. *J Heart Lung Transplant* **37**, 579-586, doi:10.1016/j.healun.2018.03.002 (2018).

11 Schmitto, J. D. *et al.* Long-term evaluation of a fully magnetically levitated circulatory support device for advanced heart failure—two-year results from the HeartMate 3 CE Mark Study. *European journal of heart failure* **21**, 90-97, doi:10.1002/ejhf.1284 (2019).

12 Saeed, D. *et al.* Two-Year Outcomes in Real World Patients Treated with Heartmate 3^{TM} Left Ventricular Assist Device for Advanced Heart Failure: Data from the ELEVATE Registry. *The Journal of Heart and Lung Transplantation* **38**, S67, doi:10.1016/j.healun.2019.01.153 (2019).

13 Heatley, G. *et al.* Clinical trial design and rationale of the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy With HeartMate 3 (MOMENTUM 3) investigational device exemption clinical study protocol. *J Heart Lung Transplant* **35**, 528-536, doi:10.1016/j.healun.2016.01.021 (2016).

14 Mehra, M. R. *et al.* A Fully Magnetically Levitated Circulatory Pump for Advanced Heart Failure. *N Engl J Med* **376**, 440-450, doi:10.1056/NEJMoa1610426 (2016).

15 Uriel, N. & Mehra, M. Long-Term Burden of Hemocompatibility Related Adverse Events in the MOMENTUM 3 Trial: Final Analysis of the 1028 Patient Cohort. *The Journal of Heart and Lung Transplantation* **38**, S67, doi:10.1016/j.healun.2019.01.152 (2019).

16 Netuka, I. *et al.* A Trial of Complete Withdrawal of Anticoagulation Therapy in the Heartmate 3 Pump. *The Journal of Heart and Lung Transplantation* **38**, S113, doi:10.1016/j.healun.2019.01.264 (2019).

17 Consolo, F., Raimondi Lucchetti, M., Tramontin, C., Lapenna, E. & Pappalardo, F. Do we need aspirin in HeartMate 3 patients? *European journal of heart failure*, doi:10.1002/ejhf.1468 (2019).

Clinical Investigation Plan

18 Lim, H. S., Ranasinghe, A., Mascaro, J. & Howell, N. Discontinuation of Aspirin in Heartmate 3 Left Ventricular Assist Device. *ASAIO Journal (American Society For Artificial Internal Organs: 1992)*, doi:10.1097/MAT.0000000000000859 (2018).
19 McNeil, J. J. *et al.* Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly. *New England Journal of Medicine* **379**, 1509-1518, doi:10.1056/NEJMoa1805819 (2018).
20 Katz, J. N. *et al.* Safety of reduced anti-thrombotic strategies in HeartMate II patients: A one-year analysis of the US-TRACE Study. *Journal of Heart and Lung Transplantation* **34**, 1542-1548, doi:10.1016/j.healun.2015.06.018 (2015).
21 Netuka, I. *et al.* Outcomes in HeartMate II Patients With No Antiplatelet Therapy: 2-Year Results From the European TRACE Study. *The Annals of thoracic surgery* **103**, 1262-1268, doi:10.1016/j.athoracsur.2016.07.072 (2017).
22 Van Tuyl, J. S. *et al.* Warfarin and Aspirin Versus Warfarin Alone for Prevention of Embolic Events in Patients with a HeartMate II Left Ventricular Assist Device. *ASAIO journal* **63**, 731-735, doi:10.1097/mat.0000000000000561 (2017).
23 Litzler, P. Y. *et al.* Is anti-platelet therapy needed in continuous flow left ventricular assist device patients? A single-centre experience. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery* **45**, 55-59; discussion 59-60, doi:10.1093/ejcts/ezt228 (2014).
24 Schmitto, J. D. *et al.* in *International Society of Heart and Lung Transplantation.*

Clinical Investigation Plan

CRD_971
ARIES HM3
Antiplatelet **R**emoval and Hemocompat**I**bility **E**vent**S** with the **H**eart**M**ate **3** Pump

Version	C
Date	MAR 13, 2020
Steering Committee	Mandeep Mehra MD, MSc, FRCP (Lon) - Chair Nir Uriel MD, MSc Francis Pagani MD, PhD Ulrich Jorde MD Jason Katz MD, MHS Finn Gustafsson MD, PhD Ivan Netuka MD, PhD
Planned Number of Sites	Up to 50 sites
Geographies	International
Clinical Investigation Type	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 versus vitamin K antagonist with placebo
Sponsor	Abbott 168 Middlesex Turnpike Burlington, MA 01803 USA
Randomization and Treatment Arm Medication Logistics	WebEZ (ALMAC Clinical Services)
Electronic Data Capture Software	Oracle Clinical
CIP Author (Current Version)	Daniel Crandall, PhD
Abbott Medical Expert	Robert Kormos, MD, FACS, FRCS (C), FAHA

Clinical Investigation Plan

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I have read and agree to adhere to the clinical investigation plan and all regulatory requirements applicable in conducting this clinical investigation.

Site Principal Investigator

Printed name:
Signature:
Date:

Clinical Investigation Plan

TABLE OF CONTENTS

Clinical Investigation Plan

Clinical Investigation Plan

COMPLIANCE STATEMENT:
This clinical investigation will be conducted in accordance with this Clinical Investigation Plan, the Declaration of Helsinki, applicable Good Clinical Practices and regulations (e.g., US 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 812, and OUS ISO14155:2011) and the appropriate local legislation(s). The most stringent requirements, guidelines or regulations must always be followed. The conduct of the clinical investigation will be approved by the appropriate Institutional Review Board (IRB)/Ethics Committee (EC) of the respective investigational site and by the applicable regulatory authorities.

Clinical Investigation Plan

1.0 INTRODUCTION

Heart failure (HF) is a growing epidemic, with 915,000 new cases diagnosed each year, resulting in over 1 million hospitalizations and costs the United States (US) healthcare system over $30 billion annually[1]. Left ventricular assist devices (LVAD) are increasingly being used for treating patients with advanced heart failure as they have demonstrated improved survival over optimal medical management[2]. Progressively improving outcomes with newer LVAD technology has led to LVAD therapy becoming a mainstay in the treatment of advanced heart failure[3], however, LVAD therapy has been beleaguered by hemocompatibility related adverse events – namely thrombosis, stroke and bleeding[4]. Within the prospective randomized multicenter MOMENTUM 3 clinical trial, the HeartMate 3 (HM3) Left Ventricular Assist System (LVAS; Abbott, Chicago, IL, Study Sponsor) showed a decrease in hemocompatibility related adverse events relative to the HeartMate II (HMII) LVAS (Abbott, Chicago, IL)[5]. This included decreases in pump thrombosis[6], stroke[7-9], and bleeding[9] event rates. Despite these noted improvements a high residual risk of bleeding persists in patients treated with the HM3 LVAD[9]. Patients implanted with the HM3 pump are treated with a combination of antiplatelet and anticoagulation therapy but the role and implications of this regimen in determining the burden of hemocompatibility related adverse events have not been adequately investigated[9,10]. Whether antiplatelet therapy is essential in concert with anticoagulation in treating such patients remains unknown.

This clinical investigation is a prospective, randomized, double-blinded, placebo-controlled study of advanced heart failure patients treated with the HM3 with two different antithrombotic regimens: vitamin K antagonist with aspirin versus vitamin K antagonist with placebo. The objective of this investigation is to study the safety and efficacy of an anti-platelet-free antithrombotic regimen in patients with advanced heart failure treated with the HM3 LVAS.

This clinical investigation will be conducted in accordance with this clinical investigation plan (CIP). All investigators involved in the conduct of the clinical investigation will be qualified by education, training, or experience to perform their tasks and this training will be documented appropriately.

1.1 Background and Rationale

1.1.1 Background

The CE Mark trial (clinicaltrials.gov identifier: NCT02170363) for the HM3 LVAD was a prospective, multicenter, single arm trial that enrolled 50 subjects at 10 sites. Six-month outcomes from this trial demonstrated 92% (confidence interval 83-97%) survival and led to the CE Mark approval of the HM3. Analysis of longer term data demonstrated a 2-year survival of 74 ± 6%[11]. No instances of device thrombosis were observed in this cohort at 2 years[11]. Subjects will be followed through 5 years as a condition of CE Mark approval.

After approval, the ELEVATE (Evaluating the HeartMate 3 with Full MagLev Technology in a Post-Market Approval Setting; clinicaltrials.gov identifier: NCT02497950) registry was initiated to collect real-world data (i.e. there were no enrollment criteria) on consecutive HM3 patients at 26 total centers in Europe, Israel, Singapore, and Kazakhstan. The study enrolled 463 primary implant patients, 19 pump exchange patients, and collected only outcome data on an additional 58 patients who were unable to provide consent due to a study outcome (n=57 death, n=1 explant). The ELEVATE trial reported, for the primary implant cohort at 2-years, actuarial survival of 83.4%, and adverse events of stroke in 10%, suspected pump thrombosis in 1.5%, and bleeding in 34%[12].

The MOMENTUM 3 study (clinicaltrials.gov identifier: NCT02224755) was a prospective, randomized, multicenter, non-blinded, clinical trial that enrolled 1,028 patients at 69 sites in the US. The study randomized patients to receive either the HM3 or HMII LVAD. The study design incorporated an initial safety phase that evaluated 30 subjects at 5 sites prior to study expansion[13]. The primary objective of the trial was to evaluate the safety and efficacy of using the HM3 LVAD in indicated patients at two timepoints: 6 months (short-term n=294) and 2 years (long-term n=366)[13]. The primary endpoint was a composite of survival free of disabling stroke or survival free of reoperation to replace or remove the device (for reasons other than recovery)[14]. The secondary endpoint, which the study was powered to assess, was freedom from pump exchange through 2-years of follow-up in the full cohort of 1028 patients. All study endpoints were successfully met[6,8,9]. The MOMENTUM 3 trial reported the full cohort HM3 actuarial survival at 2-years as 79.0% and stroke rates of 9.9%, suspected pump thrombosis rates of 1.4%, and bleeding rates of 43.7%[9]. An analysis of the burden of hemocompatibility related adverse events showed improved survival free of hemocompatibility related adverse events with the HM3 over the HMII at 6 months[5] and 2 years[15]. Within the full cohort HM3 arm of MOMENTUM 3, at all time points, a cohort of patients were noted without aspirin as a part of their anti-thrombotic regimen, specifically at 6-months n=72/446 (16%), at 1-year n=78/371 (21%), at 18-months n=73/314 (23%), and at 2-years n=64/286 (22%)[9]. The MOMENTUM 3 study will continue to follow patients through 5-years post-implant as a condition of approval. After full enrollment in the MOMENTUM 3 study, a single arm (HM3 only) continued access protocol (CAP) was initiated while the MOMENTUM 3 IDE patients were being followed. This CAP study enrolled 1685 patients who will be followed for 2 years post implant.

A single center in Europe has investigated the use of the HM3 with low intensity anticoagulation (INR 1.5-1.9) in select patients, and reported positive outcomes[10]. These outcomes lead to the full removal of anticoagulation therapy in a subset of the low intensity anticoagulation patients, with favorable outcomes[16]. Additionally two reports from Europe have emerged on their initial experience with warfarin monotherapy with the HM3[17,18]. Both studies conclude it may be safe to remove aspirin therapy from HM3 patients and called for further evaluation of the effects of discontinuation of aspirin in HM3 patients. Specifically, in a multicenter, retrospective, observational study performed at the San Raffaele Scientific Institute in Milan and A.O. Brotzu in Cagliari, Italy, patients were stratified based on bleeding risk; patients with a HAS-BLED score ≥ 4 or who experienced a post-operative bleeding event were considered high risk[17]. Patients at high bleeding risk were discharged on warfarin monotherapy with INR targeted to 2.0-2.5 whereas the remaining patients were discharged with warfarin (INR 2.0-2.5) and aspirin (100mg/day) antithrombotic therapy[17]. In the other study at the University Hospital Birmingham, United Kingdom, a retrospective analysis of a prospective audit of a change in their institutional standard of care was conducted[18]. The center implemented as standard of care the discontinuation of aspirin therapy after >3 months or following a bleeding complication.

1.1.2 Rationale for Conducting this Clinical Investigation

Patients implanted with LVADs are typically treated with a combination of antiplatelet and anticoagulant therapy but the role and implications of this regimen in determining the burden of hemocompatibility related adverse events in patients implanted with the HM3 LVAS have not been adequately investigated[9,10]. Furthermore, a recent study showed that aspirin, in older, healthy adults without an LVAD, was associated with increased risk of major bleeding, including upper gastrointestinal bleeding, without a reduction in thromboembolic events including ischemic stroke[19]. Whether antiplatelet therapy is essential in concert with anticoagulation in treating LVAD patients remains unknown.

Hemocompatibility related adverse events, both thrombotic and hemorrhagic, are highly interrelated. Frequently changes to a patient's antithrombotic therapy that occur in the setting of hemocompatibility related adverse events increase the propensity toward opposing events. Specifically, treatment of a thrombotic event with additional antithrombotic intensity may result in a hemorrhagic event or vise-versa. While these events may be commonly discussed discretely, decoupling them in the setting of a patient population predisposed to both events is not possible, which can lead to difficulty interpreting the results of clinical studies or, in the worst-case scenario, studies with little or no interpretive value. As such, this study focuses on de novo LVAD implants and the first events, prior to such modifications to the treatment arm antithrombotic regimen while encouraging investigators to maintain the randomized treatment arm therapy as long as clinically permissible, in an effort to avoid such confounding factors.

Bleeding events with the HM3, while decreased in comparison to a predicate device, remain burdensome[9]. All major prospective clinical trials conducted with the HM3 (MOMENTUM 3, CE Mark) have been in the context of a prescribed antithrombotic regimen of aspirin in concert with vitamin K antagonist. Within clinical studies[9,10,16], as institutional changes to their standard of care[18], or in response to increased bleeding risk[17], modifications to the HM3 anticoagulation regimen have been explored. Prior to the introduction of the HM3, which has a decreased thrombotic profile relative to the HMII, studies investigating the need for aspirin within the HMII antithrombotic regimen were conducted[20-23]. The experience with the HMII, the improved outcomes with the HM3 and the early experience of single centers exploring modification to the antithrombotic regimen in HM3 patients provide evidence for the clinical equipoise in HM3 antithrombotic therapy and forms the basis for randomization of patients to aspirin (100mg) vs placebo arms within this trial.

2.0 CLINICAL INVESTIGATION OVERVIEW

2.1 Clinical Investigation Objective

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

2.2 Hypothesis

Withdrawal of antiplatelet therapy from the antithrombotic regimen of HM3 pump patients will not adversely affect safety or efficacy of the HM3 and may reduce non-surgical bleeding.

2.3 Device(s) To Be Used in the Clinical Investigation

This Clinical Trial investigates the treatment of advanced heart failure with the HM3 and if the use of antiplatelet therapy is required as part of the antithrombotic regimen. Refer to the HM3 Instruction for Use (IFU) in your country for additional details.

Clinical Investigation Plan

Table 1 – Device Details

Device name	Model/Type	Serial/Lot Controlled	Manufacturer	Investigational or Market Released
HeartMate 3 (HM3) Left Ventricular Assist System (LVAS)	106523	Standard Commercial Controls	Abbott	The HM3 will be Market Released in all geographies included in this international study

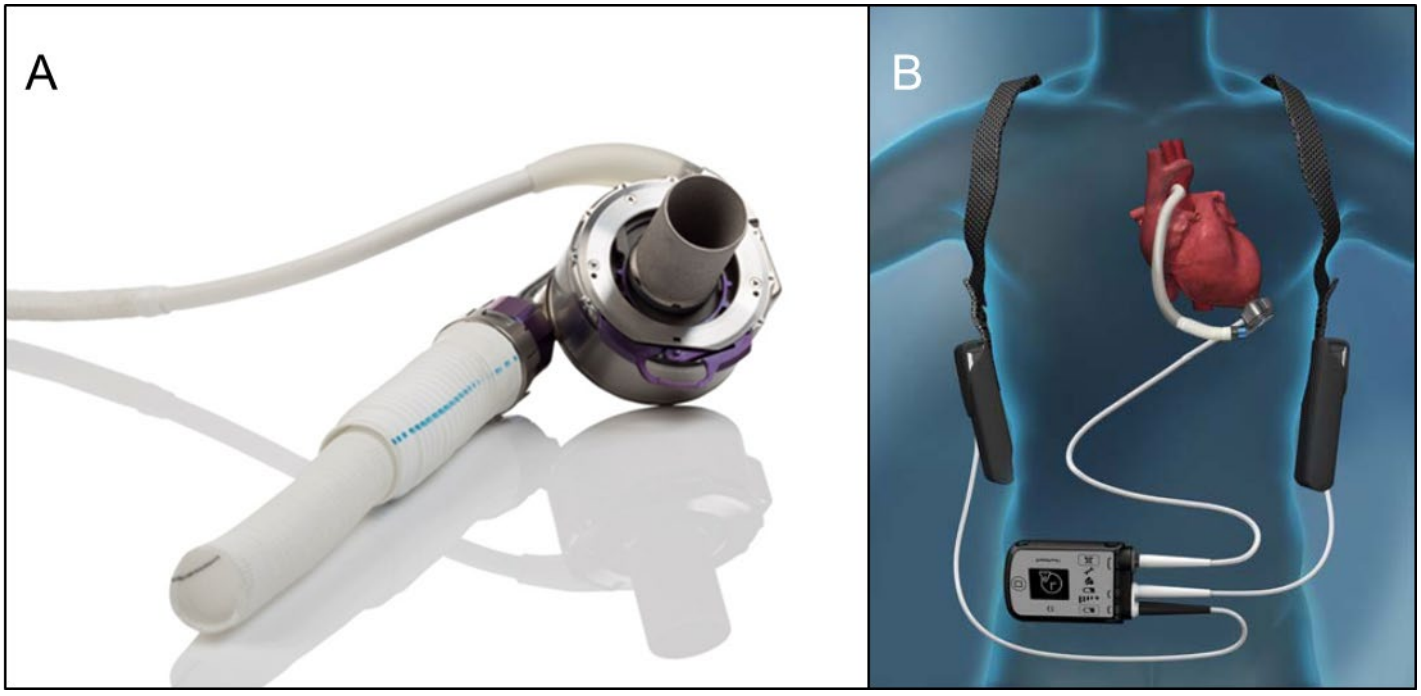


Figure 1 – HeartMate 3 LVAD (A) and System during Battery-powered Operation (B): The HM3 LVAS consists of an LVAD with an outflow graft and modular driveline cable, a pump controller and a power source (i.e. portable Batteries, Power Module, or Mobile Power Unit).

2.3.1 Indication for Use

The HM3 is market released in all geographies participating in this study, therefore refer to the local IFU for the local indication. In the US, the HM3 LVAS is indicated for providing mechanical circulatory support in patients with advanced refractory left ventricular heart failure (e.g. pending cardiac transplantation or myocardial recovery, or for permanent support). In Europe, the HM3 LVAS is intended to provide long term hemodynamic support in patients with advanced, refractory left ventricular heart failure. It is intended either for temporary support, such as a bridge to cardiac transplantation (BTT), or as permanent

destination therapy (DT) and it is intended for use inside or outside the hospital. In Canada, The HM3 LVAS is indicated for providing mechanical circulatory support in patients with advanced refractory left ventricular heart failure (e.g., pending cardiac transplantation or myocardial recovery, or for permanent support).

2.3.2 Description of the Device(s) Under Investigation

The HM3 LVAS consists of a centrifugal LVAD with an outflow graft and modular driveline cable, a pump controller and a power source (i.e. portable Batteries, Power Module, or Mobile Power Unit). The HM3 LVAD is comprised of an Inflow Cannula, a Pump Cover, a Lower Housing, a Screw Ring to attach the Pump Cover to the Lower Housing, a Motor, the Outflow Graft, the Outflow Graft Clip (if required), and a Pump Cable.

The HM3 LVAD has a displacement volume of 80 milliliters and weighs 200 grams. All blood contacting surfaces are composed of titanium (LVAD body and centrifugal rotor) or gelatin-impregnated woven polyester (outflow graft). The HM3 LVAD is designed to reduce adverse events associated with LVAD thrombosis. Primary design features include full magnetic levitation and large flow gaps, which minimize the shear stress imparted onto the blood elements.

The HM3 Controller is an extracorporeal interface device that receives power from the Power Module, Mobile Power Unit, or portable Batteries, and appropriately delivers that power to the HM3 LVAD. It is the primary user interface and has several important functions including:

- operating condition display,
- source of audible and visible alarms,
- communication link for transferring event/period log and alarm information, and
- battery backup in the case of full power disconnection.

The HM3 LVAD and Controller are sterilized using 100% ethylene oxide. Please refer to the local IFU for additional information regarding the device used in this clinical investigation.

2.3.3 Device Accountability

All devices used in this study will be commercial stock at each investigative site. The HM3 is commercially available and approved for the patient population enrolled in this study; therefore, study specific device accountability is not required. The standard commercial practices for device tracking, return and reporting to the Sponsor's Product Performance Group should be followed in accordance with local practices.

2.4 Treatment Arm Medication

2.4.1 Project Management

ALMAC Clinical Services will manufacture the blinded treatment arm medication at their facility at 25 Fretz Road, Souderton, PA 18964. The medication shall consist of 100mg aspirin blinded against a matching placebo. Distribution logistics, site inventory management, patient randomization and treatment arm medication bottle requisition will be coordinated by ALMAC Clinical Services' WebEZ system. Treatment arm medication will be stored in Souderton PA and may be stored in international depot sites administered by ALMAC including Craigavon, Northern Ireland and Singapore, prior to dispatch to sites. Medication accountability will be performed at their facility in Durham, NC or may be performed at depot sites in Craigavon, Northern Ireland or Singapore. Treatment arm medication accountability will include pill counts

of any bottle requisitioned to a patient and opened, as well as reconciliation of unused bottles that were not requisitioned to a patient or otherwise remain sealed, prior to destruction. All bottles should be returned to ALMAC or reported as lost within the Abbott electronic data capture system (EDC).

ALMAC Clinical Services is a part of ALMAC Group Limited headquartered at ALMAC House, 20 Seagoe Industrial Estate, Craigavon, BT63 5QD, Northern Ireland (Registration Number: NI 41905).

ALMAC Clinical Services responsibilities will be, but not limited to, the following:

- Treatment arm medication manufacture (blinded aspirin with placebo-to-match), including packaging and labelling (due to country-specific requirements treatment arm medication bottle labeling may vary)
- Patient randomization via the ALMAC WebEZ system
- Supplying treatment arm medication to sites including maintaining adequate site supply
- Providing support dispensing to study subjects via the ALMAC WebEZ system
- Treatment arm medication accountability, including both used and unused drug bottle returns

2.4.2 Treatment Arm Blinding

This study shall use 100mg aspirin, blinded against a placebo-to-match. Sites should reach out to the sponsor immediately regarding unblinding questions.

2.4.3 Treatment Arm Bottle Dispensing

Initial dispensing of the treatment arm bottle will occur upon randomization. Subjects will begin taking the treatment arm medication within 24 hours of randomization. Subjects will be resupplied 1 bottle at Month 3, Month 6, and Month 9 follow-up visits and 2 bottles at month 12 and every 6 months thereafter until study closure. Dispensing will be controlled at the sites with the use of ALMAC Clinical Services' WebEZ system. At each dispensing time point, the designated site personnel will log on to the WebEZ system, enter information required for randomization or resupply, and requisition a bottle to dispense to the subject from the on-site stock.

Each bottle will be tracked by individual bottle number. The WebEZ system will provide sites with the bottle number to be dispensed to a given subject. Bottle details should be tracked per patient by sites. Site supply and resupply shipments will be automatically controlled by ALMAC Clinical Services.

If a subject reports a lost or empty bottle of treatment arm medication or is unable to attend a resupply visit, the designated site personnel will log onto the WebEZ system to requisition a replacement bottle from the onsite supply. The replacement bottle may be shipped overnight to the subject, or the subject may choose to retrieve the replacement bottle from the site in person.

Subjects should always be sufficiently supplied with treatment arm medication until their next resupply visit. Each bottle will contain 120 capsules of the treatment arm medication, which is a sufficient supply for the period leading up to the subject's next visit, including the acceptable visit windows. Sites should carefully schedule follow up visits to ensure subjects are always sufficiently supplied.

2.4.4 Antithrombotic Therapy

Antithrombotic therapy throughout the study should consist of a vitamin K antagonist (e.g. warfarin, fluindione, phenprocoumon, etc.) and the treatment arm medication. No additional anti-platelet agents

will be added while patients are on the treatment arm medication. The treatment arm medication will be taken once daily by mouth. Vitamin K antagonist therapy will be per standard of care (SOC) with a target INR of 2.0-3.0. The use of aspirin and a vitamin K antagonist is normal clinical practice at many centers and is part of the HM3 IFU.

2.4.5 Treatment Arm Medication Accountability

To ensure treatment arm medication accountability, all bottles including (if applicable) all unused doses will be returned to ALMAC Clinical Services by the site. Subjects will be instructed to return the bottle and any unused doses of the treatment arm medication at each resupply visit.

The bottles and unused doses will be shipped (at the Sponsor's expense) per country- or region-specific Treatment Arm Medication Accountability Return Instructions.

In the event that a site has several bottles or unused portions to return to ALMAC Clinical Services, return shipments may be combined into a batch shipment. Empty research bottles and unused doses should not be stored on site and should be shipped to ALMAC Clinical Services within 14 days of receipt from the subject. Treatment Arm Medication Accountability Return Instructions will be provided during training.

2.4.6 Aspirin Response Testing

US-based patients receiving the treatment arm medication will have their response to aspirin assessed by serum thromboxane B2 testing. Testing will be performed by a core lab (Corgenix, Broomfield, Colorado). To retain the study blind, sites will not receive the results of the test. Samples will be collected and processed by the sites at baseline, 3, 6, and 12 months post-implant. Samples will be stored frozen at the sites until they are shipped (within 15 days of collection; overnight shipment Monday-Thursday with sufficient dry ice to retain frozen state) to Corgenix at:

Corgenix Clinical Laboratory
ATTN: General Supervisor
11575 Main Street
Suite 400
Broomfield CO 80020

Additional sample processing, storage, and shipment details will be provided in the ARIES HM3 Aspirin Response Instructions.

NOTE: Additional antiplatelet testing or platelet function testing, beyond the core lab test, should not be performed while patients are on the treatment arm medication, as it may result in un-blinding of the subject or the investigator.

3.0 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 versus vitamin K antagonist with placebo. Subjects will be randomized in a 1:1 ratio.

Clinical Investigation Plan

The clinical investigation has been designed to involve as little pain, discomfort, fear, and any other foreseeable risk as possible for subjects. Refer to the Risks Analysis section of the clinical investigation plan for details.

The clinical investigation will be conducted at up to 50 centers worldwide. Greater than 50% of the patients enrolled in this study will be from centers based in the United States. The primary and secondary endpoints will be evaluated according to the statistical section (Section 8 and in the study statistical analysis plan; 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 has final study visit) and all data have been collected and adjudicated. Exceptions will be justified in the study blinding plan (e.g. 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.

3.1 Clinical Investigation Procedures and Follow-up Schedule

The study flow chart (Figure 2) and the follow-up schedule of this clinical investigation are described below.

Clinical Investigation Plan

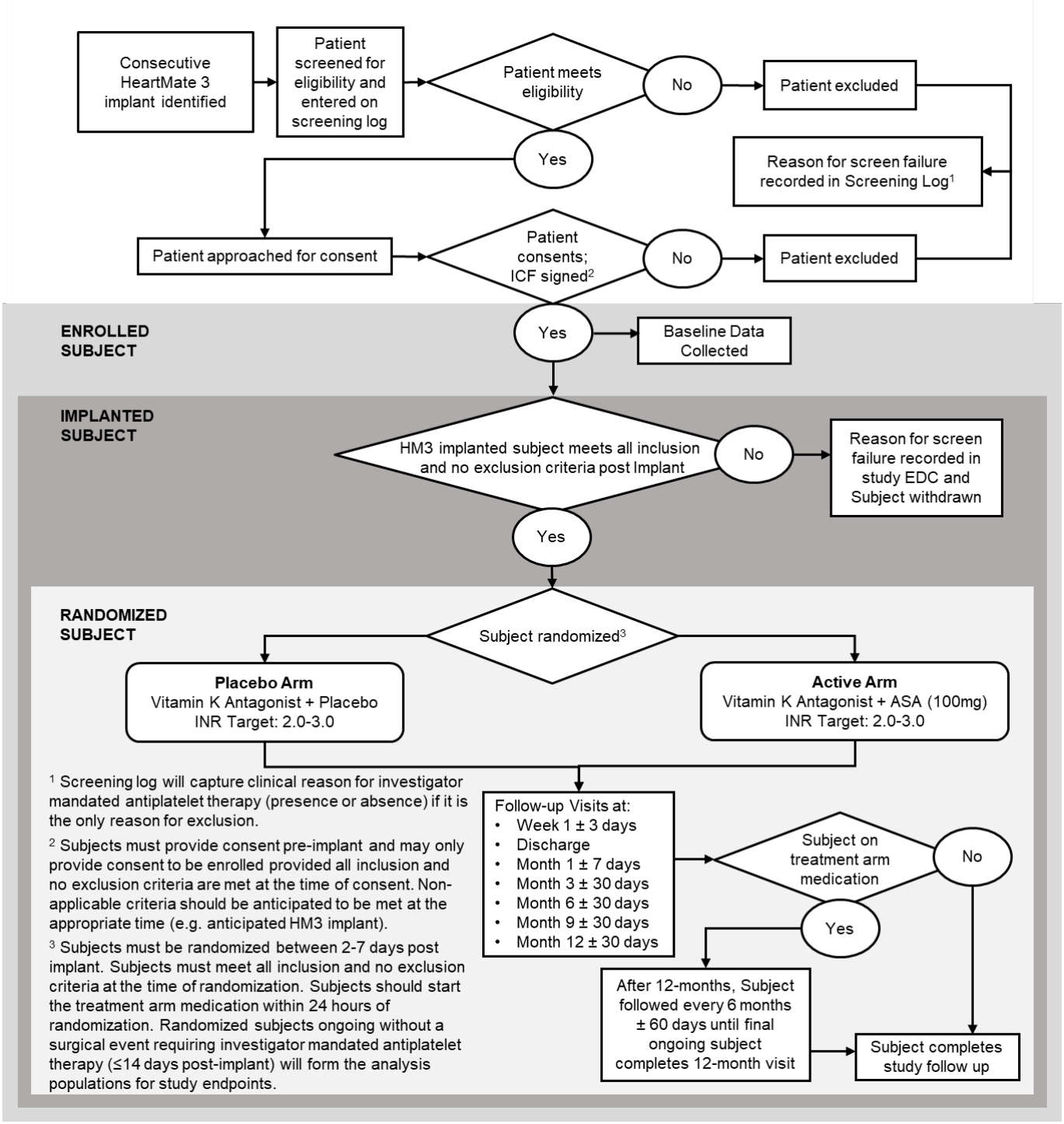


Figure 2 – Clinical Investigation Flow Chart

3.2 Measures Taken to Avoid and Minimize Bias

This study is designed to minimize bias by blinding all subjects, site personnel, sponsor personnel, and the CEC to the randomly assigned treatment regimen. Furthermore, screening logs will be captured including details on patients who are excluded from the study only because of investigator mandated antiplatelet therapy (presence or absence) prior to or after consent to understand any effect of selection bias on the generalizability of the study.

3.3 Suspension or Early Termination of the Clinical Investigation

While no formal statistical rule for early termination of the clinical investigation for insufficient effectiveness of the device under investigation is defined by the Sponsor or Steering Committee, the Sponsor reserves the right to discontinue the clinical investigation at any stage or reduce the follow-up period with suitable written notice to the investigator. Possible reason(s) may include, but are not limited to:

- Unanticipated adverse device effect (e.g., UADE) occurs and it presents an unreasonable risk to the participating subjects
- An oversight committee (e.g., Steering Committee, DSMB) makes a recommendation to stop or terminate the clinical investigation (such as in the event of higher frequency of anticipated adverse device effects)
    - The Data Safety Monitoring Board will create independent rules for study oversight including prespecified rules for recommending cessation of the study, which will be captured in the DSMB charter. In the event these rules are met, the sponsor will meet with the Steering Committee. The Sponsor will notify sites and, if agreed with the Steering Committee, enrollment in the study will be paused.
- Further study progress is cancelled.

Should the clinical investigation be discontinued by the Sponsor, subjects will be followed per routine hospital practice with device-related AEs reported to the Sponsor as per vigilance/commercial reporting requirements. The investigator shall return all clinical investigation materials (including both partially used and unused treatment arm medication bottles) to ALMAC or the Sponsor, as appropriate, and provide a written statement to the IRB/EC (if applicable). All applicable clinical investigation documents shall be subject to the same retention policy as detailed in Section 11.5 of the CIP.

A Principal Investigator, IRB/EC or regulatory authority may suspend or prematurely terminate participation in the clinical investigation at the investigational site(s) for which they are responsible. The investigators will follow the requirements specified in the Clinical Trial Agreement.

If the Sponsor suspends or prematurely terminates the clinical investigation at an individual site in the interest of safety, the Sponsor will inform all other Principal Investigators.

If suspension or premature termination occurs, the Sponsor will remain responsible for providing resources to fulfill the obligations from the CIP and existing agreements for following the subjects enrolled in the clinical investigation, and the Principal Investigator or authorized designee will promptly inform the enrolled subjects at his/her site, and return patients to their standard medical treatment.

4.0 ENDPOINTS

4.1 Primary Endpoint and Rationale

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 is defined as any event occurring > 14-days post implant.
[2] - Major Hemocompatibility Related Adverse Events include:

- 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 between the two groups. Additional secondary endpoints will also be evaluated to monitor effects on other safety and efficacy 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 the 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. Refer to section 8 of this CIP and the SAP for details.

4.2 Secondary Endpoint

As secondary endpoints:

- Non-surgical Major Hemorrhagic Events
- Non-surgical Major Thrombotic Events
- Survival
- Stroke Rates,
- Pump Thrombosis Rates
- Bleeding Rates, including:
    - Non-surgical Bleeding
    - Moderate Bleeding
    - Severe Bleeding
    - Fatal Bleeding
    - GI Bleeding

will be compared between the two arms of the study as detailed in section 8 of this CIP and the SAP.

4.3 Descriptive Endpoints

This study will also assess changes in the Hemocompatibility Score, Rehospitalization, and Economic Cost Implications as a result of removal of antiplatelet therapy from the antithrombotic regimen. Refer to section 8 of this CIP and the SAP for details.

5.0 SUBJECT SELECTION AND WITHDRAWAL

5.1 Subject Population

This clinical investigation will enroll male and female subjects from the advanced heart failure population who, as part of their standard course of treatment, will receive a HM3 LVAD. Subjects are considered enrolled when they provide written informed consent. Subjects must meet all applicable eligibility criteria and provide written informed consent prior to the conduct of any investigation-specific procedures not considered standard of care. Furthermore, patients must meet all randomization eligibility requirements at randomization. Only randomized subjects will continue to be followed in this study. Subjects not meeting randomization eligibility requirements will be considered screen failures and withdrawn from the study. Reason(s) for not meeting randomization eligibility requirements will be captured in the study EDC. Randomized subjects ongoing without a surgical adverse event, defined as ≤14 days post-implant, requiring investigator mandated antiplatelet therapy will form the analysis population for study endpoints. Details are available in section 8 of this CIP and the SAP.

5.2 Subject Screening and Informed Consent

5.2.1 Subject Screening

Patients receiving an LVAD at study sites should be considered for enrollment. All patients evaluated for inclusion in the clinical study, including those who provide informed consent and are enrolled, will be recorded on the site screening log. Rationale for exclusion from the trial will be recorded. Specifically, reasons may include refusal to consent, did not meet eligibility criteria or other specified reasons. To monitor for selection bias in enrollment, any patient excluded exclusively due to an investigator mandated antiplatelet therapy (either mandated antiplatelet presence or mandated absence of antiplatelets) will require specific clinical reasons recorded on the screening log.

Potential subjects presenting at the clinical sites will be fully informed about the clinical investigation, following the established informed consent process (described in Section 5.2.2). Once informed consent is obtained, subjects are considered enrolled. Thereafter, all subjects will have required baseline data beyond site standard of care captured and US-based patients will have blood drawn for baseline aspirin responsiveness testing (per section 2.4.6). Subjects who do not meet enrollment or randomization criteria will be considered screen failures.

5.2.2 Informed Consent

The Investigator or his/her authorized designee will conduct the informed consent process, as required by applicable regulations and the center's IRB/EC. This process will include a verbal discussion with the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate, such as details of clinical investigation procedures, anticipated benefits, and potential risks of clinical investigation participation. Subjects must be informed about their right to withdraw from the clinical

investigation at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled. Withdrawal from the clinical investigation will not jeopardize their future medical care or relationship with the investigator.

During the discussion, the Principal Investigator or his/her authorized designee will avoid any improper influence on the subject and will respect the subject's legal rights. Financial incentives will not be given to the subject. The subject shall be provided with the informed consent form written in a language that is understandable to the subject and has been approved by the center's IRB/EC. The subject shall have adequate time to review, ask questions, and consider participation. The Principal Investigator or his/her authorized designee will make efforts to ensure that the subject understands the information provided. If the subject agrees to participate, the informed consent form must be signed and dated by the subject and thereafter by the person obtaining the consent prior to any clinical investigation-specific procedures beyond SOC. The signed original will be filed in the subject's hospital or research charts, and a copy will be provided to the subject.

Failure to obtain informed consent from a subject prior to clinical investigation enrollment should be reported to Sponsor within 5 working days and to the reviewing center's IRB/EC according to the IRB's/ EC's reporting requirements.

If, during the clinical investigation, new information becomes available that can significantly affect a subject's future health and medical care, the Principal Investigator or his/her authorized designee will provide this information to the subject. If relevant, the subject will be asked to confirm their continuing informed consent in writing.

In addition, an authorization for use and disclosure of the subject's protected health information, in accordance with the Health Insurance Portability and Accountability Act (HIPAA) or local equivalent, as applicable, must be obtained from the subject. This may be incorporated into the main ICF or captured as a standalone document.

This study will not permit informed consent via legally authorized representatives. Therefore, incapacitated individuals, including the mentally handicapped or individuals without legal authority or individuals under the age of 18 or local age of legal consent, are excluded from the study population. Furthermore, individuals unable to read or write are excluded from the study population.

5.3 Eligibility Criteria

Assessment for general eligibility criteria is based on the medical records of the site and an interview with a candidate patient. If some of the clinical and laboratory tests are not included in site standard tests, they must be done but after written informed consent is obtained. Patients must meet ALL of the inclusion criteria to be considered for the clinical investigation. If ANY of the exclusion criteria are met, the patient is excluded from the clinical investigation and cannot be enrolled. If the subject is found after the time of informed consent but prior to randomization to no longer meet any of the inclusion criteria, or to meet any of the exclusion criteria (randomization eligibility), the subject will not be randomized and will be considered a screen failure and withdrawn from the study.

5.3.1 Inclusion Criteria

1. Subject will receive the HeartMate 3 per standard of care (SOC) in accordance with the approved indications for use in the country of implant.
2. Subject will receive the HeartMate 3 as their first durable VAD.
3. Subject must provide written informed consent prior to any clinical investigation related procedure.
4. In patients of child bearing capability, subject will not be currently pregnant or breastfeeding and on appropriate contraception.

5.3.2 Exclusion Criteria

1. Post-implant additional temporary or permanent mechanical circulatory support (MCS).
2. Post-implant Investigator mandated antiplatelet therapy for other conditions (including mandated presence or absence of antiplatelet agent).
3. Patients who are nil per os (NPO) post-implant through day 7.
4. Subjects with a known allergy to acetylsalicylic acid (aspirin).
5. Participation in any other clinical investigation(s) involving an MCS device, or interventional investigation(s) likely to confound study results or affect study outcome.
6. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements, or impact the scientific soundness of the clinical investigation results.

5.4 Subject Enrollment

Once informed consent is obtained, subjects are considered enrolled. Subject data entry into the EDC will begin following enrollment into the clinical investigation. Subject data will be collected following enrollment to the clinical investigation until the subject is withdrawn, experiences an outcome (transplant, explant, exchange, or death), or completes study follow-up.

Subjects who provide informed consent and are subsequently found to not meet inclusion/exclusion criteria prior to randomization or otherwise do not proceed to randomization will be withdrawn in accordance with section 5.5 of this CIP. Subjects who experience a surgical adverse event prior to day 14 that requires investigator mandated antiplatelet therapy (either presence or absence) will be withdrawn and not included in the analysis population. Subjects who expire prior to day 14 will not be included in the analysis population. All patients considered for this study, including enrolled subjects not included in the analysis population, will be reported in the study consort diagram.

5.4.1 Enrollment of Medicare Beneficiaries

This clinical investigation will enroll both Medicare beneficiaries and private payors in the US. Because this study enrolls Medicare beneficiaries, it conforms to all standards of Medicare coverage requirements. The Risks and Benefits in section 15 of this CIP describe how all enrolled subjects, including Medicare beneficiaries, may be affected by the hypothesis under investigation. The demographics representative of LVAD therapy reflect primarily a CMS population. Common complications associated with LVADs are frequently associated with hemocompatibility-related adverse events such as pump thrombosis, stroke and bleeding events. Improvements in contemporary LVAD technology with the HeartMate 3 LVAD have shown significant improvement in reduction of pump

thrombosis, stroke and bleeding, but bleeding events persist at a high incidence. If bleeding events could be reduced with the withdrawal of antiplatelet therapy from the antithrombotic regiment with HM3, this could improve clinical outcomes for Medicare beneficiaries and have added relevancy to their treatment plan. For this purpose, it is important that Medicare beneficiaries are studied in this trial so that relevant outcomes may be translated more broadly.

To further characterize the portion of the subjects enrolled in the clinical investigation that display characteristics consistent with the Medicare population based on age, the clinical investigation results will be analyzed by age (< 65 years and ≥ 65 years) to ensure that the outcomes are similar between the Medicare and non-Medicare populations. Additional subgroup analyses are detailed in section 8.5.

5.4.2 Historically Under-Represented Demographic Subgroups

The Sponsor intends to implement the FDA's guidance on sex-specific data in medical device clinical investigations to ensure adequate representation of women and other traditionally under-represented demographic subgroups in this clinical investigation. As noted in the guidance, some barriers to participation of women and ethnic minorities in clinical investigations have traditionally been:

- Lack of understanding about main obstacles to participation of such subgroups in clinical research
- Inclusion/exclusion criteria potentially not needed to define the clinical investigation population may unintentionally exclude specific subgroups
- Under diagnosis of disease etiologies and pathophysiology leading to under referral of demographic subgroups
- Sex differences in disease etiology, which predispose one sex to LVAD therapy
- Avoidance of specific subgroups by investigators and Sponsors due to the perception that it takes more time and resources to recruit them
- Family responsibilities limiting women's ability to commit time for follow-up requirements

The Sponsor will take the following steps to ensure adequate representation of women and racial or ethnic minorities in this clinical investigation:

- All patients receiving an LVAD at enrolling sites will be considered for this study and this data will be reviewed regularly
- The Sponsor will provide training to investigational site personnel to ensure adequate representation of these demographic subgroups
- As appropriate and necessary, the Sponsor will retrain sites on the importance of recruiting and retaining subjects in the clinical investigation if trends in withdrawal or selection bias are noted
- The Sponsor will approach sites without bias or consideration for specific demographic subgroups
- The Sponsor will have informed consent materials in alternative languages and will work with sites and IRBs/ECs on recruitment materials

5.5 Subject Withdrawal

If a subject does not meet all inclusion criteria, or meets at least one exclusion criteria after the subject is enrolled (consented), but prior to randomization, the subject will be considered a screen failure and withdrawn and will not be included in the analysis populations.

Those enrolled (consented) subjects that meet all inclusion criteria and no exclusion criteria post implant will be randomized within 2-7 days post-implant (the day of implant is day 0). However, if these subjects do not meet the randomization eligibility criteria, are not randomized, never start the treatment arm regimen, experience a surgical event (≤ 14 days post implant) that requires investigator mandated anti-platelet therapy or experience an outcome ≤ 14 days post implant then they will be withdrawn.

Each randomized subject shall remain in the clinical investigation until completion of the required follow-up period; however, a subject's participation in any clinical investigation is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit. Conceivable reasons for discontinuation may include, but not be limited to, the following:

- Subject outcome including death, transplant, or device explant or exchange
- Physician or subject voluntary withdrawal
- Subject lost-to follow-up as described below.

The Sponsor must be notified of the reason(s) for subject discontinuation. The site will provide this information to the Sponsor. Investigators must also report this to their respective IRB/EC as defined by their institution's procedure(s).

No additional follow–up will be required or data recorded from subjects once withdrawn from the clinical investigation, except for the reason and status at the time of withdrawal (deceased/alive). Subjects withdrawn from the study will cease treatment arm medication and be transitioned to an anticoagulation regiment in accordance with site standard of care by the investigator.

In case of subject withdrawal of consent, the site should make attempts to schedule the subject for a final clinical investigation visit. At this final follow-up visit, the following will be recorded, with the subject's permission:

- Subject status (deceased/alive)
- Any adverse event details prior to withdrawal of consent

<u>Lost-to-Follow-up</u>

If all attempts at contacting the subject have been exhausted, then the subject is considered lost-to-follow-up Site personnel shall make all reasonable efforts to locate and communicate with the subject (and document these efforts in the source documents), including the following, at each contact time point:

- A minimum of two telephone calls on different days over the specified follow-up windows to contact the subject should be recorded in the source documentation, including date, time and initials of site personnel trying to make contact.
- If these attempts are unsuccessful, a letter (certified, if applicable) should be sent to the subject.

- If a subject misses one or more non-consecutive follow-up contact time points, it will be considered a missed visit. The subject may then return for subsequent visits.

Note: Telephone contact with General Practitioner, non-clinical investigation cardiologist or relative without the presence of the subject or indirect documentation obtained via discharge letters will not be considered as subject contact.

Sites should attempt to retrieve unused portions of the treatment arm medication in subjects lost-to-follow, which should be returned to ALMAC Clinical Services per section 2.4.5.

5.5.1 Incidental Use of Aspirin Containing Products

At baseline and at each scheduled visit, subjects should be provided with the Sponsor provided list of aspirin containing products. At each visit post-implant, subjects should be asked if they have taken or been prescribed (by non-study physicians) any of the medications containing aspirin or aspirin-like compounds and, if so for what duration. Responses will be captured in the EDC. If a subject reports or other evidence of incidental aspirin use is obtained (i.e. a prescription which the patient confirms from a non-investigator healthcare provider) lasting for a duration of > 7 days, the subject will be withdrawn from the study.

5.6 Transition to Open Label

During a subject's clinical course, post-randomization events may result in the investigator mandating antiplatelet therapy. The mandate may consist of the presence of an antiplatelet or the absence of all antiplatelets from the patient's antithrombotic regimen in response to clinical events. These subjects should remain in the study for the full 12-month study follow up whenever possible. Investigators may cease administration of the treatment arm medication for up to 72 hours without transitioning the subject to open label. In these instances, the treatment arm medication is no-longer administered, and investigator initiates their mandated therapy. If the cessation extends beyond 72 hours, these subjects are considered to have transitioned to open label and may not resume the treatment arm medication after transition.

Transition to open label does not constitute unblinding. Investigators will not know which randomized treatment arm patients who transition to open label were initially allocated. Study blinding will continue in patients transitioned to open label.

Clinical events which resulted in the transition to open label will be documented in the EDC. Subjects who transition to open label after 12 months will be considered to have completed the study required follow up at12 months post implant. Subjects who transition to open label after 12-months of study follow up will be considered to have completed study follow up at that time except if a subject has experienced a stroke or potential stroke neurologic adverse event prior to transitioning to open label, then they will be followed for an additional 60-days post event for MRS score evaluation. In this case, the subject is considered to have reached end of study follow up upon completion of the MRS evaluation.

5.7 Number of Subjects

This study will enroll enough subjects to randomize 628 subjects in the clinical investigation. No site may randomize more than 15% of the total number of randomized subjects without Sponsor authorization.

5.8 Total Expected Duration of the Clinical Investigation

The expected duration of each subject's participation is at least 12 months and up to 36 months post-implant. Scheduled visits and data collection for this clinical investigation will occur at Baseline, Implant, Randomization, Week 1 ± 3 days, Discharge, Month 1 ± 7 days, Month 3 ± 30, Month 6 ± 30 days, Month 9 ± 30 days, Month 12 ± 30 days and, in patients still on the treatment arm medication, follow up will continue every 6 months ± 60 days until the final ongoing patient completes their month 12 follow up visit. Subjects not on the treatment arm medication will be exited from the trial at the conclusion of their month 12 follow-up visit. The expected duration of enrollment is 24 months. Therefore, the total duration of the clinical investigation is expected to be 36 months.

6.0 TREATMENT AND EVALUATION OF ENDPOINTS

6.1 Avoidance of Additional Antiplatelet Medications

Subjects on the treatment arm medication will not be prescribed or administered additional antiplatelet medications.

6.2 Avoidance of Platelet Function Testing

Antiplatelet testing or platelet function testing should not be performed while patients are on the treatment arm medication, except for Aspirin Response Testing per Section 2.4.6. The results of protocol specified Aspirin Response Testing will not be provided the physician or patient through the follow up period. Performing additional antiplatelet testing or platelet function testing may result in un-blinding of the subject or the investigator. Un-blinding of a subject or investigator will be considered a protocol deviation. Sites should address any questions related to potential unblinding to the Sponsor.

6.3 Study Activities and Procedures

The assessments in table 2 will occur throughout the study.

Table 2 – Schedule of Assessments

Assessment	Baseline	Implant	Randomization	Discharge	Week 1 (± 3 days)	Month 1[1] (± 7 days)	Month 3[1] (± 30 days)	Month 6[1] (± 30 days)	Month 9[1] (± 30 Days)	Month 12[1] (± 30 days)	Every 6 months ± 60 days thereafter	As Occurs/ Unscheduled
Inclusion/ Exclusion	X		X									
Informed Consent	X											
Demographics	X											

Clinical Investigation Plan

Assessment	Baseline	Implant	Randomization	Discharge	Week 1 (± 3 days)	Month 1[1] (± 7 days)	Month 3[1] (± 30 days)	Month 6[1] (± 30 days)	Month 9[1] (± 30 Days)	Month 12[1] (± 30 days)	Every 6 months ± 60 days thereafter	As Occurs/ Unscheduled
General and Cardiac Medical History	X											
Coagulation Assessment	X[4]											
Right Heart Catheterization	X[2]											X[4]
Modified Rankin Score (MRS)	X											X
Incidental Use of Aspirin Containing Products	X			X	X	X	X	X	X	X	X	
Vital Signs	X			X	X	X	X	X	X	X		X
Laboratory Assessments	X[3]				X	X	X	X	X	X		X[4]
Anticoagulation/Antiplatelet Medications Log	X	X		X	X	X	X	X	X	X	X[9]	X
Echocardiogram	X[2]				X[4]	X[4]	X[4]	X[4]	X[4]	X[4]		X[5]
Other Medications	X					X	X	X	X	X		X
Sample for Core Lab (ASA response, US only)	X						X	X		X		
QOL and Functional Capacity	X						X	X		X		
Implant Data		X										X[6]
Enrollment	X[7]											
Randomization			X									
Pump Parameters		X			X	X	X	X	X	X		X[5]
Bottle Requisition via WebEZ			X				X	X	X	X	X[8]	X
Bottle Dispensing/Return Log			X				X	X	X	X	X[8]	X
Return Used Bottle to ALMAC for Accountability							X	X	X	X	X[8]	X
Initial Discharge Data				X								
Cardiac Arrhythmias Assessment (e.g. EGM, EKG)	X				X	X	X	X	X	X		X
Subject Status				X	X	X	X	X	X	X	X[8]	
INR & LDH Log	X			X	X	X	X	X	X	X		X
Death												X
Withdrawal (early termination)												X
Transition to Open Label												X
Hospitalizations												X
Adverse Events												X
Device Deficiencies												X
Operative Procedures (excluding primary implant)												X

[1] *For follow-up visit scheduling, one month = 30 days.*

[2] *Most recent results within 30 days prior to implant, if collected as SOC.*

[3] *Most recent results obtained within 30 days prior to implant will be permitted as baseline data.*

[4] *If performed as SOC.*

[5] *At time of suspected thrombotic adverse event or pump exchange, if performed as SOC.*

[6] *Pump exchange data collection includes all required implant data for HM3 to HM3 exchanges and all relevant data for HM3 to other LVAD exchanges.*

[7] *Subject is considered enrolled upon signing of the informed consent form.*

[8] *Subjects on the treatment arm medication will be followed every six months after the 12-month visit. Safety monitoring including adverse events, outcomes and device deficiencies and other associated "as occurs" procedures will be collected*

[9] *Only Treatment Arm Medication use will be logged after the completion of the 12 month visit.*

The clinical study will be conducted in accordance with the CIP. All parties participating in the implementation of the study will be qualified to perform their designated tasks by education, training, and experience. Applicable documentation will be maintained.

Clinical Investigation Plan

No study activities may begin until the site has received written Sponsor approval. Copies of written approval from the IRB and/or the relevant regulatory authorities, as well as all required regulatory documents must be received by the Sponsor before approval will be given.

6.4 Baseline

The baseline assessments in table 3 will be performed.

Table 3 – Baseline Data Collection

Study Activity	Data Collection
Informed Consent	Informed consent details
Inclusion/Exclusion	Subject's eligibility details
Demographics	Age, height, gender, ethnicity (except where prohibited by regulation), race (except where prohibited by regulation), blood type, INTERMACS profile, and NYHA class
General and Cardiac Medical History	Etiology of HF, duration of HF, therapeutic intent (BTT/BTC/DT), arrhythmias, prosthetic valve(s), history of stroke, diabetes, smoking, history of bleeding (diverticular disease, diagnosed arteriovenous malformations (AVMs), GI ulcer(s), anemia and/or erythropoietin treatment), aortic stenosis, hypertension, history of MI, peripheral thromboembolism, coronary stents, CABG, substance abuse (drug/alcohol), drug/radiation toxicity, peripheral vascular disease, carotid artery disease, cardiac rhythm management device, intra-aortic balloon pump, other pre-implant circulatory support, CardioMEMS, and HIV status
Modified Rankin Score	Modified Rankin Score (MRS)
Vital Signs	Weight, blood pressure, and heart rate
Anticoagulation/Antiplatelet Medications	Vitamin K antagonist (e.g. warfarin, fluindione, phenprocoumon, etc.), clopidogrel, dipyridamole, other anticoagulation agents, other vitamin K antagonists, direct thrombin inhibitors, etc. (including treatment arm medication) *All new medications started, or current medications stopped during the follow-up period must be recorded. All dose changes (including IV titrations as total daily dose) during the follow-up period must be recorded with the exclusion of vitamin K antagonist. Only the type, start and stop dates, and target INR will be collected for vitamin K antagonist.*
Other Medications	ACE inhibitors, inotropes, ARBs, beta blockers, antiarrhythmics, statins, nitrates, allopurinol, aldosterone blockers, antibiotics, diuretics, insulin and antidiabetic medications, and other cardiovascular medications

Study Activity	Data Collection
Laboratory Assessments[1]	Hemoglobin (Hgb), Hematocrit (Hct), White Blood Cell Count (WBC), Platelets (PLT), Creatinine (Cr), Estimated Glomerular Filtration Rate (eGFR), LDH and INR, liver function tests (AST, ALT, total bilirubin, albumin, pre-albumin), blood urea nitrogen (BUN) Collected only if SOC: Activated Partial Thromboplastin Time (aPTT), Partial Thromboplastin Time (PTT), Plasma free Hgb (PHgb), D-Dimers, P Selectin, and fibrinogen. For diabetic patients: HbA1c, brain natriuretic peptide (BNP) or N-terminal pro-BNP (NT-pro-BNP) and fasting glucose
Coagulation Assessment[2]	Collected only if prior testing performed or SOC: Tests may include but are not limited to HIT, protein C deficiency, protein S deficiency, antithrombin deficiency, plasminogen deficiency, lupus anticoagulant, factor V Leiden, prothrombin G20210A mutation, and primary antiphospholipid syndrome
Right Heart Catheterization[2]	Central venous pressure (CVP) or right atrial pressure (RAP), systolic, diastolic and mean pulmonary artery pressure (PAS, PAD, PAM), pulmonary capillary wedge pressure (PCWP), cardiac output (CO), and cardiac index (CI)
Echocardiogram[2]	Type of assessment, LVEF, LVEDD, LVESD, AI, MR, TR, PR, including severity and/or grade, and presence of LV or LA thrombus, and aortic valve opening ratio
QOL and Functional Capacity	EQ-5D-5L, 6-minute Walk Test (if subject is able, reason must be provided if not performed), NYHA Class, INTERMACS Profile

[1] Most recent results obtained within 30 days prior to implant will be permitted as baseline data.
[2] If collected per standard of care, most recent results within 30 days prior to implant.

6.5 Implant Procedure

The data in table 4 will be collected for each subject's HM3 implant procedure.

Table 4 – Implant Procedure Data Collection

Study Activity	Data Collection
HM3 System Information	VAD serial number, reference number and date of implant of entire implanted system
Implant Data	Presence of intracardiac (LA or LV) thrombus, concurrent procedures, Factor VII administration, vitamin K administration, anti-fibrinolytic administration, pump position, transfusions (whole blood, packed red blood cells [PRBC], fresh frozen plasma [FFP], platelets, cryoprecipitate, Cell Saver), cardiopulmonary bypass (CPB) time, and total implant time, procedure initiation/completion time, additional post-implant MCS
Pump Parameters	Pump Speed, Pump Flow, Pulsatility Index, and Pump Power

6.6 Randomization

Only subjects who have provided informed consent, been enrolled, been implanted with the HM3 and subsequently met all inclusion and no exclusion criteria (randomization eligibility) will be randomized in the study. Randomization will be performed through ALMAC Clinical's WebEZ system. Subjects will be randomized 1:1, by site, and in permuted blocks of 4. Prior to randomizing a patient in WebEZ, patients will have been initialized in the Sponsor's EDC portal upon enrollment and obtained a subject ID number, which will also be used as the patient identifier in the WebEZ system. Subjects should begin taking the treatment arm medication within 24 hours of randomization.

6.7 Initial Discharge Data

Upon discharge from the initial hospitalization for the implant procedure, the days hospitalized, including the days in the Intensive Care Unit, will be collected. Vital signs and subject status will be recorded along with anticoagulation/antiplatelet medications, LDH, and INR logs.

6.8 Scheduled Follow-up for All Subjects

The required assessments (detailed in tables 2 and 6), follow-up schedule, and associated visit windows (table 5) are generally aligned with SOC LVAD patient follow up and MCS registry data collection. All follow-up visits are based on the initial implant date. The windows for each follow-up visit are as follows:

Table 5 – Follow-up Visit Windows

Randomization	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7+
2-7 days	Week 1 ± 3 days	Month 1 ± 7 days	Month 3 ± 30 days	Month 6 ± 30 days	Month 9 ± 30 days	Month 12 ± 30 days	Every 6 Months ± 60 days

The follow-up visit must occur within the designated window. Follow-up assessments for a single visit do not have to occur on the same date, but must occur within the designated window, or will be considered a protocol deviation. The Sponsor understands that some lab results may be received several days after the visit has occurred, in these instances the date the lab occurred is considered as the date the blood draw occurred. All subjects should be asked, at each follow up visit after discharge, if they were seen at an outside facility. If so, medical records from any facility that has seen the patient must, with the subject's consent, be requested and reviewed for potential adverse events.

For subjects not on the treatment arm medication, the completion of the Month 12 visit will signify completion of the study, with the exception of some lab results that may be received after the visit has occurred, no other assessments or study related activities may be performed after the final visit has occurred, even if later assessments are performed within the acceptable window. Month 12 assessments (including required laboratory assessments blood draws) not collected by the date of the final visit will be considered protocol deviations.

Subjects on the treatment arm medication will continue to be followed every 6 months after their month 12 visit until the final ongoing patient completes their month 12 visit or experiences a study outcome. Upon close of enrollment, the sponsor will notify sites of the anticipated date of study conclusion which will be 12 months after the last patient enrolls. All required visit data must be collected by the final visit, as outlined above.

Clinical Investigation Plan

Table 6 – Scheduled Follow-Up Visit Data Collection through 12-months

Study Activity	Definition
Subject Status	Whether the subject is ongoing on HM3 LVAD support, if not, what was the outcome the patient experienced
Vital Signs	Weight, blood pressure and method of blood pressure measurement
Pump Parameters	Pump Speed, Pump Flow, Pulsatility Index, and Pump Power
Cardiac Arrhythmias	Atrial (fibrillation/flutter), ventricular (fibrillation/VT), and treatment
Anticoagulation / Antiplatelet Medications	All changes made during the follow-up period *All new medications started, or current medications stopped during the follow-up period must be recorded. All dose changes (including IV titrations) during the follow-up period must be recorded with the exclusion of* vitamin K antagonist. *Only the type, start and stop dates, and target INR will be collected for* vitamin K antagonist.
Other Medications	ACE inhibitors, inotropes, ARBs, beta blockers, antiarrhythmics, statins, nitrates, allopurinol, aldosterone blockers, antibiotics, diuretics, insulin and antidiabetic medications, and other cardiovascular medications
Treatment Arm Bottle Dispensing/Return Log	All bottles dispensed during the follow-up period (Month 3, 6 and 9 follow-up visits only), including replacement bottles that are dispensed outside of the follow-up schedule, bottle status (lost by patient, returned to ALMAC) and shipping information. All bottles and unused doses must be returned to ALMAC Clinical within 14 days of receipt from subject.
Laboratory Assessments	Hemoglobin (Hgb), Hematocrit (Hct), White Blood Cell Count (WBC), Platelets (PLT), Creatinine (Cr), Estimated Glomerular Filtration Rate (eGFR), liver function tests (AST, ALT, total bilirubin, albumin, pre-albumin), blood urea nitrogen (BUN) Log Data (all measurements during the follow up period will be collected with, at a minimum, 1 reading within each follow up window): LDH and INR. <u>Collected only if SOC:</u> Activated Partial Thromboplastin Time (aPTT), Partial Thromboplastin Time (PTT), Plasma free Hgb (PHgb), D-Dimers, P Selectin, and fibrinogen. For diabetic patients: HbA1c, brain natriuretic peptide (BNP) or N-terminal pro-BNP (NT-pro-BNP) and fasting glucose *<u>Note</u>: To protect blinding of the study, platelet function testing (including ASA resistance testing) will not be performed while patient is on the treatment arm medication, except as outlined in section 2.4.6.*
[1] Echocardiogram	LVEF, LVEDD, LVESD, AI, MR, TR, PR, including severity and/or grade, and presence of LV or LA thrombus, and aortic valve opening ratio
QOL and Functional Capacity	EQ-5D-5L, 6-minute Walk Test, NYHA Class, INTERMACS Profile

[1] If collected per SOC.

6.8.1 Continued follow up beyond 12-months post implant

Subjects on the treatment arm medication will be followed every six months after the 12-month follow up visit until the final ongoing subject reaches the 12 month visit or experiences a study outcome. Only treatment arm medication details, subject status (including death, withdrawal, or transplant) along with adverse events and device deficiencies will be collected along with additional supportive data should adverse events or device deficiencies occur. If a patient's clinical course after 12 months of follow up requires transition to open-label, the patient will be considered to have reached the end of study follow up unless the transition to open label is due to a stroke, in which case the patient should be followed for an additional 60-days to capture the MRS score. The clinical reason for transition to open-label will be captured. Subjects transitioned to open label prior to 12 months of follow up should be followed to their 12-month follow up.

6.9 Unscheduled Visits

6.9.1 Adverse Events

For additional details regarding adverse events, refer to section 7. Data related to adverse events will be collected as they occur. Depending on the type of adverse event, relevant data will be collected.

6.9.1.1 Neurologic Adverse Events

Modified Rankin Scores (MRS) scores will be captured at:

- Baseline,
- The time of any stroke or potential stroke events, and
- 60-days after any stroke or potential stroke events to adjudicate the severity of the event.

MRS will be determined by an independent assessor, defined as an independent, trained, and certified clinician. Event severity will be determined based on MRS, specifically MRS > 3 as disabling versus MRS ≤ 3 as nondisabling. Strokes will be characterized as ischemic or hemorrhagic in etiology with ischemic-hemorrhagic conversion considered an ischemic stroke.

6.9.2 Operative Procedures

Data related to any cardiac or non-cardiac operative procedures, excluding the primary HM3 LVAD implant, occurring after enrollment will be collected. Operative procedures must be reported to the Sponsor through the EDC system within three days of awareness of the event or, at the latest, if the operation is unknown to the implanting site (i.e. occurring at another facility), during the next follow-up visit. For pump exchanges, additional implant data will be collected, including exchange status and pump exchange type.

6.9.3 Hospitalizations

All hospitalizations, excluding the primary implant hospitalization, with associated reasons will be captured during the follow-up period for all subjects. While hospitalized, the follow-up visit assessments will continue to be performed according to the follow-up schedule. Hospitalizations must be reported to the Sponsor through the EDC system within three days of awareness or discovery of the event or, at the latest, if the hospitalization is unknown to the implanting site (i.e. occurring at another facility), during the next follow-up visit.

6.9.4 Outcomes

Subjects will be followed for at least 12 months and until the final ongoing subject reaches their 12 month visit or an outcome is reached, whichever occurs first. Outcomes include death, heart transplantation, device explant, and withdrawal from the study. Outcomes must be reported to the Sponsor through the EDC system immediately upon discovery of the event. Subjects should continue follow up through 12-months whenever possible, even in the instance the subject has transitioned to open-label (e.g. due to pump thrombosis the investigator believes the patient should remain on open-label aspirin therapy).

If a subject receives a pump exchange during the follow-up period, this event will be considered a device explant outcome and data will be collected on the pump exchange procedure but not after. If a subject has a device explanted for suspected or confirmed pump thrombosis, the pump will be returned to the Sponsor for analysis. Standard commercial processes will be used for pump return.

6.10 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 all adverse events have been adjudicated. Questions related to unblinding should be directed to the Sponsor.

6.11 Patient Reported Outcome (PRO) Measure

The Coordinator or designee will administer patient-reported outcome questionnaires. It is important the subject understands the meaning of all words and instructions in the questionnaires. The subject should be instructed to ask any questions about the questionnaires if further explanation is needed. Once the questionnaires are completed, the Coordinator or designee will review for completeness to verify that all questions have been answered according to the directions provided.

The following PRO measures will be collected according to the requirements of the questionnaire and this CIP.

- EQ-5D-5L - EuroQOL

The EQ-5D-5L is a standardized measure of health status developed by the EuroQOL Group in order to provide a simple, generic measure of health for clinical and economic appraisal. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of healthcare as well as in population health surveys. The questionnaire will take approximately two minutes to complete.

The EQ-5D-5L consists of two components – the EQ-5D-5L descriptive system and the EQ Visual Analogue scale (VAS). For the descriptive system, five dimensions are measured (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension has five levels: 1=none, 2=slight, 3=moderate, 4=severe, and 5=extreme. The respondent indicates his or her health state by ticking in the box against the most appropriate statement in each of the five dimensions. The VAS is scored from 0 (worst health) to 100 (best health).

7.0 ADVERSE EVENTS

To comply with worldwide standards and guidelines on clinical investigation adverse event reporting, the Sponsor has adopted uniform and worldwide applicable standard definitions and reporting timelines to be used and adhered to by the investigators.

7.1 Definition

7.1.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects.

7.1.2 Serious Adverse Event

If the AE meets any of the criteria below, it is regarded as a serious adverse event (SAE).

a) Led to a death,

b) Led to a serious deterioration in health of the subject, that either resulted in

   1. a life-threatening illness or injury, or
   2. a permanent impairment of a body structure or a body function, or
   3. in-patient hospitalization or prolongation of existing hospitalization, or
   4. medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
   5. chronic disease

c) Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note: A planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a serious deterioration in health, is not considered to be an SAE.

7.1.3 Device Deficiency

Device deficiency is defined as an inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling. This includes the failure of the device to meet its performance specifications or otherwise perform as intended. Note: Performance specifications include all claims made in the labeling of the device.

7.2 Device Relationship

Determination of whether there is a reasonable possibility that the HM3 LVAS caused or contributed to an AE is to be determined by the Investigator and recorded on the appropriate CRF form. Determination should be based on assessment of temporal relationships, evidence of alternative etiology, medical/biologic plausibility, and patient condition (pre-existing condition).

7.2.1 Unanticipated Serious Adverse Device Effect (USADE)

Unanticipated Serious adverse device effect (USADE) refers to any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

7.3 Adverse Event and Device Deficiency/Device Malfunction Reporting

7.3.1 Adverse Event Reporting

Safety surveillance and reporting starts as soon as the patient is enrolled in the clinical investigation. Adverse events occurring prior to randomization which disqualify a patient for randomization, but occur after consent, will be captured in the EDC and, if necessary, should be reported to the sponsor through standard commercial practices. Safety surveillance and reporting will continue until the last follow-up visit has been performed, the subject is deceased, the subject concludes participation in the clinical investigation or the subject withdraws from the clinical investigation. All adverse event, deaths, and device deficiency data will be collected throughout the time period defined above and will be reported to the Sponsor on a CRF. Additional information about an adverse event should be updated within the appropriate CRF. An offline form will be made available to allow the investigator to report SAEs in the event the entry cannot be made in the EDC. This offline form can be submitted by email to AdverseEvent@abbott.com. This does not replace the EDC reporting system. All information must still be entered in the EDC system as soon as feasible.

Unchanged, chronic, non-worsening or pre-existing conditions are not AEs and should not be reported.

Abnormal laboratory values will not be considered AEs unless:

- the investigator determined that the value is clinically significant,
- the abnormal lab value required intervention, or
- the abnormal lab value required subject withdrawal from the clinical investigation, or
- the abnormal lab value meets the definition of an adverse event.

All adverse events will be collected on each subject throughout the follow up period – until the subject reaches an outcome or withdraws or until the study ends. Causes of death will be captured for all subjects who expire during follow up.

<u>SAE Reporting</u>

The investigator should report all SAEs to the Sponsor as soon as possible but no later than outlined below.

Clinical Site	Reporting timelines
All Sites	SAEs must be reported to the Sponsor no later than 3 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

The date the site staff became aware the event met the criteria of an SAE must be recorded in the source document. The Investigator will further report the SAE to the local IRB/EC according to the institution's IRB/EC reporting requirements.

7.3.2 Unanticipated Serious Adverse Device Effect Reporting to Sponsor and IRB/EC

The Sponsor requires the Investigator to report any USADE to the Sponsor within 3 calendar days of the investigator's knowledge of the event, unless local requirements are more stringent, and to the IRB/EC per IRB/EC requirements.

7.3.3 Device Deficiency Reporting

All device deficiencies/malfunctions should be reported on the appropriate CRF form.

The investigator should report all device deficiencies/malfunctions to the Sponsor as soon as possible but no later than outlined below.

Clinical Sites	Reporting timelines
All Sites	Device deficiencies/malfunctions must be reported to the Sponsor no later than 3 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

Device deficiencies/malfunctions should be reported to the IRB/EC per the investigative site's local requirements.

An offline form will be made available to allow the investigator to report device deficiencies/malfunctions in the event that the entry cannot be made in the EDC system. This offline form can be submitted by email to AdverseEvent@abbott.com. This does not replace the EDC reporting system. All information must still be entered in the EDC system as soon as feasible.

7.3.4 Adverse Event Reporting to Country Regulatory Authorities by the Sponsor

The Sponsor will report SAEs and reportable device deficiencies/malfunctions to the country regulatory authority, per local requirements.

Note: Reportable device deficiencies/malfunctions include device deficiencies/malfunctions that might have led to an SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

Clinical investigation SAEs and device deficiencies/malfunctions reportable per MedDEV 2.7/3 regulations will be submitted to European Competent Authorities by the Sponsor's Clinical Safety Group. The Sponsor's Clinical Safety Group's contact details can be found in Appendix III.

8.0 STATISTICAL CONSIDERATIONS

The following section describes the statistical methods for the clinical investigation. Additional details on statistical analyses, including justification of clinical investigation design, sensitivity analyses, poolability analyses, subgroup analyses and analysis of descriptive endpoints, will be maintained in a separate Statistical Analysis Plan (SAP).

8.1 Analysis Populations

8.1.1 Modified Intention to Treat Population (mITT)

The Modified Intention to Treat Population (mITT) will include all randomized subjects with the following exception:

1. Subjects who experience a surgical adverse event, defined as ≤14 days post-implant, requiring investigator mandated antiplatelet therapy
2. Subjects who expire, are transplanted, or withdrawn within 14 days of implant

Non-surgically related major hemocompatibility related adverse events will only be analyzed up to the transition to open label. Subjects will be analyzed according to the treatment arm assigned at randomization. The mITT population will be used for all analyses unless noted differently in one sensitivity analysis.

8.1.2 Intent-To-Treat (ITT) Population

The ITT population will consist of all subjects randomized. Subjects will be analyzed according to the treatment arm assigned at randomization. The ITT population will only be used for one sensitivity analysis of the primary endpoint.

8.2 Statistical Analyses

8.2.1 Primary Endpoint Hypothesis

The primary endpoint hypothesis is formally expressed as:

$$H_0: \pi_{placebo} \leq \pi_{aspirin} - \Delta$$
$$H_a: \pi_{placebo} > \pi_{aspirin} - \Delta$$

where $\pi_{placebo}$ and $\pi_{aspirin}$ are the percentage of subjects who successfully achieve the composite endpoint in the placebo and aspirin groups and where Δ is the non-inferiority margin fixed at 10%. Justification of the non-inferiority margin is included in the SAP.

8.2.2 Primary Endpoint Analyses Methodology

The primary endpoint composite success rate will be calculated for each treatment arm based on the number of subjects who successfully meet the primary endpoint divided by the total number of subjects in the mITT population. The placebo arm will be considered non-inferior to the aspirin arm if the lower boundary of the one-sided 97.5% confidence limit of the risk difference in the composite success between treatment arms (Placebo-arm minus Aspirin-arm) is greater than the non-inferiority margin (-10%).

8.2.3 Secondary Endpoint Analyses

The secondary endpoints will be analyzed using the mITT Populations. Details of the secondary endpoint analyses are provided in the SAP. The secondary endpoints are:

- Non-surgical Major Hemorrhagic Events
- Non-surgical Major Thrombotic Events
- Survival
- Stroke Rates,
- Pump Thrombosis Rates
- Bleeding Rates, including:
  - Non-surgical Bleeding
  - Moderate Bleeding
  - Severe Bleeding
  - Fatal Bleeding
  - GI Bleeding

8.2.4 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[4]. The HCS will be calculated for each subject in 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, for any cause, after randomization and initiation of the study treatment, divided by the number of subjects in the mITT. The number of rehospitalizations per treatment arm will also be presented as rehospitalizations per patient year of support. Details of the analysis are presented in the SAP.

Economic Cost: Health resource utilization will be assessed by comparing days hospitalized (categorized by intensive care vs general ward) between groups in the mITT Population with cost implications compared based on cost of hospitalization, per day hospitalized.

8.3 Sample Size Calculation and Assumptions

Results from the MOMENTUM 3 trial were used to derive a point estimate of 71% survival to 1 year free of any major hemocompatibility related adverse events in the aspirin treated arm. It is assumed that in the absence of aspirin a 2% improvement in the composite endpoint will be noted, mainly due to the reduction of bleeding complications without a change in thromboembolic complications. Based on these assumptions 220 patients will need to be randomized in each arm (440 total) to achieve 80% power to

prove that the placebo group is non-inferior to the aspirin group using a non-inferiority margin of 10% with the Farrington-Manning risk difference approach to non-inferiority at a one-sided alpha = 0.025. To account for an expected 30% dropout rate associated with events occurring 2-14 days post implant, up to 628 patients will be randomized in the trial. Sample size calculations were performed using PASS 15 software.

8.4 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.

8.5 Subgroup Analysis

A subgroup analysis will be performed to examine the consistency of results for the primary endpoint across specific populations. Analysis will be performed using Fisher's exact test. No subgroup specific labeling claims are intended for the primary endpoint and no adjustment will be made for multiplicity. Subgroups to be examined include, but are not limited to, gender, age (stratified by median age), age (less than 65 vs 65 and greater), race, INTERMACS profile (INTERMACS 1-2 vs INTERMACS 3+), TTR and surgical implant method. If home monitoring of anticoagulation is used in some sites but not others, a subgroup analysis based on home monitoring will be conducted.

8.6 Multiplicity

This study includes a single primary endpoint and no Type 1 error adjustment is required.

8.7 Pooling Strategy

An analysis will be performed to assess if data can be pooled among study sites and geographic regions. A detailed description of the pooling analysis is included in the SAP.

8.8 Procedures for Accounting for Missing Data

Primary endpoint data is unambiguous. Missing primary endpoint data is not expected due to monitoring activities. No imputation is planned for primary endpoint data.

8.9 Planned Interim Analysis

No interim analyses to stop the trial early for futility or success are planned for this study.

8.10 Statistical Criteria for Termination

There are no statistical criteria for termination of this clinical investigation.

8.11 Success Criteria

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).

8.12 Deviations from Statistical Plan

Any major changes to the statistical plan will be documented in an amendment to the statistical plan. Less significant changes to the planned analyses will be documented in the final report.

9.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/institution will permit direct access to source data/documents for the purpose of performing clinical investigation-related monitoring, audits, IRB/EC review and regulatory inspections.

Subjects providing informed consent are agreeing to allow clinical investigation monitors or regulatory authorities including foreign countries to review, in confidence, any records identifying the subjects in this clinical investigation. This information may be shared with regulatory agencies; however the Sponsor undertakes not to release the subject's personal and private information otherwise.

10.0 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Selection of Clinical Sites and Investigators

The Sponsor will select investigators qualified by training and experience to participate in the clinical investigation. Sites will be selected based upon review of a recent site assessment, if applicable, and the qualifications of the investigators who will participate in the clinical investigation.

10.2 Clinical Investigation Finances and Agreements

The clinical investigation will be financed by Abbott. Investigational sites will be compensated by Abbott for participation in the clinical investigation per the conditions of agreement between the Sponsor and the Investigational site.

10.3 CIP Amendments

Approved CIP amendments will be provided to the Investigators by the Sponsor prior to implementing the amendment. The Principal Investigator is responsible for notifying the IRB/EC or equivalent committee of the CIP amendment (administrative changes) or obtaining IRB's/EC's approval of the CIP amendment (changes in subject care or safety), according to the instructions provided by the Sponsor with the CIP amendment.

Acknowledgement/approval by the IRB/EC of the CIP amendment must be documented in writing prior to implementation of the CIP amendment. Copies of this documentation must also be provided to the Sponsor.

10.4 Training

10.4.1 Site Training

All Investigators and clinical investigation personnel are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, a site initiation visit, or other appropriate training sessions. Over-the-phone or self-training may take place as required. Training of Investigators and clinical investigation personnel will include, but is not limited to, the CIP requirements, electronic case report form completion, WebEZ functionality, and clinical investigation personnel responsibilities. All Investigators and clinical investigation personnel that are trained must sign a training log (or an equivalent) upon completion of the training. Prior to signing the training log, Investigators and clinical investigation personnel must not perform any CIP-related activities that are not considered standard of care at the site.

10.5 Monitoring

Sponsor and/or designee will monitor the clinical investigation over its duration according to the CIP-specific monitoring plan which will include the planned extent of source data verification.

Prior to initiating any procedure, the Sponsor monitor (or delegate) will ensure that the following criteria are met:

- The investigator understands and accepts the obligation to conduct the clinical investigation according to the CIP and applicable regulations and has signed the Investigator Agreement or the Clinical Trial Agreement, as applicable.
- The Investigator and his/her staff should have sufficient time and facilities to conduct the clinical investigation and should have access to an adequate number of appropriate subjects to conduct the clinical investigation.
- Source documentation (including original medical records) must be available to substantiate proper informed consent procedures, adherence to CIP procedures, adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, and device information.
- The Investigator/site will permit access to such records. A monitoring visit sign-in log will be maintained at the site. The Investigator will agree to dedicate an adequate amount of time to the monitoring process. The Investigator and/or research coordinator will be available for monitoring visits. It is expected that the Investigator will provide the monitor with a suitable working environment for review of clinical investigation-related documents.

10.6 Deviations from the CIP

The Investigator should not deviate from the CIP for any reason except in cases of medical emergencies when the deviation is necessary to protect the rights, safety and well-being of the subject or eliminate an apparent immediate hazard to the subject. In that event, the Investigator will notify Sponsor immediately by phone or in writing and will also file required protocol deviation documentation.

No waivers for CIP deviations will be granted by the Sponsor. All deviations must be reported to the Sponsor using the Deviation CRF. The occurrence of protocol deviations will be monitored by the Sponsor for evaluation of investigator compliance to the CIP and regulatory requirements and dealt with according to written procedures. Investigators will inform their IRB/EC or equivalent committee of all CIP deviations in accordance with their specific IRB/EC or equivalent committee reporting policies and procedures.

In the event of repeated non-compliance, as determined by the Sponsor, a Sponsor's monitor or company representative will attempt to secure compliance by one or more of the following (and not limited to):

- Visiting the investigator and/or delegate
- Telephoning the investigator and/or delegate
- Corresponding with the investigator and/or delegate

Repeated non-compliance with the signed agreement, the CIP or any other conditions of the clinical investigation may result in further escalation in accordance with the Sponsor's written procedures, including securing compliance or, at its sole discretion, Sponsor may terminate the investigator's participation in the clinical investigation.

Deviations from the protocol include, but are not limited to:

- 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.

10.7 Quality Assurance Audit

A Sponsor representative or designee may request access to all clinical investigation records, including source documentation, for inspection during a Quality Assurance audit.

1. The Sponsor shall prepare an audit plan as well as the operating procedures for the related duties, and conduct audits in accordance with the audit plan and the operating procedures.
2. Individual engaged in auditing (hereinafter referred to as "auditor") shall be different than those in charge of medical device development or monitoring.
3. The auditor shall prepare an audit report documenting the matters confirmed in the audit to certify and verify that the audit has been conducted, and submit them to the Sponsor.

In the event that an investigator is contacted by a Regulatory Agency in relation to this clinical investigation, the Investigator will notify Sponsor immediately. The Investigator and Research Coordinator must be available to respond to reasonable requests and audit queries made during the audit process. The Investigator must provide Sponsor with copies of all correspondence that may affect the review of the current clinical investigation (e.g., Form FDA 483, Inspectional Observations, Warning Letters, Inspection Reports, etc.). Sponsor may provide any needed assistance in responding to regulatory audits.

10.8 Committees

10.8.1 Steering Committee

The Steering Committee is assigned by the Sponsor and consists of investigators. The Steering Committee will remain blinded to the treatment group assignments throughout the study. The Sponsor will also be represented on the committee. The Steering Committee is responsible for overseeing the scientific and operational aspects of the clinical investigation. This committee will meet regularly to monitor subject enrollment, general data collection and non-compliance with the CIP at individual centers, to review and act upon recommendations of the Data Safety Monitoring Board (DSMB), to review operational issues that may arise and warrant a CIP amendment or other corrective action and to determine policy regarding any publications arising from data generated from the performance of the clinical investigation. The Steering Committee or designee will determine policy and strategies regarding individual presentations and/or publications arising from clinical investigation generated data. The committee will also review all external requests for accessing clinical investigation-related data and strategies aligning with the Sponsor's presentation and publication team expectations. The Sponsor will align with the committee to ensure the Sponsor's applicable policies and Standard Operating Procedures are followed.

10.8.2 Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board (DSMB) is an independent multidisciplinary group restricted to individuals free of apparent significant conflicts of interest. The source of these conflicts may be financial, scientific, or regulatory in nature. The DSMB is typically composed of at least two physicians with experience relevant to the clinical investigation and a biostatistician. The DSMB will meet within 3 months of study initiation for protocol/study training and to discuss oversight rules including first data review point, recurring data review points, and formal rules for recommending study cessation. Formal rules for recommending study cessation will be determined by the DSMB prior to review of safety data. The DSMB will have access to unblinded datasets, so they may properly assess any safety signal that may arise during the conduct of the study.

The DSMB will serve in an advisory role to the Sponsor to ensure safety by reviewing cumulative data from the clinical investigation at prescribed intervals for the purpose of safeguarding the interests of enrolled subjects and those patients yet to be enrolled, as well as the continuing validity and scientific merit of the clinical investigation. The composition, frequency of the meetings and the statistical monitoring guidelines will be described in detail in the DSMB charter.

The DSMB may consider a recommendation for modifications or termination of the clinical investigation based on any perceived safety concerns regardless of statistical significance. The recommendations of the DSMB are not binding, and all final decisions related to clinical investigations modifications rest with the Sponsor in consultation with the study Steering Committee.

10.8.3 Clinical Events Committee (CEC)

The Clinical Events Committee (CEC) is an independent adjudication body comprised of qualified physicians who are not participants in the clinical investigation. The CEC will remain blinded to the subjects' treatment arm assignments. The CEC will review and adjudicate pre-specified events reported by investigators or identified by Safety personnel for the clinical investigation as defined in the CEC charter and according to definitions provided in this CIP. The CEC will adjudicate all deaths, neurologic

dysfunction, pump thrombosis events, bleeding events, and arterial peripheral thromboembolism events including events that could be adjudicated to one of these categories.

11.0 DATA HANDLING AND RECORD KEEPING

Sponsor and/or its affiliates will maintain documentation of the systems and procedures used in data collection for the duration of the clinical investigation.

CRF data collection will be performed through a secure web portal and only authorized personnel will access the Electronic Data Capture (EDC) system using a unique username and password to enter, review or correct data. Passwords and electronic signatures will be strictly confidential.

The data will be subjected to consistency and validation checks within the EDC system and supplemental review by the Sponsor.

At the conclusion of the clinical investigation, completed CRF images with the date-and-time stamped electronic audit trail indicating the user, the data entered, and any reason for change (if applicable) will be provided to the investigational sites, if requested.

For the duration of the clinical investigation, the Investigator will maintain complete and accurate documentation including, but not limited to, medical records, clinical investigation progress records, laboratory reports, CRFs, signed ICFs, correspondence with the IRB/EC and clinical investigation monitor/Sponsor, adverse event reports, and information regarding subject discontinuation or completion of the clinical investigation.

11.1 Protection of Personally Identifiable Information

The Sponsor respects and protects personally identifiable information collected or maintained for this clinical investigation.

The Sponsor implements technical and physical access controls to ensure that Personal Information is accessible only to and processed only on a ‘need to know’ basis, including periodic review of access rights, and revocation of access when an individual’s employment is terminated or the individual transitions to a role that does not require access to Personal Information, and appropriate restrictions on physical access to premises, facilities, equipment, and records containing Personal Information.

The Sponsor requires the investigational sites to transfer into Sponsor’s data management systems only pseudonymous Personal Information (key-coded) necessary to conduct the Clinical Investigation, such as the patient’s medical condition, treatment, dates of treatment, etc. The Sponsor discloses as part of the clinical investigation informed consent process that some Sponsor representatives still may see Personal Information at the participating sites for technical support of the participating physicians on the device implant or procedures, monitoring and quality control purposes. Confidentiality of Personal Information will be observed by all parties involved at all times throughout the clinical investigation. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data.

The Sponsor data management systems and processes were designed, developed, and tested according to industry standards to appropriately safeguard Confidential Information (including any Personal Information) against unauthorized access and/or interference by third parties, intrusion, theft, destruction, loss or alteration. Clinical Investigation data are encrypted in transit and at rest.

The Sponsor maintains a Privacy Incident procedure that complies in all respects with Applicable Law and industry best practices.

11.2 Data Management Plan

A Data Management Plan (DMP) will describe procedures used for data review, data cleaning, and issuing and resolving data discrepancies. If appropriate, the DMP may be updated throughout the duration of the clinical investigation. All revisions will be tracked and document-controlled.

11.3 Source Documentation

Regulations and GCP require the Investigator to maintain information in the subject's original medical records that corroborates data collected on the CRFs. In order to comply with these regulatory requirements/GCP, the following information should be included in the subject record at a minimum and if applicable to the clinical investigation:

- Medical history/physical condition of the subject before involvement in the clinical investigation sufficient to verify CIP entry criteria
- Dated and signed notes on the day of entry into the clinical investigation referencing the Sponsor, CIP number, subject ID number and a statement that informed consent was obtained
- Dated and signed notes from each subject visit (for specific results of procedures and exams)
- Adverse events reported and their resolution, including supporting documents, such as discharge summaries, catheterization laboratory reports, ECGs, and lab results including documentation of site awareness of SAEs and of investigator assessment of device relationship for SAEs.
- CIP-required laboratory reports and other tests, reviewed and annotated for clinical significance of out of range results (if applicable).
- Notes regarding CIP-required and prescription medications taken during the clinical investigation (including start and stop dates)
- Subject's condition upon completion of or withdrawal from the clinical investigation
- Any other data required to substantiate data entered into the CRF
- Patient reported outcome measures may be completed using CRF worksheets. These serve as the source documentation.

11.4 Case Report Form Completion

Primary data collection based on source-documented hospital and/or clinic chart reviews will be performed clearly and accurately by site personnel trained on the CIP and CRF completion. The investigator will ensure accuracy, completeness, legibility and timeliness of the data reported to the Sponsor on the CRFs and in all required reports.

Data on CRFs will be collected for all subjects that are enrolled into the clinical investigation.

Only authorized site personnel will be permitted to enter the CRF data through the EDC system deployed by the Sponsor. An electronic audit trail will be used to track any subsequent changes of the entered data.

11.5 Record Retention

The Sponsor and Investigator/Site will archive and retain all documents pertaining to the clinical investigation as per the applicable regulatory record retention requirements. The Investigator must obtain permission from Sponsor in writing before destroying or transferring control of any clinical investigation records.

12.0 ETHICAL CONSIDERATION

12.1 Institutional Review Board/Medical Ethics Committee Review and Approval

Institutional Review Board (IRB)/ Ethics Committee (EC) approval for the CIP and ICF/other written information provided to the patient will be obtained by the Principal Investigator at each investigational site prior to consenting and enrolling patients in this clinical investigation. The approval letter must be received prior to the start of this clinical investigation and a copy must be provided to the Sponsor.

Any amendments to the CIP as well as associated ICF changes will be submitted to the IRB/EC and written approval obtained prior to implementation, according to each institution's IRB/EC requirements.

No changes will be made to the CIP or ICF or other written information provided to the patient without appropriate approvals, including IRB/EC, the Sponsor, and the regulatory agencies (if applicable).

Until the clinical investigation is completed, the Investigator will advise his/her IRB/EC of the progress of this clinical investigation, per IRB/EC requirements. Written approval must be obtained from the IRB/EC yearly to continue the clinical investigation, or according to each institution's IRB/EC requirements.

No investigative procedures other than those defined in this CIP will be undertaken on the enrolled subjects without the written agreement of the IRB/EC and the Sponsor.

13.0 CLINICAL INVESTIGATION CONCLUSION

The clinical investigation will be concluded when:

- All sites are closed AND
- The final report has been provided to investigators (within one year of the end of the investigation) or the Sponsor has provided formal documentation of clinical investigation closure.

Upon conclusion of the study (when the last subject completes their 12 month follow up), investigators will return patients to their standard of care aspirin use. Study blinding will be maintained, even after

patients transition to their standard of care aspirin use, at the conclusion of the investigation. Refer to section 6.10 for additional details on study blinding.

14.0 REPORTS AND PUBLICATIONS

14.1 Sponsor Reports

The Sponsor will submit study progress reports to all principle investigators for submission to reviewing IRBs/ECs at least yearly. The sponsor will submit a final report to appropriate regulatory bodies and to all principle investigators for submission to all reviewing IRBs/ECs and participating investigators within one year after completion or termination. The Sponsor will comply with all other reporting requirements.

14.2 Publication Policy

The data and results from the clinical investigation are the sole property of the Sponsor. The Sponsor shall have the right to access and use all data and results generated during the clinical investigation. The Investigators will not use clinical investigation-related data without the written consent of the Sponsor for any purpose other than for clinical investigation completion or for generation of publication materials, as referenced in the Clinical Trial Agreement. Single-center results are not allowed to be published or presented before the multi-center results. Any proposals for publications or presentations by the investigators must be reviewed and approved by the Sponsor in a timely manner to enable Sponsor review in compliance with the Sponsor's publication policy set forth in the Clinical Trial Agreement.

14.3 Trial Registration

The Sponsor will register the clinical trial on www.clinicaltrials.gov, in accordance with the International Committee of Medical Journal Editors guidelines, or any other applicable guidelines. The Sponsor shall be responsible for any such registration and results posting as required by ClinicalTrials.gov. Investigational sites shall not take any action to register the trial. A full report of the pre-specified outcomes, including any negative outcomes, will be made public through the ClinicalTrials.gov website according to the requirements of Section 801 of the FDA Amendments Act. If this clinical investigation is terminated early, the Sponsor will make every effort to hasten the release of the pre-specified outcomes through ClinicalTrials.gov website.

15.0 RISK ANALYSIS

15.1 Anticipated Clinical Benefits

Withdrawal of aspirin from the antithrombotic regimen of HM3 pump patients will not adversely affect safety and efficacy and may reduce non-surgical bleeding.

15.2 Foreseeable Adverse Events and Anticipated Adverse Device Effects

Risks associated with the specified device and aspirin treatment arm are available in the local IFU and expected to be similar to those reported in the Short-Term (6 months post-implant)[6] and Full Cohort (24

months post-implant)[9] cohort of the MOMENTUM 3 Clinical Trial, which are described in Table 7. There may be risks related to the device that are unknown at present. Likewise, the exact frequency of the risk associated with the placebo treatment arm are not known, but are hypothesized to be similar to the aspirin arm.

Table 7 – Expected Incidence Rate of Adverse Events

Adverse Event	Short-Term (6-month) MOMENTUM 3 Results[6] n=151:	Full Cohort (24-month) MOMENTUM 3 Results[9] n=515
Death	11%	19%
Bleeding	33%	44%
Cardiac Arrhythmia	31%	36%
Hepatic Dysfunction	5%	5%
Driveline Infection	12%	23%
Blood Infection	9%	15%
Localized Infection (not associated with LVAS)	31%	41%
Stroke	8%	10%
Other Neurological Dysfunction	6%	12%
Renal Dysfunction	11%	14%
Respiratory Failure	22%	22%
Moderate or Severe Right Heart Failure	30%	34%
Suspected Device Thrombosis	0%	1.4%

15.3 Residual Risks Associated with the Clinical Investigation, as Identified in the Risk Analysis Report

No additional Residual Risks associated exclusively with the withdrawal of aspirin from the antithrombotic regimen have been identified at this time. Refer to the local IFU for warning and caution statements associated with the HM3.

15.4 Risks Associated with Participation in this Clinical Investigation

There are no known additional risks for the clinical population and hypothesis under investigation.

15.5 Possible Interactions with Protocol-Required Concomitant Medications

Anti-platelet medications, which in this study are replaced by the treatment arm medication which may be active aspirin or a placebo, are typically required as standard of care for LVAD patients along with vitamin K antagonists and as such no new possible interactions are expected. No new medications are introduced in this study. For further detail, refer to the prescribing information for the anticoagulants in use – specifically vitamin K antagonists (e.g. warfarin, fluindione, phenprocoumon, etc.) or aspirin.

15.6 Steps Taken to Control or Mitigate Risks

Mitigations and treatment for all adverse events should be per the current practice standards/standards of care as determined by the investigator, except for the antithrombotic therapy for mitigation of thrombotic risk in enrolled patients, which is the subject of this study.

Subject risk from study participation will be mitigated by ensuring that only experienced LVAD personnel will be involved in the care of research subjects. In addition to providing local product specific IFU, study staff will have undergone product, implant and study training prior to initiating study activities, and all subjects will be closely monitored throughout the study duration at pre-specified time points to assess their clinical status.

Specific information applicable to this study are listed below.

- Inclusion/Exclusion criteria avoid patients who are at an inordinately elevated risk for complications including, but not limited to, women who are or may become pregnant, patients with a known allergy to aspirin, and patients who require aspirin therapy or lack of aspirin therapy post-implant in the opinion of the investigator.
- It is suggested that patients possess a minimum 5th grade educational level and shall be versed in basic computer literacy (i.e., Microsoft Windows® and Office software).
- All users, including clinicians, patients, and caregivers, must be trained on system operation and safety before use.
- All implanting surgeons must be trained on HeartMate 3 surgical implant technique.
- Clinical procedures (including LVAS settings) should be conducted under the direction of the prescribing physician (Authorized Personnel) only.
- A data safety monitoring board (DSMB) will be monitoring adverse event data at regular intervals independently specified to assure safety is maintained throughout the study. In the event of an unacceptable safety profile, the DSMB will make a recommendation to pause or stop study enrollment while the DSMB, Sponsor, and steering committee determine if additional actions are necessary. Formal rules for making a recommendation to stop the study will be independently determined by the DSMB prior to data review. Rules will be contained within the DSMB Charter.

15.7 Risk to Benefit Rationale

The HM3 is a safe and effective treatment for advanced, refractory heart failure, and the medical benefits outweigh the risks of harm to the patient. MCS therapy is proven to be an effective treatment for advanced, refractory heart failure. The HM3 is an advancement in MCS technology and complies with all relevant international standards.

There have been no additional risks identified with the HM3 beyond what has been established with other VAD devices in clinical trials that have not been effectively mitigated within this trial; the risks are comparable or superior to the HMII.

All identified risks were managed through the risk management process and reduced as much as possible. The overall residual risks have been deemed acceptable, per the risk management process, and in consideration of the benefits provided by the therapy. The risk benefit analysis “basis for acceptance” for each of the residual risks are documented in the HeartMate 3 Risk Management Report.

Removal of antiplatelet agents from the antithrombotic therapy of HM3 patients may reduce bleeding This study hypothesizes that there will be no additional thrombotic risk based on the growing body of

scientific evidence that shows the HM3 has a low thromboembolic profile[5,9,11]. However, bleeding events, while decreased in comparison to a predicate device, remain burdensome[9]. All major prospective clinical trials conducted with the HM3 (MOMENTUM 3, CE Mark) have been in the context of a prescribed antithrombotic regimen of aspirin in concert with vitamin K antagonist. Within clinical studies[9,10,16], as institutional changes to their standard of care[18], or in response to increased bleeding risk[17], modifications to the HM3 anticoagulation regimen have been explored. Prior to the introduction of the HM3, which has a decreased thrombotic profile relative to the HMII, studies investigating the need for aspirin within the HMII antithrombotic regimen were conducted[20-23].

In conclusion, for the intended patient population, the probable medical benefits of the HM3 outweigh the overall residual risk and may be improved in the absence of antiplatelet agents as part of the antithrombotic regimen. This study aims to conclusively determine if antiplatelet agents are required as part of the HM3 antithrombotic regimen.

Clinical Investigation Plan

APPENDIX I: ABBREVIATIONS AND ACRONYMS

Abbreviation	Term
ACE	Angiotensin Converting Enzyme
AE	Adverse Event
AI	Aortic Insufficiency
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
ARB	Angiotensin II Receptor Blockers
AST	Aspartate Aminotransferase
AVM	Arterio-venous malformation
BTC	Bridge-to-Candidacy
BTT	Bridge-to-Transplant
BUN	Blood Urea Nitrogen
CABG	Coronary Artery Bypass Graft
CEC	Clinical Events Committee
CI	Cardiac Index
CIP	Clinical Investigation Plan
CK	Creatinine Kinase
CK-MB	Creatinine Kinase Muscle/Brain
CMS	Centers for Medicare and Medicaid SERVICES
CNS	Central Nervous System
CO	Cardiac Output
CPB	Cardiopulmonary Bypass
Cr	Creatinine
CRF	Case Report Form
CT	Computed Tomography
CVP	Central Venous Pressure
DMP	Data Management Plan
DSMB	Data Safety Monitoring Board
DT	Destination Therapy
EC	Ethics Committee
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EGM	Intracardiac electrogram
EKG	Electrocardiogram
ELEVATE	Evaluating the HeartMate 3 with Full MagLev Technology in a Post-Market Approval Setting
EQ-5D-5L	EuroQOL 5 Dimension 5 Level questionnaire
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GI	Gastrointestinal
HAS-BLED	Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs or Alcohol

Clinical Investigation Plan

Abbreviation	Term
HbA1c	Glycated Hemoglobin
HCS	Hemocompatibility Score
Hct	Hematocrit
HF	Heart Failure
Hgb	Hemoglobin
HIE	Hypoxic-ischemic injury
HIPAA	Health Insurance Portability and Accountability Act
HIT	Heparin Induced Thrombocytopenia
HM3	HeartMate 3
HMII	HeartMate II
ICF	Informed Consent Form
ICH	Intracranial Hemorrhage
IFU	Instructions for Use
INR	International Normalized Ratio
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
ITT	Intention to Treat
IRB	Institutional Review Board
LA	Left Atrium
LAAO	Left Atrial Appendage Occlusion
LDH	Lactate dehydrogenase
LV	Left Ventricle
LVAD	Left Ventricular Assist Device
LVAS	Left Ventricular Assist System
LVEDD	Left Ventricular End Diastolic Diameter
LVEF	Left Ventricular Ejection Fraction
LVESD	Left Ventricular End Systolic Diameter
MCS	Mechanical Circulatory Support
MedDEV	Medical Device Directives
MI	Myocardial Infarction
mITT	Modified Intention to Treat
MOMENTUM3	Multi-center Study of MagLev Technology in Patients Undergoing MCS Therapy With HeartMate 3™ IDE Study
MR	Mitral Regurgitation
MRI	Magnetic Resonance Imaging
MRS	Modified Rankin Score
NPO	Nil per os. Latin for “Nothing through the Mouth”.
NYHA	New York Heart Association
OUS	Outside the United States
PAD	Diastolic Pulmonary Artery Pressure
PAM	Mean Pulmonary Artery Pressure
PAS	Systolic Pulmonary Artery Pressure
PCWP	Pulmonary Capillary Wedge Pressure
PHgb	Plasma Free Hemoglobin

Clinical Investigation Plan

Abbreviation	Term
PLT	Platelets
PR	Pulmonary Regurgitation
PRBC	Packed Red Blood Cells
PRO	Patient Reported Outcome
PTFE	Polytetrafluoroethylene
PTT	Partial Thromboplastin Time
QOL	Quality of Life
RAP	Right Atrial Pressure
RHF	Right Heart Failure
RVAD	Right Ventricular Assist Device
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	Standard of Care
tPA	Tissue Plasminogen Activator
TR	Tricuspid Regurgitation
UADE	Unanticipated Adverse Device Effect
UNOS	United Network for Organ Sharing
UADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analogue Scale
VT	Ventricular Tachycardia
WBC	White Blood Cells

Clinical Investigation Plan

APPENDIX II: DEFINITIONS

ADVERSE EVENT DEFINITIONS:

1. Bleeding

VAD-IMPLANT-RELATED BLEEDING:
VAD-implantation-related bleeding (includes concomitant cardiac or non-cardiac surgical procedures) that requires:

- Reoperation after closure of incision or incisions used to implant the VAD for the purpose of controlling bleeding
- If ≥ 50 kg, ≥ 4U packed red blood cells (PRBC) within any 48-hour period during first 7 days post implant.
- If < 50 kg, ≥ 20 cc/kg packed red blood cells (PRBC) within any 24-hour period during first 7 days post implant.
- Or any transfusion from 8-14 days

or exhibits:

- Chest tube output > 2L within a 24-h period

MODERATE:
Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for a Severe or Surgical Bleeding Definitions but meets the following criteria:

- requiring nonsurgical, medical intervention by a healthcare professional;
  and
- leading to hospitalization or increased level of care (unscheduled clinical visit or use of emergency services).

SEVERE:

- Type A: (Meets any of the below)
  - Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL (provided hemoglobin drop is related to bleed)
  - Any transfusion with overt bleeding
- Type B: (Meets any of the below)
  - Overt bleeding plus hemoglobin drop 5 g/dL or greater (provided hemoglobin drop is related to bleed)
  - Cardiac tamponade
  - Bleeding requiring surgical intervention for control (excluding dental, nasal, skin, or hemorrhoid)
  - Hypotension attributable to bleeding and requiring intravenous vasoactive agents for hemodynamic support
  - Intracranial Hemorrhage that does not meet the definition of hemorrhagic stroke
- Type C1: Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

- Type C2: Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

2. Cardiac Arrhythmias

Any documented arrhythmia that results in clinical compromise (e.g., diminished VAD flow, oliguria, pre-syncope or syncope) that requires hospitalization or occurs during a hospital stay. Cardiac arrhythmias are classified as 1 of 2 types:

- Sustained ventricular arrhythmia requiring defibrillation or cardioversion.
- Sustained supraventricular arrhythmia requiring drug treatment or cardioversion.

3. Device Thrombosis

Device thrombosis is an event in which the pump or its conduits contain a thrombus that results in or could potentially induce circulatory failure. Suspected device thrombus is an event in which clinical or pump parameters suggest thrombus on the blood contacting components of the pump, cannula, or grafts. Signs and symptoms should include at least 2 of the 3 following criteria:

- Presence of hemolysis
- Worsening heart failure or inability to decompress the left ventricle
- Abnormal pump parameters

Suspected pump thrombus should be accompanied by 1 or more of the following events or interventions:

- Treatment with intravenous anticoagulation (e.g., heparin), intravenous thrombolytics (e.g., tPA), or intravenous antiplatelet therapy (e.g., eptifibatide, tirofiban)
- Pump replacement
- Pump explantation
- Urgent transplantation (UNOS status 1A)
- Stroke
- Arterial non-CNS thromboembolism
- Death

Confirmed device thrombus is an event in which thrombus is confirmed by the Sponsor's returned product analysis to be found within the blood contacting surfaces of device inflow cannula or outflow conduit or grafts. This can also be reported via direct visual inspection or by incontrovertible contrast radiographic evidence or by the absence of an appropriate Doppler flow signal that results in or could potentially induce circulatory failure or result in thromboembolism.

4. Hemolysis*

A plasma-free hemoglobin value that is greater than 40 mg/dl, concomitant with a rise in serum LDH above three times the upper limit of normal, in association with clinical signs

associated with hemolysis (e.g., anemia, low hematocrit, hyperbilirubinemia) occurring after the first 72 hours post-implant.
*Hemolysis in the presence of worsening heart failure or inability to decompress the left ventricle or abnormal pump parameters should be reported as suspected device thrombosis, not as hemolysis

5. Hepatic Dysfunction

An increase in any two of the following hepatic laboratory values (total bilirubin, aspartate aminotransferase/AST and alanine aminotransferase/ALT) to a level greater than three times the upper limit of normal for the hospital, beyond 14 days post-implant (or if hepatic dysfunction is the primary cause of death).

6. Hypertension

Blood pressure elevation of a mean arterial pressure greater than 110 mm Hg, despite anti-hypertensive therapy.

7. Major Infection

A clinical infection accompanied by pain, fever, drainage and/or leukocytosis that is treated by anti-microbial agents (non-prophylactic). A positive culture from the infected site or organ should be present unless strong clinical evidence indicates the need for treatment despite negative cultures. The general categories of infection are listed below:

Localized Non-Device Infection

Infection localized to any organ system or region (e.g. mediastinitis) without evidence of systemic involvement (see sepsis definition), ascertained by standard clinical methods and either associated with evidence of bacterial, viral, fungal or protozoal infection, and/or requiring empirical treatment.

Percutaneous Site and/or Pump Infection

A positive culture from the skin and/or tissue surrounding the drive line or from the tissue surrounding the external housing of a pump implanted within the body, coupled with the need to treat with antimicrobial therapy, when there is clinical evidence of infection such as pain, fever, drainage, or leukocytosis.

Internal Pump Component, Inflow or Outflow Tract Infection

Infection of blood-contacting surfaces of the LVAD documented by positive site culture.

Sepsis

Evidence of systemic involvement by infection, manifested by positive blood cultures and/or hypotension.

8. Myocardial Infarction

Two categories of myocardial infarction will be identified:

Peri-Operative Myocardial Infarction

The clinical suspicion of myocardial infarction together with CK-MB or Troponin > 10 times the local hospital upper limits of normal, found within 7 days following VAD implant

together with ECG findings consistent with acute myocardial infarction. (This definition uses the higher suggested limit for serum markers due to apical coring at the time of VAD placement and does not use wall motion changes because the apical sewing ring inherently creates new wall motion abnormalities.)

Non-Perioperative Myocardial Infarction
The presence at > 7 days post-implant of two of the following three criteria:

- Chest pain which is characteristic of myocardial ischemia,
- ECG with a pattern or changes consistent with a myocardial infarction, and
- Troponin or CK (measured by standard clinical pathology/laboratory medicine methods) greater than the normal range for the local hospital with positive MB fraction (≥ 3% total CK). This should be accompanied by a new regional LV or RV wall motion abnormality on a myocardial imaging study.

9. Neurologic Dysfunction

Any new, temporary or permanent, focal or global neurological deficit, ascertained by a standard neurological history and examination administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests and consultation note; or an abnormality identified by surveillance neuroimaging. The examining physician will classify the event as defined below:

- Transient ischemic attack*, defined as an acute transient neurological deficit conforming anatomically to arterial distribution cerebral ischemia, which resolves in < 24 hours and is associated with no infarction on brain imaging (head CT performed >24 hours after symptom onset; or MRI)
- Ischemic Stroke*: a new acute neurologic deficit of any duration associated with acute infarction on imaging corresponding anatomically to the clinical deficit, or a clinically covert ischemic stroke seen by surveillance imaging, without clinical findings of stroke or at the time of event recognition.
- Hemorrhagic Stroke*: a new acute neurologic deficit attributable to intracranial hemorrhage (ICH), or a clinically covert ICH seen by surveillance imaging, without clinical findings of ICH at the time of event recognition.
- Encephalopathy: Acute new encephalopathy** due to hypoxic-ischemic injury (HIE), or other causes, manifest as clinically evident signs or symptoms, or subclinical electrographic seizures found by complete neurological diagnostic evaluation to be attributable to acute global or focal hypoxic, or ischemic brain injury not meeting one of ischemic stroke or ICH events as defined above.
- Seizure of any kind
- Other neurological event (non-CNS event): examples include neuro muscular dysfunction or critical care neuropathy

*Modified Rankin Score (MRS) will be used to classify the severity of all strokes. MRS will be captured at baseline, the time of stroke, and at 60 days post-stroke. MRS will be determined by an independent assessor, defined as an independent, trained, and certified clinician. Severity will be defined as disabling (MRS > 3) or nondisabling (MRS ≤ 3). MRS is defined below.
**Acute encephalopathy is a sign or symptom of some underlying cerebral disorder, and is manifest as depressed consciousness with or without any associated new global or multifocal neurologic deficits in cranial nerve, motor, sensory, reflexes and cerebellar function.

10. Renal Dysfunction

Two categories of renal dysfunction will be identified:

Acute Renal Dysfunction

Abnormal kidney function requiring dialysis (including hemofiltration) in Subjects who did not require this procedure prior to implant, or a rise in serum creatinine of greater than 3 times baseline or greater than 5 mg/dL sustained for over 48 hours.

Chronic Renal Dysfunction

An increase in serum creatinine of 2 mg/dl or greater above baseline, or requirement for hemodialysis sustained for at least 90 days.

11. Respiratory Failure

Impairment of respiratory function requiring reintubation, tracheostomy or the inability to discontinue ventilatory support within six days (144 hours) post-VAD implant. This excludes intubation for reoperation or temporary intubation for diagnostic or therapeutic procedures.

12. Right Heart Failure

Symptoms and signs of persistent right ventricular dysfunction requiring RVAD implantation, or requiring inhaled nitric oxide or inotropic therapy for a duration of more than 14 days at any time after LVAD implantation. To compare to prior studies, this study will begin collecting details of events involving nitric oxide or inotropic therapy for a duration of more than 7 days, whereas reportable right heart failure will begin at 14 days of therapy.

To further stratify right heart failure (RHF) events, the following criteria will be used to identify a sub-category of persistent, clinically significant RHF events:

- Death due to right heart failure or
- RVAD or
- Hospitalization with primary diagnosis of decompensated heart failure with evidence of right heart support or
- Post-discharge inotropes or

- > 30 consecutive days on inotropes.

13. Arterial Peripheral Thromboembolism

An acute systemic arterial perfusion deficit in any non-cerebrovascular organ system due to thromboembolism confirmed by one or more of the following:

1) Standard clinical and laboratory testing
2) Operative findings
3) Autopsy findings

This definition excludes neurological events.

14. Venous Thromboembolism Event

Evidence of venous thromboembolic event (e.g. deep vein thrombosis, pulmonary embolism) by standard clinical and laboratory testing.

15. Other

An event that causes clinically relevant adverse changes in the Subject's health (e.g. cancer) not otherwise categorized above.

Clinical Investigation Plan

NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION

NYHA Classification	Definition
I	Cardiac disease without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea or anginal pain.
II	Cardiac disease resulting in slight limitation of physical activity. Subjects are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
IIIA	Cardiac disease resulting in marked limitations of physical activity. Subjects are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IIIB	Cardiac disease resulting in marked limitations of physical activity. Subjects are comfortable at rest. Mild physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV*	Cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Clinical Investigation Plan

INTERMACS PROFILE

INTERMACS Profile*	Definition
1	Critical cardiogenic shock describes a patient who is “crashing and burning”, in which a patient has life-threatening hypotension and rapidly escalating inotropic pressor support, with critical organ hypoperfusion often confirmed by worsening acidosis and lactate levels.
2	Progressive decline describes a patient who has been demonstrated “dependent” on inotropic support but nonetheless shows signs of continuing deterioration in nutrition, renal function, fluid retention, or other major status indicator. Patient profile 2 can also describe a patient with refractory volume overload, perhaps with evidence of impaired perfusion, in whom inotropic infusions *cannot be maintained* due to tachyarrhythmias, clinical ischemia, or other intolerance.
3	Stable but inotrope dependent describes a patient who is clinically stable on mild-moderate doses of intravenous inotropes (or has a temporary circulatory support device) after repeated documentation of failure to wean without symptomatic hypotension, worsening symptoms, or progressive organ dysfunction (usually renal). It is critical to monitor nutrition, renal function, fluid balance, and overall status carefully in order to distinguish between a patient who is truly stable at Patient Profile 3 and a patient who has unappreciated decline rendering this person a Patient Profile 2. This patient may be either at home or in the hospital.
4	Resting symptoms describes a patient who is at home on oral therapy but frequently has symptoms of congestion at rest or with ADL. He or she may have orthopnea, shortness of breath during ADL such as dressing or bathing, gastrointestinal symptoms (abdominal discomfort, nausea, poor appetite), disabling ascites or severe lower extremity edema. This patient should be carefully considered for more intensive management and surveillance programs, by which some may be recognized to have poor compliance that would compromise outcomes with any therapy.
5	Exertion Intolerant describes a patient who is comfortable at rest but unable to engage in any activity, living predominantly within the house or housebound. This patient has no congestive symptoms, but may have chronically elevated volume status, frequently with renal dysfunction, and may be characterized as exercise intolerant.
6	Exertion Limited also describes a patient who is comfortable at rest without evidence of fluid overload, but who is able to do some mild activity. Activities of daily living are comfortable and minor activities outside the home such as visiting friends or going to a restaurant can be performed, but fatigue results within a few minutes of any meaningful physical exertion. This patient has occasional episodes of worsening symptoms and is likely to have had a hospitalization for heart failure within the past year.
7	Advanced NYHA Class 3 describes a patient who is clinically stable with a reasonable level of comfortable activity, despite history of previous decompensation that is not recent. This patient is usually able to walk more than a block. Any decompensation requiring intravenous diuretics or hospitalization within the previous month should make this person a Patient Profile 6 or lower.

MODIFIED RANKIN SCORE (MRS)

MRS	Definition[1]
0	No observed neurological symptoms
1	No significant neurological disability despite symptoms; able to carry out all usual duties and activities
2	Slight neurological disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate neurological disability; requiring some help, but able to walk without assistance
4	Moderate severe neurological disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe neurological disability; bedridden, incontinent and requiring constant nursing care and attention as a result of a neurological deficit
6	Dead

NON-SURGICAL

Greater than 14 days post implant.

[1] van Swieten J, Koudstaal P, Visser M, Schouten H, *et al* (1988). "Interobserver agreement for the assessment of handicap in stroke Subjects". *Stroke* **19** (5): 604-607

Clinical Investigation Plan

APPENDIX III: STUDY CONTACT INFORMATION

Contact information for each participating clinical site is available under separate cover by contacting the Project Management.

Project Management Contact

Nina Sinanovic
Abbott
3200 Lakeside Drive
Santa Clara, CA, 95054
USA
Phone: +1 408 845 0655
E-mail: nina.sinanovic@abbott.com

Clinical Safety Contact

Venu Parimi
Medical Safety Monitor
168 Middlesex Turnpike
Burlington, MA, 01803
USA
E-mail: AdverseEvent@abbott.com

Requests for further clarifications on submitted reports can be sent to clinicalsafety@abbott.com.

Clinical Investigation Plan

APPENDIX IV: INFORMED CONSENT FORM

The study template informed consent form is available under a separate cover.

Clinical Investigation Plan

APPENDIX V: MONITORING PLAN

A copy of the Monitoring Plan can be obtained upon request from the Sponsor Clinical Project Manager.

Clinical Investigation Plan

APPENDIX VI: DEVICE POSITION SUBSTUDY PROTOCOL

Study Title	**Assessment of HeartMate 3 Device Position using a Radiopaque Marker Positioned on the Aortic Root**
Study Phase	Substudy within the ARIES Clinical Study
Rationale	Implantation of a durable left ventricular assist device (LVAD) is now the most frequently utilized surgical therapy for treatment of patients with advanced heart failure (HF) refractory to medical management. Previous studies have demonstrated that inflow cannula malposition, which occurs 1) due to incorrect surgical placement, or 2) as a consequence of device migration, is associated with significant adverse events including pump thrombosis, stroke and persistent heart failure due to the inability to provide adequate left ventricular unloading and device flow.(**1**) Specific surgical configurations have not been studied in depth, and its influence on hemocompatatibility-related events associated with LVAD therapy remains poorly understood.(**2**) Thrombogenesis in patients with an LVAD is at least, in part, attributable to nonphysiological blood flow characteristics: shear environments, as well as high spatial gradients and high-frequency temporal fluctuations, which lead to platelet activation. This adverse hemodynamic environment may be exacerbated by malposition of the LVAD inflow cannula. Anecdotal evidence suggests that surgical implantation of the inflow cannula at different angles with respect to the apical ventricular axis influences LVAD thrombosis.(**3-5**) Prior studies investigating inflow cannula malposition have utilized various reference lines to determine optimal inflow cannula position. Typically, these reference lines utilize the spine as a vertical reference line and a horizontal line drawn perpendicular to the vertical line usually positioned at the apex of the right diaphragm serves as a horizontal reference point.(**3-5**) However, this approach does not take into consideration differences in anatomy of the heart in relation to the spine and diaphragms. Optimal inflow position in oriented to the orifice of the mitral valve. Thus, the utility of these reference lines to identify the orifice of the mitral valve is brought into question. This substudy utilizes a simple technique to identify a more anatomical reference point to assess HeartMate 3 inflow cannula position. A radiopaque surgical marker (i.e., surgical clip) will be 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. The surgical clips used in this study are generally standard to use in cardiac surgery for both hemostasis and as radiopaque markers. They have been used for the development of this substudy in 4 LVAD implants with a cumulative follow up of 245-days post-implant at a single center without safety concerns (data not published). The location of the clip reduces the likelihood of interference with the coronary artery. Placement of the clips will be under direct visualization and will not prolong the implant procedure. Participation in this substudy is not expected to present appreciable additional risk. This substudy will not affect the main objectives of the ARIES HM3 clinical trial.

Clinical Investigation Plan

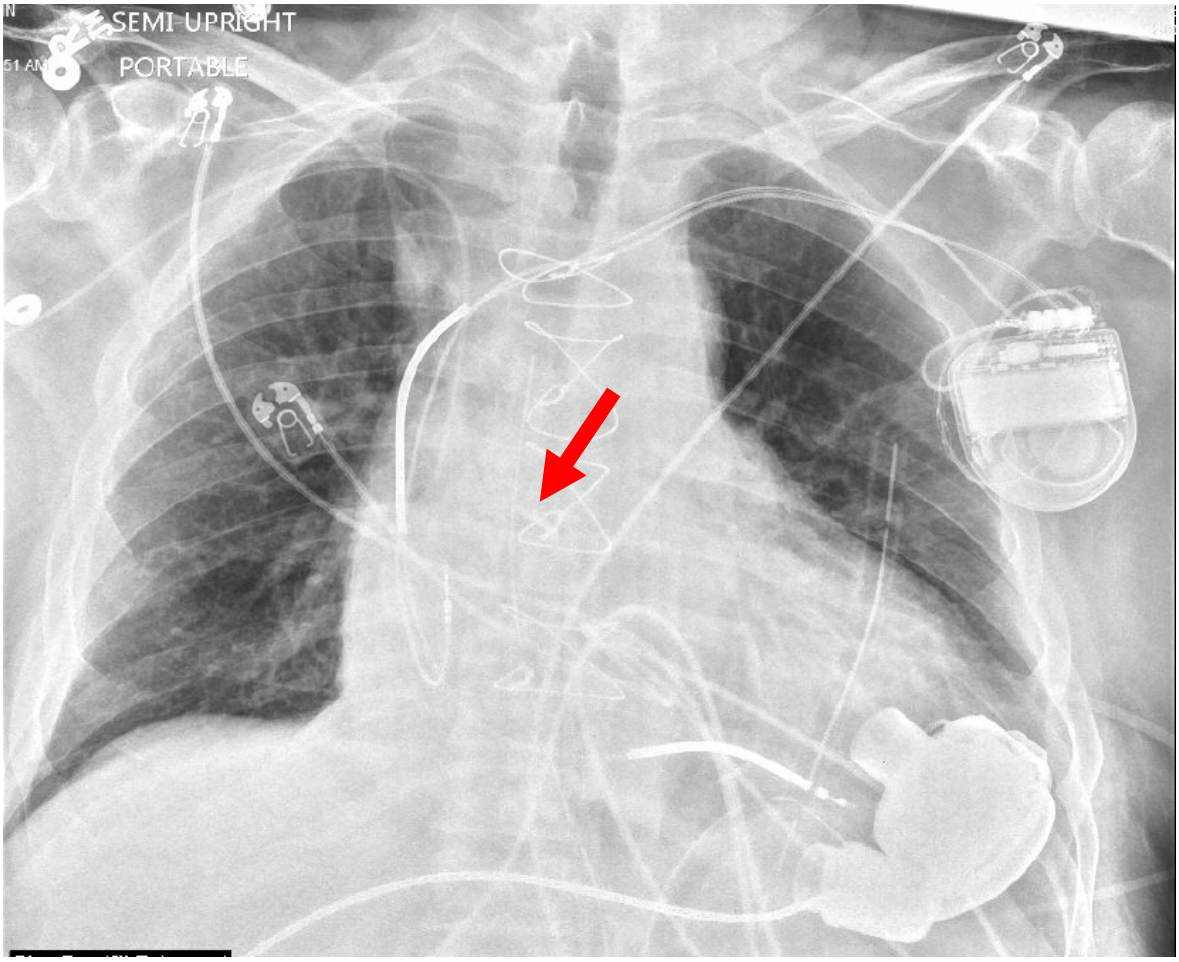
	The hypothesis of this sub-study is to develop and validate a surgical marker to serve as a consistent anatomical landmark to allow for accurate evaluation of the HeartMate 3 inflow canula position at the time of implant and subsequently, over time. We further hypothesize that differences in inflow canula positions and their changes over time may correlate with clinical outcomes.
Primary Objectives	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. Validation will be performed by assessing: 1. The safety and feasibility of placing and visualizing the radiopaque marker; 2. The variation in cannula angulation relative to the radiopaque marker and cannula positional changes over time; 3. The relationship between the initial cannula angulation or its change over time with adverse clinical outcomes and functional capacity, as an exploratory analysis.
Study Populations	Subjects enrolled in the ARIES HM3 study who also meet eligibility requirements for this substudy at participating centers.
Study Design	Multi-center, prospective, non-controlled, non-randomized, observational sub-study within ARIES
Number of Subjects	Per ARIES HM3 study
Number of Centers	Up to 10 Centers
Duration of Subject Participation	Per ARIES HM3 study
Inclusion Criteria	1. Subjects enrolled within the ARIES HM3 study.
Exclusion Criteria	1. In the judgement of the implanting surgeon, that placement of the radiopaque surgical marker would have unacceptable risk based upon technical reasons or patient anatomy. 2. Subjects undergoing placement of the HeartMate 3 device through a minimally-invasive approach where sternotomy or upper sternotomy will not be performed and access to the anterior surface of the aorta below the sino-tubular ridge is not feasible.

Clinical Investigation Plan

Intervention	A radiopaque surgical marker (i.e., surgical clip) will be placed on the anterior surface of the aortic root midway between the sino-tubular ridge of the aorta and the ostia of the right coronary artery. The radiopaque marker will include placement of 2 standard surgical clips (manufacturer, size, picture; see **Figures 1, 2A and B, 3 and 4**) attached to the adventitia of the aorta and positioned as described above.
Assessments	Anteroposterior (AP) and lateral radiographs will be captured prior to discharge (but within 30 days of implant) and at the 3-month follow up visit. Radiographs will be obtained by a fixed radiography (fixed x-ray) and sent to the study sponsor in DICOM format. If standard of care (SOC), chest x-ray computed tomography (CT) scans will be obtained in addition to the radiographs.
References	1. Chivukula VK, Beckman JA, Prisco AR, et al. Left ventricular assist device inflow cannular angle and thrombosis risk. Circulation: Heart Failure. 2018;11:e004325. 2. Mancini D, Colombo PC. Left ventricular assist devices: a rapidly evolving alternative to transplant. J Am Coll Cardiol. 2015;65:2542–2555. 3. Taghavi S, Ward C, Jayarajan SN, Gaughan J, Wilson LM, Mangi AA. Surgical technique influences HeartMate II left ventricular assist device thrombosis.**Ann Thorac Surg**. 2013; 96:1259–1265. 4. Atkins BZ, Hashmi ZA, Ganapathi AM, Harrison JK, Hughes GC, Rogers JG, Milano CA. Surgical correction of aortic valve insufficiency after left ventricular assist device implantation.**J Thorac Cardiovasc Surg.** 2013; 146:1247–1252. 5. Bhama J, Eckert C, Lockard K, Shiose A, Bermudez C, Teuteberg J, Ramani R, Simon M, Badhwar V, Kormos R. Does LVAD inflow cannula position contribute to the development of pump thrombosis requiring device exchange?**J Am Coll Cardiol**. 2013; 61:E719.

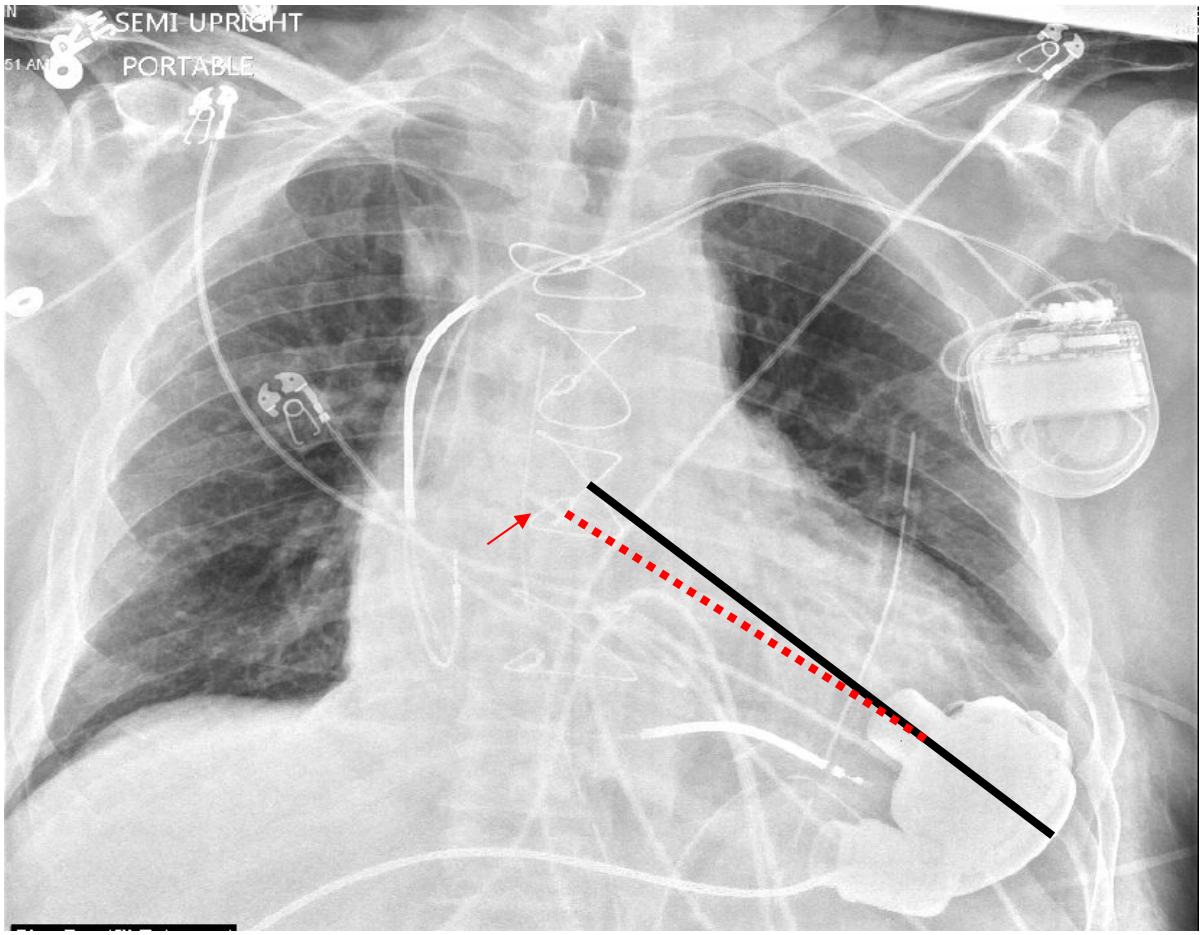
Clinical Investigation Plan

Figure 1: Acceptable Anteroposterior and Lateral Chest Radiograph Demonstrating Placement of a Radiopaque marker (two standard surgical clips). Clips are placed on the anterior surface of the aorta positioned halfway between the sino-tubular ridge of the aorta and the right coronary artery. Note: the full body of the HM3 is visible within the radiograph.



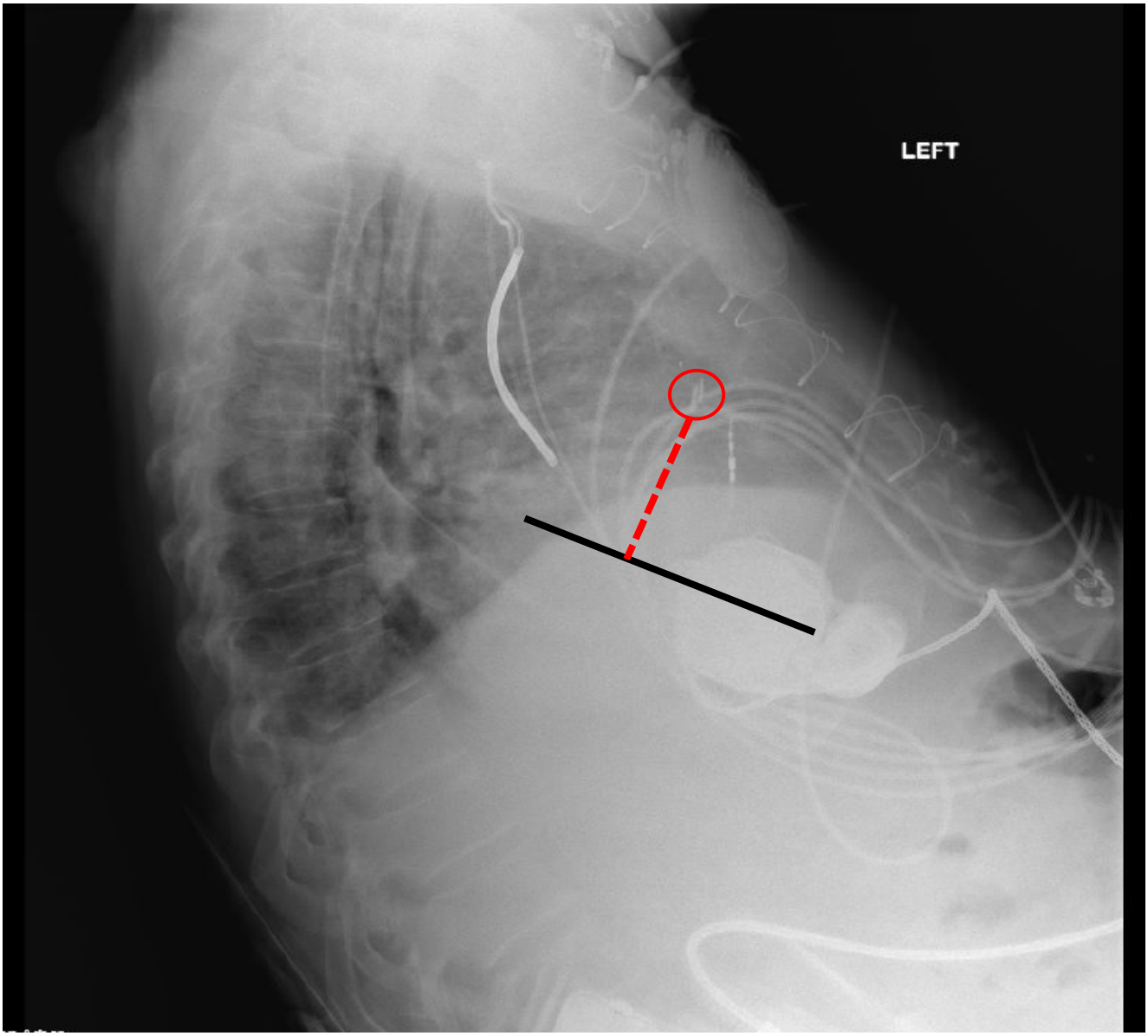
Clinical Investigation Plan

Figure 2A: Measurement Method on Anteroposterior and Lateral Chest Radiograph. Radiopaque marker (two standard surgical clips) on the anterior surface of the aorta is positioned halfway between the sino-tubular ridge of the aorta and the right coronary artery (Red Arrow). Black line indicates center line of the HeartMate 3 inflow canula. The dotted red line indicates the degree of deviation from the reference point (surgical radiopaque marker).



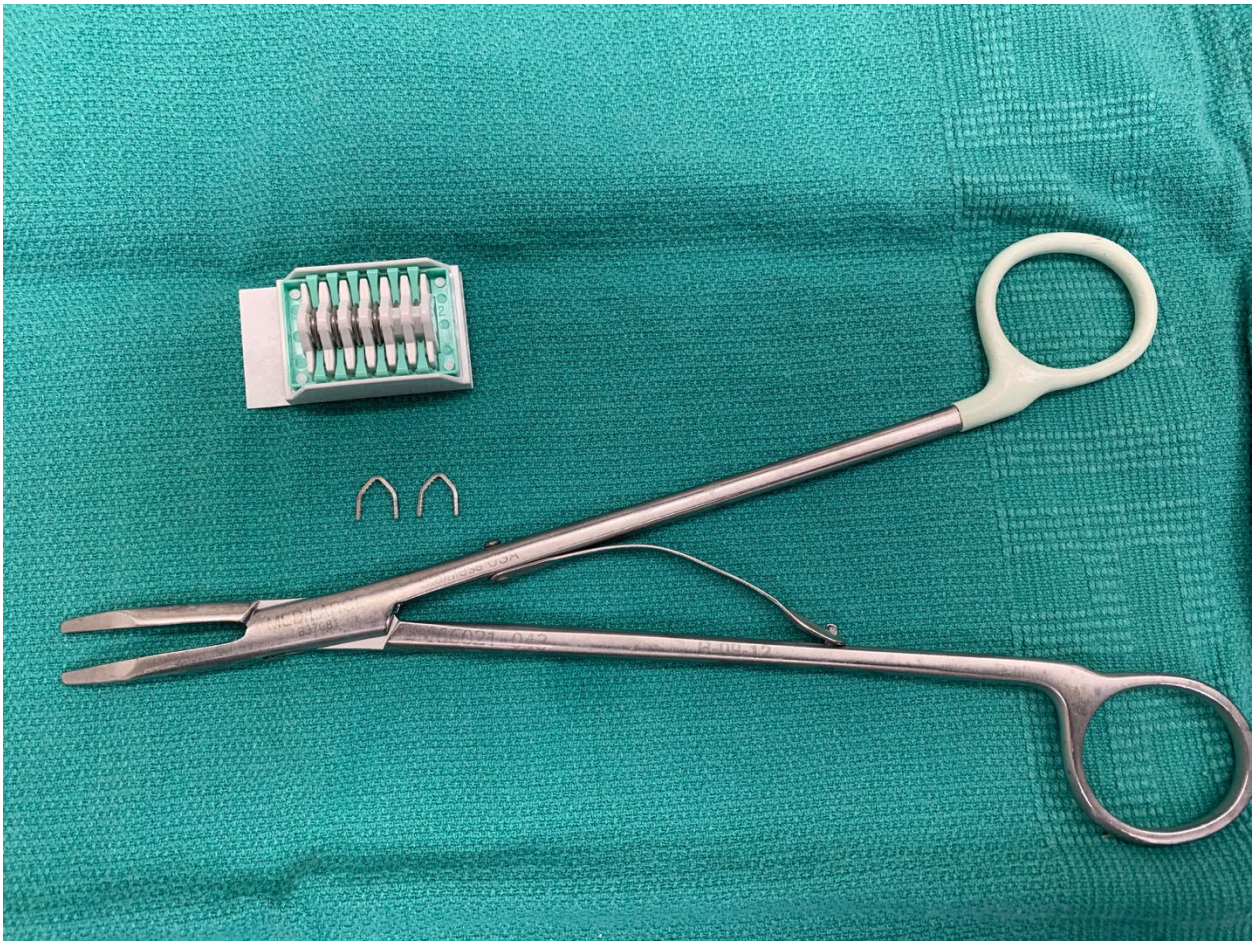
Clinical Investigation Plan

Figure 2B: Measurement Method on Anteroposterior and Lateral Chest Radiograph. Radiopaque marker (two standard surgical clips) on the anterior surface of the aorta is positioned halfway between the sino-tubular ridge of the aorta and the right coronary artery (Red Circle). Black line indicates center line of the HeartMate 3 inflow canula. The dotted red line indicates the degree of deviation from the reference point (surgical radiopaque marker).



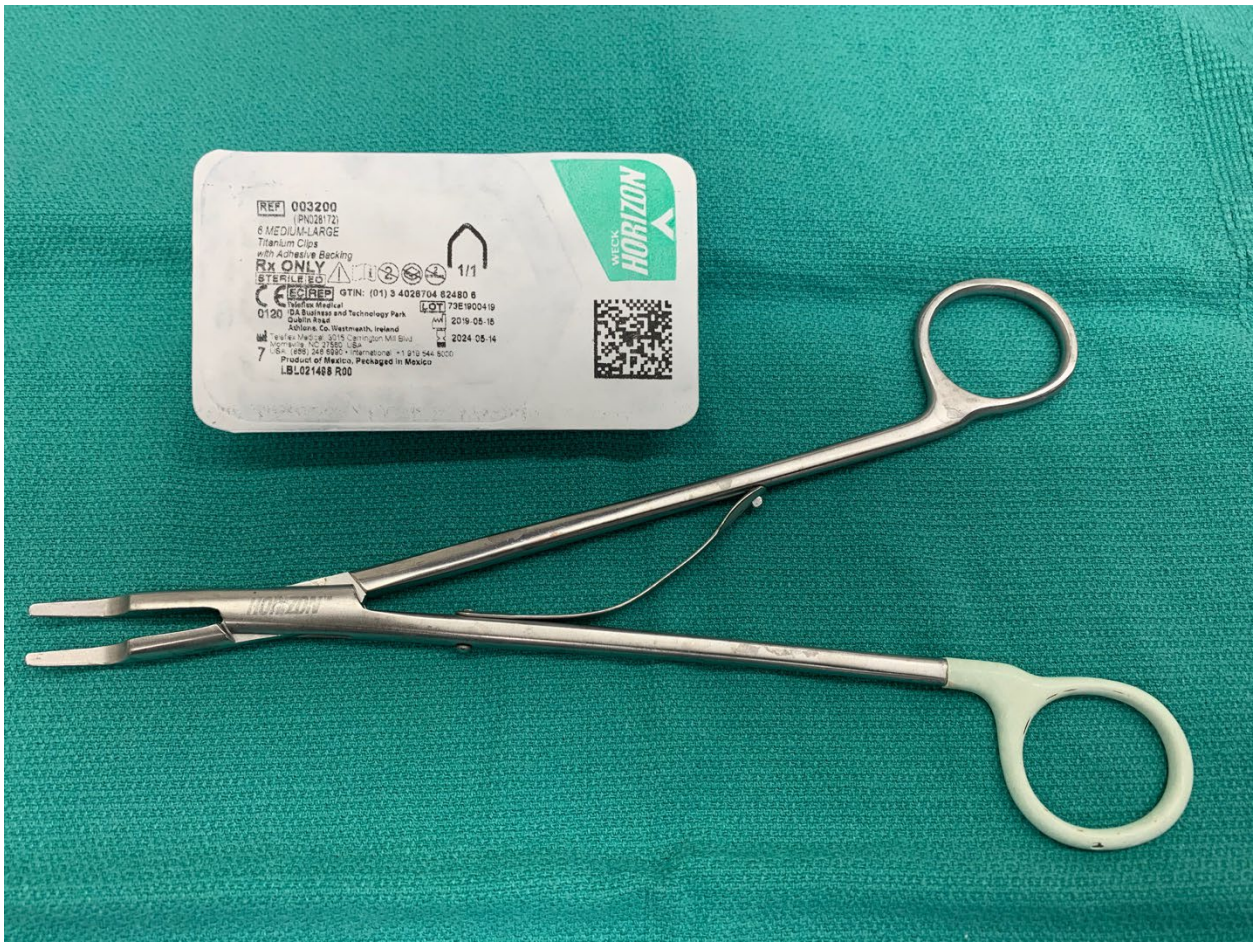
Clinical Investigation Plan

Figure 3: Radiopaque Surgical Marker



Clinical Investigation Plan

Figure 4: Radiopaque Surgical Marker



Clinical Investigation Plan

APPENDIX VII: REVISION HISTORY

This CIP may be amended as appropriate by the Sponsor. Rationale will be included with each amended version in the revision history table below. The version number and date of amendments will be documented.

IRB/EC and relevant Regulatory Authorities, if applicable, will be notified of amendments to the CIP.

Amendment Number	Version	Date	Details	Rationale
Not Applicable	A	22AUG2019	First release of CIP	NA
1	B	15JAN2020	DSMB is unblinded; Sponsor is fully blinded.	The DSMB has independently requested access to unblinded data to perform safety review.
			Update Statistics Section to reflect updated analysis plan including removal of superiority analysis, combining secondary and safety endpoints, adding secondary endpoints.	The statistical analysis plan of the study has been updated.
			Add Device Position Substudy	Assess implant cannula position, changes over time and their potential impact on outcomes
			Clarify transition to open label and add 72-hour cessation window	Allow 72-hour cessation of treatment arm medication prior to transition to open label for treatment of adverse events.
			Add “Other” Adverse Event Definition and clarify Moderate Bleeding definition	All adverse events will be collected.
			Remove 45 CFR part 46 from Compliance Statement	Regulation not applicable to this study
			Minor corrections and clarifications throughout	n/a

Clinical Investigation Plan

2	C	13MAR2020	Relabeled Primary Endpoint analysis population as mITT population and defined ITT Population	Using more unified definitions of populations as well as defining an ITT population for a sensitivity analysis
			Corrected 97.5% confidence limit in primary endpoint analysis method	Correction

Clinical Investigation Plan

APPENDIX VIII: CIP SUMMARY

Clinical Investigation Name and Number	ARIES HM3 CRD_971
Title	**A**ntiplatelet **R**emoval and Hemocompat**I**bility **E**vent**S** with the **H**eart**M**ate **3** Pump
Background	Heart failure (HF) is a growing epidemic, with 915,000 new cases diagnosed each year, resulting in over 1 million hospitalizations and costs the United States (US) healthcare system over $30 billion annually[1]. Left ventricular assist devices (LVAD) are increasingly being used for treating patients with advanced heart failure as they have demonstrated improved survival over optimal medical management[2]. Progressively improving outcomes with newer LVAD technology has led to LVAD therapy becoming a mainstay in the treatment of advanced heart failure[3], however, LVAD therapy has been beleaguered by hemocompatibility related adverse events – namely thrombosis, stroke and bleeding[4]. Within the prospective randomized multicenter MOMENTUM 3 clinical trial, the HeartMate 3 (HM3) Left Ventricular Assist System (LVAS; Abbott, Chicago, IL, Study Sponsor) showed a decrease in hemocompatibility related adverse events relative to the HeartMate II (HMII) LVAS (Abbott, Chicago, IL)[5]. This included decreases in pump thrombosis[6], stroke[7-9], and bleeding[9] event rates. Despite these noted improvements a high residual risk of bleeding persists in patients treated with the HM3 LVAD[9]. Patients implanted with the HM3 pump are treated with a combination of antiplatelet and anticoagulation therapy but the role and implications of this regimen in determining the burden of hemocompatibility related adverse events have not been adequately investigated[9,10]. Whether antiplatelet therapy is essential in concert with anticoagulation in treating such patients remains unknown.
Objective	To study the safety and efficacy of an anti-platelet-free antithrombotic regimen in patients with advanced heart failure treated with the HM 3 LVAS
Hypothesis	Withdrawal of aspirin from the antithrombotic regimen of HM3 pump patients will not adversely affect safety and efficacy and may reduce non-surgical bleeding
Clinical Investigation Design	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 versus vitamin K antagonist with placebo

Clinical Investigation Plan

Device Under Investigation and Indications	HeartMate 3 Left Ventricular Assist System (LVAS) In the US, the HM3 LVAS is indicated for providing mechanical circulatory support in patients with advanced refractory left ventricular heart failure (e.g. pending cardiac transplantation or myocardial recovery, or for permanent support). In Europe, the HM3 LVAS is intended to provide long term hemodynamic support in patients with advanced, refractory left ventricular heart failure. It is intended either for temporary support, such as a bridge to cardiac transplantation (BTT), or as permanent destination therapy (DT) and it is intended for use inside or outside the hospital. In Canada, The HM3 LVAS is indicated for providing mechanical circulatory support in patients with advanced refractory left ventricular heart failure (e.g., pending cardiac transplantation or myocardial recovery, or for permanent support).
Treatment Arm Medication	Aspirin (100 mg– active ingredient: Acetylsalicylic acid) OR Placebo (ALMAC Group, Craigavon, UK)
Study Sites	Up to 50 US and international sites
Patient Protection Procedures	This study will employ an independent clinical events committee (CEC), which will remain blinded to subject randomization, to adjudicate primary endpoint related adverse events. Study monitoring will be performed by an independent data safety monitoring board (DSMB), which will be unblinded to population randomization and determine independent rules for safety oversight.
Primary Endpoint	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

Clinical Investigation Plan

Primary Endpoint Evaluation	The primary endpoint composite success rate will be calculated for each treatment arm based on the number of subjects who survive to 12 months with no primary endpoint events divided by the total number of subjects in the Modified Intention to Treat Population (mITT) population. The placebo arm will be considered non-inferior to the aspirin arm if the lower boundary of the one-sided 97.5% confidence limit of the risk difference in the composite success between treatment arms (Placebo-arm minus Aspirin-arm) is greater than the non-inferiority margin (10%).
Number of Subjects Required for Inclusion in Clinical Investigation	Results from the MOMENTUM 3 trial were used to derive a point estimate of 71% survival to 1 year free of any major hemocompatibility related adverse events in the aspirin treated arm. It is assumed that in the absence of aspirin a 2% improvement in the composite endpoint will be noted, mainly due to the reduction of bleeding complications without a change in thromboembolic complications. Based on these assumptions 220 patients will need to be enrolled in each arm (440 total) to achieve 80% power to prove that the placebo group is non-inferior to the aspirin group using a non-inferiority margin of 10% with the Farrington-Manning risk difference approach to non-inferiority at a one-sided alpha = 0.025. To account for an expected 30% dropout rate associated with events occurring 2-14 days post implant, up to 628 patients will be randomized in the trial. Sample size calculations were performed using PASS 15 software.

Secondary Endpoint	• Non-surgical Major Hemorrhagic Events
	• Non-surgical Major Thrombotic Events
	• Survival
	• Stroke Rates,
	• Pump Thrombosis Rates
	• Bleeding Rates, including:
	  ○ Non-surgical Bleeding
	  ○ Moderate Bleeding
	  ○ Severe Bleeding
	  ○ Fatal Bleeding
	  ○ GI Bleeding

Descriptive Endpoints	Hemocompatibility Score, Rehospitalizations, Economic Cost Implications

Clinical Investigation Plan

Subject Follow-up	– Baseline – Implant – Randomization – Discharge – Week 1 ± 3 days – Month 1 ± 7 days – Month 3 ± 30 days – Month 6 ± 30 days – Month 9 ± 30 days – Month 12 ± 30 days – Every 6 month ± 60 days until last subject has completed the 12-month follow-up.
Inclusion Criteria	• Subject will receive the HeartMate 3 per standard of care (SOC) in accordance with the approved indications for use in the country of implant. • Subject will receive the HeartMate 3 as their first durable VAD. • Subject must provide written informed consent prior to any clinical investigation related procedure. • In patients of child bearing capability, not currently pregnant and on appropriate contraception.
Exclusion Criteria	• Post-implant additional temporary or permanent mechanical circulatory support (MCS) post-implant (other than the HM3 LVAD). • Post-implant Investigator mandated antiplatelet therapy for other conditions (including mandated presence or absence of antiplatelet agent). • Patients who are nil per os (NPO) post-implant through day 7. • Subjects with a known allergy to acetylsalicylic acid. • Participation in any other clinical investigation(s) involving an MCS device, or interventional investigation(s) likely to confound study results or affect study outcome. • Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements, or impact the scientific soundness of the clinical investigation results.

Clinical Investigation Plan

APPENDIX IX: REFERENCES

1 Mozaffarian, D. *et al.* Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation* **133**, e38-360, doi:10.1161/CIR.0000000000000350 (2016).
2 Rose, E. A. *et al.* Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med* **345**, 1435-1443, doi:10.1056/NEJMoa012175 (2001).
3 Cook, J. L. *et al.* Recommendations for the Use of Mechanical Circulatory Support: Ambulatory and Community Patient Care: A Scientific Statement From the American Heart Association. *Circulation* **135**, e1145-e1158, doi:10.1161/CIR.0000000000000507 (2017).
4 Mehra, M. R. The burden of haemocompatibility with left ventricular assist systems: a complex weave. *Eur Heart J* **40**, 673-677, doi:10.1093/eurheartj/ehx036 (2019).
5 Uriel, N. *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* **135**, 2003-2012, doi:10.1161/CIRCULATIONAHA.117.028303 (2017).
6 Mehra, M. R. *et al.* A Fully Magnetically Levitated Circulatory Pump for Advanced Heart Failure. *N Engl J Med* **376**, 440-450, doi:10.1056/NEJMoa1610426 (2017).
7 Colombo Paolo, C. *et al.* Comprehensive Analysis of Stroke in the Long-Term Cohort of the MOMENTUM 3 Study. *Circulation* **139**, 155-168, doi:10.1161/CIRCULATIONAHA.118.037231 (2019).
8 Mehra, M. R. *et al.* Two-Year Outcomes with a Magnetically Levitated Cardiac Pump in Heart Failure. *N Engl J Med* **378**, 1386-1395, doi:10.1056/NEJMoa1800866 (2018).
9 Mehra, M. R. *et al.* A Fully Magnetically Levitated Left Ventricular Assist Device - Final Report. *N Engl J Med* **0**, null, doi:10.1056/NEJMoa1900486 (2019).
10 Netuka, I. *et al.* Evaluation of low-intensity anti-coagulation with a fully magnetically levitated centrifugal-flow circulatory pump-the MAGENTUM 1 study. *J Heart Lung Transplant* **37**, 579-586, doi:10.1016/j.healun.2018.03.002 (2018).
11 Schmitto, J. D. *et al.* Long-term evaluation of a fully magnetically levitated circulatory support device for advanced heart failure—two-year results from the HeartMate 3 CE Mark Study. *European journal of heart failure* **21**, 90-97, doi:10.1002/ejhf.1284 (2019).
12 Saeed, D. *et al.* Two-Year Outcomes in Real World Patients Treated with Heartmate 3^{TM} Left Ventricular Assist Device for Advanced Heart Failure: Data from the ELEVATE Registry. *The Journal of Heart and Lung Transplantation* **38**, S67, doi:10.1016/j.healun.2019.01.153 (2019).
13 Heatley, G. *et al.* Clinical trial design and rationale of the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy With HeartMate 3 (MOMENTUM 3) investigational device exemption clinical study protocol. *J Heart Lung Transplant* **35**, 528-536, doi:10.1016/j.healun.2016.01.021 (2016).
14 Mehra, M. R. *et al.* A Fully Magnetically Levitated Circulatory Pump for Advanced Heart Failure. *N Engl J Med* **376**, 440-450, doi:10.1056/NEJMoa1610426 (2016).
15 Uriel, N. & Mehra, M. Long-Term Burden of Hemocompatibility Related Adverse Events in the MOMENTUM 3 Trial: Final Analysis of the 1028 Patient Cohort. *The Journal of Heart and Lung Transplantation* **38**, S67, doi:10.1016/j.healun.2019.01.152 (2019).
16 Netuka, I. *et al.* A Trial of Complete Withdrawal of Anticoagulation Therapy in the Heartmate 3 Pump. *The Journal of Heart and Lung Transplantation* **38**, S113, doi:10.1016/j.healun.2019.01.264 (2019).
17 Consolo, F., Raimondi Lucchetti, M., Tramontin, C., Lapenna, E. & Pappalardo, F. Do we need aspirin in HeartMate 3 patients? *European journal of heart failure*, doi:10.1002/ejhf.1468 (2019).

18 Lim, H. S., Ranasinghe, A., Mascaro, J. & Howell, N. Discontinuation of Aspirin in Heartmate 3 Left Ventricular Assist Device. *ASAIO Journal (American Society For Artificial Internal Organs: 1992)*, doi:10.1097/MAT.0000000000000859 (2018).

19 McNeil, J. J. *et al.* Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly. *New England Journal of Medicine* **379**, 1509-1518, doi:10.1056/NEJMoa1805819 (2018).

20 Katz, J. N. *et al.* Safety of reduced anti-thrombotic strategies in HeartMate II patients: A one-year analysis of the US-TRACE Study. *Journal of Heart and Lung Transplantation* **34**, 1542-1548, doi:10.1016/j.healun.2015.06.018 (2015).

21 Netuka, I. *et al.* Outcomes in HeartMate II Patients With No Antiplatelet Therapy: 2-Year Results From the European TRACE Study. *The Annals of thoracic surgery* **103**, 1262-1268, doi:10.1016/j.athoracsur.2016.07.072 (2017).

22 Van Tuyl, J. S. *et al.* Warfarin and Aspirin Versus Warfarin Alone for Prevention of Embolic Events in Patients with a HeartMate II Left Ventricular Assist Device. *ASAIO journal* **63**, 731-735, doi:10.1097/mat.0000000000000561 (2017).

23 Litzler, P. Y. *et al.* Is anti-platelet therapy needed in continuous flow left ventricular assist device patients? A single-centre experience. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery* **45**, 55-59; discussion 59-60, doi:10.1093/ejcts/ezt228 (2014).

Clinical Investigation Plan

APPENDIX VII: REVISION HISTORY

This CIP may be amended as appropriate by the Sponsor. Rationale will be included with each amended version in the revision history table below. The version number and date of amendments will be documented.

IRB/EC and relevant Regulatory Authorities, if applicable, will be notified of amendments to the CIP.

Amendment Number	Version	Date	Details	Rationale
Not Applicable	A	22AUG2019	First release of CIP	NA
1	B	15JAN2020	DSMB is unblinded; Sponsor is fully blinded.	The DSMB has independently requested access to unblinded data to perform safety review.
			Update Statistics Section to reflect updated analysis plan including removal of superiority analysis, combining secondary and safety endpoints, adding secondary endpoints.	The statistical analysis plan of the study has been updated.
			Add Device Position Substudy	Assess implant cannula position, changes over time and their potential impact on outcomes
			Clarify transition to open label and add 72-hour cessation window	Allow 72-hour cessation of treatment arm medication prior to transition to open label for treatment of adverse events.
			Add “Other” Adverse Event Definition and clarify Moderate Bleeding definition	All adverse events will be collected.
			Remove 45 CFR part 46 from Compliance Statement	Regulation not applicable to this study
			Minor corrections and clarifications throughout	n/a

Clinical Investigation Plan

2	C	13MAR2020	Relabeled Primary Endpoint analysis population as mITT population and defined ITT Population	Using more unified definitions of populations as well as defining an ITT population for a sensitivity analysis
			Corrected 97.5% confidence limit in primary endpoint analysis method	Correction

Statistical Analysis Plan

CRD_971

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 1.0

May 29, 2019

Gerald J Heatley

Statistical Analysis Plan

TABLE OF CONTENTS

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 CIP 10305, the ARIES HM3 clinical investigation. This plan is based on the Version A, May 29, 2019 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 HM 3 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. Subjects will be randomized in a 1:1 ratio.

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, secondary, and safety 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), Data Safety Monitoring Board (DSMB) and sponsor personnel (with exceptions noted in the study blinding plan), 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 (e.g. data management, safety, biometrics). 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 safety and secondary endpoints will also be evaluated to monitor effects on other safety and efficacy 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)

As a secondary endpoint, non-surgical bleeding rates will be compared between the two arms of the study.

1.4.3 Safety Endpoint(s)

To assess the safety of removal of antiplatelets from the antithrombotic regimen, survival, stroke rates, and pump thrombosis rates will be compared between the two arms of the study.

1.4.4 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

Only subjects who have provided informed consent, been implanted with the HM3 and subsequently met all inclusion and no exclusion criteria will be randomized. Randomization will be performed through ALMAC Clinical's WebEZ system. Subjects will be randomized in a 1:1 ratio between the placebo and aspirin group. Randomization will be stratified by study center and assigned using a block size of 4 subjects. Prior to randomizing a patient in WebEZ, patients will have been initialized in the Sponsor's EDC portal upon enrollment and obtained a subject ID number, which will also be used as the patient identifier in the WebEZ system. Subjects should begin taking the treatment arm medication within 24 hours of randomization.

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 (with exceptions noted in the study blinding plan), the CEC, and the DSMB 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, all data have been received, and all adverse events have been adjudicated. Questions related to unblinding should be directed to the Sponsor.

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.

2.1.1 Primary Endpoint Analysis Population:

The primary endpoint analysis population will include all randomized subjects with the following exception:

1. Subjects who experience a surgical adverse event, defined as ≤14 days post-implant, requiring investigator mandated antiplatelet therapy
2. Subjects who expire, are transplanted, or withdraw within 14 days of implant

Subjects will be withdrawn at the time of an outcome (i.e. transplant, explant, exchange or study withdrawal) or censored at the time of open label. Subjects will be analyzed according to the treatment arm assigned at randomization.

2.1.2 As Treated Population

All randomized subjects with the following exception:

1. Subjects who experience a surgical adverse event, defined as ≤14 days post-implant, requiring investigator mandated antiplatelet therapy.
2. Subjects who expire, are transplanted, or withdraw within 14 days of implant.

Subjects will only be withdrawn at the time of a patient outcome (i.e. transplant or study withdrawal). Non-surgically related hemocompatibility related adverse events will continue to be analyzed beyond the time of open label.

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 are censored prior to their 12 month visit that have not reported a non-surgical hemocompatibility related adverse event 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.

A subject will not be included in the primary endpoint analysis if:

- the subject expires during the 14 day blanking period
- the subject experiences a surgically related hemocompatibility related adverse event during the14 day blanking period.

2.3.1.1 Hypothesis

The primary endpoint hypothesis is formally expressed as:

H_0: $\pi_{placebo} \leq \pi_{aspirin} - \Delta$
H_a: $\pi_{placebo} > \pi_{aspirin} - \Delta$

where $\pi_{placebo}$ and $\pi_{aspirin}$ are the percentage of subjects who successfully achieve the composite endpoint in the placebo and aspirin groups and where Δ is the non-inferiority margin.

2.3.1.2 Sample Size

Results from the MOMENTUM 3 trial were used to derive a point estimate of 71% survival to 1 year free of any major hemocompatibility related adverse events in the aspirin treated arm. It is assumed that in the absence of aspirin a 2% improvement in the composite endpoint will be noted, mainly due to the reduction of bleeding complications without a change in thromboembolic complications. Based on these assumptions 220 patients will need to be randomized in each arm (440 total) to achieve 80% power to prove that the placebo group is non-inferior to the aspirin group using a non-inferiority margin of -10% with the Farrington-Manning risk difference approach at a one-sided alpha = 0.025. To account for an expected 30% dropout rate associated with events occurring 2-14 days post implant, up to 628 patients will be randomized in the trial. Sample size calculations were performed using PASS 15 software and are included in Appendix 1.

2.3.1.3 Analysis Methods

The primary endpoint composite success rate will be calculated for each treatment arm based on the number of subjects who successfully meet the primary endpoint divided by the total number of subjects in the primary endpoint analysis population (refer to section 2.1.1). The Farrington-Manning test for the difference of proportions will be performed at the 2.5% significance level. The null hypothesis will be rejected, and the placebo arm considered non-inferior to the aspirin arm, if the lower boundary of the one-sided 95% confidence limit of the difference in the composite success between treatment arms (Placebo-arm minus Aspirin-arm) is greater than the non-inferiority margin (-10%). If the lower 95% confidence limit is also greater than 0, then the placebo will be superior to the aspirin treatment. Superiority will also be confirmed at a 1-sided 0.025 level of significance using the z-test of proportions using the normal approximation to the binomial distribution.

As a sensitivity analysis, the components of the composite endpoint will be evaluated using a Finkelstein – Schoenfeld analysis (1). Components of the composite endpoint will be arranged in the following hierarchy:

1. Death
2. Stroke
3. Pump Thrombosis
4. Bleeding
5. Arterial Thrombosis

The treatment arm that experiences the endpoint later will be considered the winner.

2.3.1.4 Justification of the Non-Inferiority Margin

Given the sample size of 220 subjects per group and a NIM of -10%, the null hypothesis would not be rejected if placebo group minus the aspirin group is less than -1%. If 71% of the aspirin group successfully achieves the primary composite endpoint, then 153 of the 220 placebo subjects (70%) would need to be successful to demonstrate non-inferiority. This small difference between groups is clinically acceptable.

2.3.1.5 Poolability Analysis

2.3.1.5.1 Multiple Geography Effect

The trial will be conducted in up to 50 sites in the United States, Europe and Canada following the same investigational plan and inclusion and exclusion criteria. The trial will be conducted following the same procedures, monitoring plan and training plan in all regions. Poolability of the primary safety endpoint across region (i.e., US vs. OUS) will be evaluated for subjects included in the primary analysis population.

To evaluate the geography effect on the primary safety endpoint, Fisher's exact test will be tested for geography effect against an alpha level of 0.15. If the p-value is less than 0.15, Abbott will examine subject demographics, baseline clinical characteristics for possible correlations and confounding factors.

2.3.1.5.2 Multiple Center Effect

Analysis will be performed by pooling data across study sites. The trial will have up to 50 sites globally. Subject enrollment is capped at 96 per site (15% of the total number of enrollments assuming dropouts). This cap per site will prevent the scenario where the results from a few sites dominate the overall study result. For the analysis of center effect, data from smaller sites may be combined for the analysis.

Smaller sites are defined as sites with fewer than 20 subjects per site. The pooling of the smaller sites will be based on the following rules:

- Sort all smaller sites based on the number of subjects per site in an ascending order. If there are ties, sort further by site number.
- Starting from the smallest site in this list, combine sites by going up the list until the combined group size first reaches 20 or larger. At this point, a super site is identified.
- Repeat the above grouping process from the next smallest site above the newly formed super site.
- The grouping process ends when all smaller sites have been accounted for.

The sizes of the super sites (which are a result of grouping smaller sites) will range between 20 and up to 38 (19+19). This represents a reasonable range of sample sizes which will provide meaningful estimates of within-sites variations and will not alter between-sites variation.

To evaluate the multiple center effect on the primary safety endpoint, Fisher's exact test will be tested for center effect against an alpha level of 0.15.

2.3.1.6 Sensitivity Analysis

To demonstrate robustness with respect to missing data, a tipping point analysis will be performed for the primary composite endpoint. This will involve imputing all possible combinations of outcomes for the primary endpoint among subjects who terminate the study prematurely without experiencing any primary endpoint events.

2.3.1.7 Subgroup Analysis

A subgroup analysis will be performed to examine the consistency of results for the primary endpoint across specific populations. Analysis will be performed on the primary endpoint analysis population, using Fisher's exact test. No subgroup specific labeling claims are intended for the primary endpoint and no adjustment will be made for multiplicity. Subgroups to be examined include, but are not limited to, gender, age (stratified by median age), age (less than 65 years vs 65 and greater), INTERMACS Profile (INTERMACS 1-2 vs INTERMACS 3+) and surgical implant method.

2.3.2 Secondary Endpoint

Non-surgical bleeding rates will be compared between the two treatment groups using the Primary Endpoint Analysis population. All subjects enrolled and randomized will be included in the analysis according to their randomization assignment. All non-surgical bleeding events that occur will be captured. Subjects who terminate the study prematurely without experiencing any non-surgical bleeding will have the time they were in the study counted in the analysis. Subjects who have their treatment group unblinded (time of open label) will be censored at that time. All non-surgical 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..

The non-surgical bleeding rate (events per patient year) will be calculated by dividing the number of non-surgical bleeding events by the cumulative duration of study exposure (years of support). Non-surgical 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.

2.3.3 Safety Endpoints

The safety endpoints will be analyzed using the Primary Endpoint Analysis and As-Treated population.

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.

The stroke rate will also be analyzed as -treated. All stokes 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). 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. Analysis will be performed while on assigned treatment and as-treated.

Pump Thrombosis: The pump thrombosis rate will be calculated based on the number of suspected 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.

The pump thrombosis rate will also be analyzed as-treated. 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.

Survival: The 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. Survival will be analyzed using the Primary Endpoint Analysis and As-Treated populations.

2.3.4 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 (2,3). The HCS will be calculated for each subject in the primary endpoint analysis 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, for any cause, after randomization and initiation of the study treatment (14 or more days post implant), divided by the number of subjects in the primary endpoint analysis population. The number of rehospitalizations per treatment arm will also be presented as rehospitalizations per patient year of support using the As-Treated population. 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 . .

2.4 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 482 subjects have data available to assess the primary endpoint.

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

As described in Section 2.3.1.6, a sensitivity analysis will be performed to determine the effect on the primary endpoint of missing data. For subjects in the primary endpoint analysis population, the data points are unambiguous and missing data is not anticipated.

2.8 Multiplicity Issues

This study includes a single primary endpoint and a non-powered secondary endpoint. Safety and descriptive endpoints are not intended to support labeling claims. Thus, multiplicity adjustment is not applicable

3.0 ADDITIONAL DATA

3.1 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.

3.2 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. The data will be presented as the number and percentage of subjects 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 and relationship to the HeartMate 3.

3.3 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.

3.4 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.

3.5 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.

3.6 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.

4.0 DOCUMENTATION AND OHER CONSIDERATIONS

All analyses will be performed using SAS® for Windows, version 9.4 or higher.

5.0 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
NIM	Non-Inferiority Margin
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

6.0 REFERENCES

1. Finkelstein DM, Schoenfeld DA. Combining mortality and longitudinal measures in clinical trials. *STAT MED*. 1999; 18:1341-1354.

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

3.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.

7.0 APPENDICES

APPENDIX A: POWER AND SAMPLE SIZE CALCULATIONS

Non-Inferiority Tests for the Difference Between Two Proportions

Numeric Results for Non-Inferiority Tests for the Difference Between Two Proportions
Test Statistic: Farrington & Manning Likelihood Score Test
H0: P1 - P2 ≤ D0 vs. H1: P1 - P2 = D1 > D0.

Target Power	Actual Power*	N1	N2	N	Ref. P2	P1|H0 P1.0	P1|H1 P1.1	NI Diff D0	Diff D1	Alpha
0.80	0.80013	220	220	440	0.7100	0.6100	0.7300	-0.1000	0.0200	0.025

* Power was computed using the normal approximation method.

Statistical Analysis Plan

CRD_971

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

John Henderson

Statistical Analysis Plan

TABLE OF CONTENTS

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. Subjects will be randomized in a 1:1 ratio.

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

Only subjects who have provided informed consent, been implanted with the HM3 and subsequently met all inclusion and no exclusion criteria will be randomized. Randomization will be performed through ALMAC Clinical's WebEZ system. Subjects will be randomized in a 1:1 ratio between the placebo and aspirin group. Randomization will be stratified by study center and assigned using a block size of 4 subjects. Prior to randomizing a patient in WebEZ, patients will have been initialized in the Sponsor's EDC portal upon enrollment and obtained a subject ID number, which will also be used as the patient identifier in the WebEZ system. Subjects should begin taking the treatment arm medication within 24 hours of randomization.

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.

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.

2.1.1 Modified Intent to Treat Population (mITT)

The mITT population will include all randomized subjects with the following exception:

1. Subjects who experience a surgical adverse event, defined as ≤14 days post-implant, requiring investigator mandated antiplatelet therapy
2. Subjects who expire, are transplanted, or withdraw within 14 days of implant

Non-surgically related major hemocompatibility related adverse events will only be analyzed up to the transition to open label. Subjects will be analyzed according to the treatment arm assigned at randomization. The mITT population will be used for all analyses unless noted differently in one sensitivity analysis.

2.1.2 Intent to Treat (ITT) Population

The ITT population will consist of all subjects randomized. Subjects will be analyzed according to the treatment arm assigned at randomization. The ITT population will only be used for one sensitivity analysis of the primary endpoint.

2.1.3 Per Protocol (PP) Population

The Per-Protocol (PP) population will consist of all randomized subjects within the mITT population excluding:

- Subjects with protocol deviations for the following:
  - Randomized subjects who do not meet eligibility requirements
  - Unblinding of subject or investigator prior to completion of study including possible unblinding by platelet function testing
  - Withdrawal of the treatment arm antithrombotic regimen without clinical reason
  - Additional antiplatelet medications added to the treatment arm antithrombotic regimen
- Subjects who transition to open label without experiencing any primary endpoint events
- Subjects who terminate the study prematurely without experiencing any primary endpoint events prior to 12 month visit

The PP population will only be used for one sensitivity analysis of the primary endpoint.

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.

2.3.1.1 Hypothesis

The primary endpoint hypothesis is formally expressed as:

H_0: $\pi_{placebo} \leq \pi_{aspirin} - \Delta$
H_a: $\pi_{placebo} > \pi_{aspirin} - \Delta$

where $\pi_{placebo}$ and $\pi_{aspirin}$ are the percentage of subjects who successfully achieve the composite endpoint in the placebo and aspirin groups and where Δ is the non-inferiority margin (NIM) fixed at 10%.

2.3.1.2 Sample Size

Results from the MOMENTUM 3 trial were used to derive a point estimate of 71% survival to 1 year free of any major hemocompatibility related adverse events in the aspirin treated arm. It is assumed that in the absence of aspirin a 2% improvement in the composite endpoint will be noted, mainly due to the reduction of bleeding complications without a change in thromboembolic complications. Based on these assumptions 220 patients will need to be randomized in each arm (440 total) to achieve 80% power to prove that the placebo group is non-inferior to the aspirin group using a non-inferiority margin of 10% with the Farrington-Manning risk difference approach at a one-sided alpha = 0.025. To account for an expected 30% dropout rate associated with events occurring 2-14 days post implant, up to 628 patients will be randomized in the trial. Sample size calculations were performed using PASS 15 software and are included in Appendix 1.

2.3.1.3 Analysis Methods

The primary endpoint composite success rate will be calculated for each treatment arm based on the number of subjects who successfully meet the primary endpoint divided by the total number of subjects in the mITT population (refer to section 2.1.1). Subjects who terminate the study prematurely (e.g. lost to follow-up or withdrawn) without experiencing any primary endpoint events prior to 12 month visit will be excluded in the denominator for the calculation of the composite success rate. The Farrington-Manning test for the difference of proportions will be performed at the 2.5% significance level. The null hypothesis will be rejected, and the placebo arm considered non-inferior to the aspirin arm, if the lower boundary of the one-sided 97.5% confidence limit of the difference in the composite success between treatment arms (Placebo-arm minus Aspirin-arm) is greater than the non-inferiority margin (10%)

2.3.1.4 Justification of the Non-Inferiority Margin

Given the sample size of 220 subjects per group and a NIM of 10%, the null hypothesis would not be rejected if placebo group minus the aspirin group is less than -1%. If 71% of the aspirin group successfully achieves the primary composite endpoint, then 153 or more patients out of the 220 placebo subjects (70%) would need to be successful to demonstrate non-inferiority.

The steering committee ruled that a small increase of 1% in the primary composite endpoint will not be a clinically meaningful difference and should be acceptable for non-inferiority, with no overriding safety concern noted within the individual safety endpoints. The individual components of the primary endpoint are evaluated independently as safety endpoints, therefore any deleterious effects of aspirin removal on individual outcomes will be reported separately.

2.3.1.5 Poolability Analysis

2.3.1.5.1 Multiple Geography Effect

The trial will be conducted in up to 50 sites worldwide including, but not limited to, the United States, Europe and Canada following the same investigational plan and inclusion and exclusion criteria. The trial will be conducted following the same procedures, monitoring plan and training plan in all regions. Poolability of the primary endpoint across region (i.e., US vs. OUS) will be evaluated for subjects included in the mITT population.

To evaluate the geography effect on the primary endpoint, Fisher's exact test will be tested for geography effect against an alpha level of 0.15. If the p-value is less than 0.15, Abbott will examine

subject demographics, baseline clinical characteristics will be examined, and outlier or influential sites will be identified.

2.3.1.5.2 Multiple Center Effect

Analysis will be performed by pooling data across study sites. The trial will have up to 50 sites globally. Subject randomization is capped at 94 per site (15% of the total number of randomized subjects assuming dropouts). This cap per site will prevent the scenario where the results from a few sites dominate the overall study result. For the analysis of center effect, data from smaller sites may be combined for the analysis. Smaller sites are defined as sites with fewer than 20 subjects per site. The pooling of the smaller sites will be based on the following rules:

- Sort all smaller sites based on the number of subjects per site in an ascending order. If there are ties, sort further by site number.
- Starting from the smallest site in this list, combine sites by going up the list until the combined group size first reaches 20 or larger. At this point, a super site is identified.
- Repeat the above grouping process from the next smallest site above the newly formed super site.
- The grouping process ends when all smaller sites have been accounted for.

The sizes of the super sites (which are a result of grouping smaller sites) will range between 20 and up to 38 (19+19). This represents a reasonable range of sample sizes which will provide meaningful estimates of within-sites variations and will not alter between-sites variation.

To evaluate the multiple center effect on the primary endpoint, Cochran-Mantel-Haenszel will be tested for center effect against an alpha level of 0.15. If the p-value is less than 0.15, subject demographics, baseline clinical characteristics will be examined, and outlier or influential sites will be identified.

2.3.1.6 Sensitivity Analysis

The following sensitivity analyses of the primary endpoint will be performed in the mITT population:

1. To demonstrate robustness with respect to missing data, a tipping point analysis will be performed for the primary composite endpoint. This will involve imputing all possible combinations of outcomes for the primary endpoint among subjects who terminate the study prematurely without experiencing any primary endpoint events.

2. In order to assess if the adequacy of anticoagulation or compliance with prescribed anticoagulation is confounding the primary endpoint result, the time in therapeutic (TTR) range will be assessed using the Rosendaal method. Time in therapeutic range will be compared between treatment groups using a Wilcoxon rank sum test. If it is determined there is a difference in TTR between treatment groups, a sensitivity analysis of the primary endpoint will be performed by stratifying the subjects by TTR. Poor anticoagulation control will be defined as a TTR less than 65%. Stratification will include subjects with TTR < 65% vs subjects with TTR ≥ 65%.

3. Sensitivity analysis of the primary endpoint will also be performed based on the time to the first primary endpoint event using the Kaplan-Meier product-limit method. Treatment arms will be tested for non-inferiority with a NIM = 10% using Com-Nougue method [3].

4. To assess the impact of transition to open label, a sensitivity analysis will be performed to include non-surgical major hemocompatibility related adverse events beyond the time of transition to open label.

The following sensitivity analysis will be performed on the ITT and PP populations:

5. The primary endpoint will be analyzed based on the time to the first primary endpoint event using the Kaplan-Meier product-limit method. Treatment arms will be tested for non-inferiority with a NIM = 10% using Com-Nougue method.

2.3.1.7 Subgroup Analysis

Subgroup analyses will be performed to examine the consistency of results for the primary endpoint across specific populations. Subgroup analyses will be performed on mITT population, using Fisher's exact test. No subgroup specific labeling claims are intended for the primary endpoint and no adjustment will be made for multiplicity. Subgroups to be examined include, but are not limited to, gender, race, age (stratified by median age), age (less than 65 years vs 65 and greater), INTERMACS Profile (INTERMACS 1-2 vs INTERMACS 3+), TTR and surgical implant method. If home monitoring of anticoagulation is used in some site but not others, a subgroup analysis based on home monitoring will be conducted.

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.

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

As described in Section 2.3.1.6, a tipping point analysis will be performed to evaluate the impact of missing data on the primary endpoint analysis result in mITT population.

Any unused or spurious data will be noted as appropriate in the final report.

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.

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

All analyses will be performed using SAS® for Windows, version 9.4 or higher.

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

APPENDIX A: POWER AND SAMPLE SIZE CALCULATIONS

Non-Inferiority Tests for the Difference Between Two Proportions

Numeric Results for Non-Inferiority Tests for the Difference Between Two Proportions
Test Statistic: Farrington & Manning Likelihood Score Test
H0: P1 - P2 ≤ D0 vs. H1: P1 - P2 = D1 > D0.

Target Power	Actual Power*	N1	N2	N	Ref. P2	P1|H0 P1.0	P1|H1 P1.1	NI Diff D0	Diff D1	Alpha
0.80	0.80013	220	220	440	0.7100	0.6100	0.7300	-0.1000	0.0200	0.025

* Power was computed using the normal approximation method.

Statistical Analysis Plan

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.

Statistical Analysis Plan

This change table chronicles major updates to the Statistical Analysis Plan and does not include minor clarifications and adjustments to vocabulary and grammar.

Current Version	No.	SAP Section (Redline Version Page number)	Previous Version Content	Current Version Content	Comments/Rationales about the change
B	1.	§1.4.2 (Page 5)	1.4.2 Secondary Endpoint(s) As a secondary endpoint, non-surgical bleeding rates will be compared between the two arms of the study. 1.4.3 Safety Endpoint(s) To assess the safety of removal of antiplatelets from the antithrombotic regimen, survival, stroke rates, and pump thrombosis rates will be compared between the two arms of the study.	1.4.2 Secondary Endpoints 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.	In response to FDA Design Consideration 1, the specific components of the composite primary endpoint are now analyzed as separate secondary endpoints, merging the secondary endpoints and safety endpoints sections.
	2.	§1.6 (Page 5)	This is a double-blind study, neither patient nor investigator will know the subject's randomization throughout the study follow up. Additionally, sponsor personnel (with exceptions noted in the study blinding plan), the CEC, and the DSMB 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, all data have been received, and all adverse events have been adjudicated. Questions related to unblinding should be directed to the Sponsor.	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.	The DSMB requested access to unblinded data for safety oversight. Refer to CIP Change Rationale (Table 1, No.4) for additional details.
	3.	§2.1.1 (Page 6)	Subjects will be withdrawn at the time of an outcome (i.e. transplant, explant, exchange or study withdrawal) or censored at the time of open label. Subjects will be analyzed according to the treatment arm assigned at randomization.	Subjects will be withdrawn at the time of an outcome (i.e. transplant, explant, exchange or study withdrawal). Non-surgically related major hemocompatibility related adverse events will only be analyzed up to the transition to open label. Subjects will be analyzed according to the treatment arm assigned at randomization.	In response to FDA Design Consideration 9, updated to state the follow-up periods included in the analysis.
	4.	§2.1.2 (Page 6)	2.1.2 As Treated Population	2.1.2 Intent to Treat (ITT) Population	This analysis population includes the same subjects analyzed as the Primary Endpoint population but will included follow-up and hemocompatibility related adverse events beyond transition to open label. This population more closely meets the definition of Intent to Treat rather than As Treated.
	5.	§2.3.1 (Page 7)	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 are censored prior to their 12 month visit that have not reported a non-surgical hemocompatibility related adverse event will also be considered a success.	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. lost-to-follow up, transitioned to open label, transplanted, or withdrawn) 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.	In response to FDA Design Consideration 11, the definition for primary endpoint success has been clarified.

Statistical Analysis Plan

Current Version	No.	SAP Section (Redline Version Page number)	Previous Version Content	Current Version Content	Comments/Rationales about the change
	6.	§2.3.1.1 (Page 7)	The primary endpoint hypothesis is formally expressed as: H_0: $\pi_{placebo} \leq \pi_{aspirin} - \Delta$ H_a: $\pi_{placebo} > \pi_{aspirin} - \Delta$ where $\pi_{placebo}$ and $\pi_{aspirin}$ are the percentage of subjects who successfully achieve the composite endpoint in the placebo and aspirin groups and where Δ is the non-inferiority margin.	The primary endpoint hypothesis is formally expressed as: H_0: $\pi_{placebo} \leq \pi_{aspirin} - \Delta$ H_a: $\pi_{placebo} > \pi_{aspirin} - \Delta$ where $\pi_{placebo}$ and $\pi_{aspirin}$ are the percentage of subjects who successfully achieve the composite endpoint in the placebo and aspirin groups and where Δ is the non-inferiority margin (NIM) fixed at 10%.	In response to FDA Design Consideration 13, the hypothesis statement was updated to clearly define the non-inferiority margin.
	7.	§2.3.1.3 (Page 8)	If the lower 95% confidence limit is also greater than 0, then the placebo will be superior to the aspirin treatment. Superiority will also be confirmed at a 1-sided 0.025 level of significance using the z-test of proportions using the normal approximation to the binomial distribution. As a sensitivity analysis, the components of the composite endpoint will be evaluated using a Finkelstein – Schoenfeld analysis (1). Components of the composite endpoint will be arranged in the following hierarchy: 1. Death 2. Stroke 3. Pump Thrombosis 4. Bleeding 5. Arterial Thrombosis The treatment arm that experiences the endpoint later will be considered the winner.	[Removed]	In response to FDA Design Consideration 1, additional simulations of the primary endpoint superiority were performed. After performing simulations, it was decided not to pursue superiority analysis of the primary endpoint as well as the sensitivity analysis using F-S method. The assumptions required for a reasonable power to assess superiority were not appropriate for this patient population.
	8.	§2.3.1.4 (Page 8)	This small difference between groups is clinically acceptable.	The steering committee ruled that a small increase of 1% in the primary composite endpoint will not be a clinically meaningful difference and should be acceptable for non-inferiority, with no overriding safety concern noted within the individual safety endpoints. The individual components of the primary endpoint are evaluated independently as safety endpoints, therefore any deleterious effects of aspirin removal on individual outcomes will be reported separately.	In response to FDA Design Consideration 3, further clinical justification of the non-inferiority margin has been added.
	9.	§2.3.1.5.2 (Page 9)	To evaluate the multiple center effect on the primary safety endpoint, Fisher's exact test will be tested for center effect against an alpha level of 0.15.	To evaluate the multiple center effect on the primary endpoint, Cochran-Mantel-Haenszel will be tested for center effect against an alpha level of 0.15. If the p-value is less than 0.15, subject demographics, baseline clinical characteristics will be examined, and outlier or influential sites will be identified.	The analysis test was changed to properly test for outcome differences across multiple strata.

Statistical Analysis Plan

Current Version	No.	SAP Section (Redline Version Page number)	Previous Version Content	Current Version Content	Comments/Rationales about the change
		§2.3.1.6 (Page 9)	[No Current Text]	In order to assess if the adequacy of anticoagulation or compliance with prescribed anticoagulation is confounding the primary endpoint result, the time in therapeutic (TTR) range will be assessed using the Rosendaal method. Time in therapeutic range will be compared between treatment groups using a Wilcoxon rank sum test. If it is determined there is a difference in TTR between treatment groups, a sensitivity analysis of the primary endpoint will be performed by stratifying the subjects by TTR. Poor anticoagulation control will be defined as a TTR less than 65%. Stratification will include subjects with TTR < 65% vs subjects with TTR ≥ 65%. Sensitivity analysis of the primary endpoint will also be performed based on the time to the first primary endpoint event using the Kaplan-Meier product-limit method. Treatment arms will be tested for non-inferiority with a NIM = 10% using Com-Nougue method[3].	In consideration to FDA Design Consideration 4, an analysis of the effect of anticoagulation on the primary endpoint was added. Additionally, another sensitivity of the primary endpoint based on time to first event survival analysis was added to explore robustness of the analysis of the primary endpoint.
	10.	§2.3.1.7 (Page 10)	A subgroup analysis will be performed to examine the consistency of results for the primary endpoint across specific populations. Analysis will be performed on the primary endpoint analysis population, using Fisher's exact test. No subgroup specific labeling claims are intended for the primary endpoint and no adjustment will be made for multiplicity. Subgroups to be examined include, but are not limited to, gender, age (stratified by median age), age (less than 65 years vs 65 and greater), INTERMACS Profile (INTERMACS 1-2 vs INTERMACS 3+) and surgical implant method.	Subgroup analyses will be performed to examine the consistency of results for the primary endpoint across specific populations. Subgroup analyses will be performed on the primary endpoint analysis population, using Fisher's exact test. No subgroup specific labeling claims are intended for the primary endpoint and no adjustment will be made for multiplicity. Subgroups to be examined include, but are not limited to, gender, race, age (stratified by median age), age (less than 65 years vs 65 and greater), INTERMACS Profile (INTERMACS 1-2 vs INTERMACS 3+), TTR and surgical implant method. If home monitoring of anticoagulation is used in some site but not others, a subgroup analysis based on home monitoring will be conducted.	In response to FDA Design Considerations 4 and 14, additional subgroup analyses were added.
	11.	§2.3.2 (Pages 10-11)	2.3.2 Secondary Endpoint Non-surgical bleeding rates will be compared between the two treatment groups using the Primary Endpoint Analysis population. All subjects enrolled and randomized will be included in the analysis according to their randomization assignment. All non-surgical bleeding events that occur will be captured. Subjects who terminate the study prematurely without experiencing any non-surgical bleeding will have the time they were in the study counted in the analysis. Subjects who have their treatment group unblinded (time of open label) will be censored at that time. All non-surgical bleeding events will be included while the subject remains on their randomization assignment until the last	2.3.2 Secondary Endpoints The secondary endpoints will be analyzed using the Primary Endpoint Analysis and ITT populations. 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-	In response to FDA Design Consideration 1, secondary endpoints are now grouped from former secondary and safety endpoints under the same heading and will analyze the components of the primary endpoint individually including distinct hemorrhagic and thrombotic outcomes.

Statistical Analysis Plan

Current Version	No.	SAP Section (Redline Version Page number)	Previous Version Content	Current Version Content	Comments/Rationales about the change
			randomized patient has been followed to one year. This will result in some subjects being followed for more than one year. The non-surgical bleeding rate (events per patient year) will be calculated by dividing the number of non-surgical bleeding events by the cumulative duration of study exposure (years of support). Non-surgical 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. 2.3.3 Safety Endpoints The safety endpoints will be analyzed using the Primary Endpoint Analysis and As-Treated population. 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. The stroke rate will also be analyzed as -treated. All stokes 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). 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. Analysis will be performed while on assigned treatment and as-treated. Pump Thrombosis: The pump thrombosis rate will be calculated based on the number of suspected 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. The pump thrombosis rate will also be analyzed as-treated. All suspected pump thrombosis that occurs 14 or more days post	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. Survival will be analyzed using the Primary Endpoint Analysis and ITT populations. 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. The stroke rate will also be analyzed using the ITT population. 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. 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. The pump thrombosis rate will also be analyzed for the ITT population. 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	

Statistical Analysis Plan

Current Version	No.	SAP Section (Redline Version Page number)	Previous Version Content	Current Version Content	Comments/Rationales about the change
			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. Survival: The 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. Survival will be analyzed using the Primary Endpoint Analysis and As-Treated populations.	treatment will continue to be followed). The pump thrombosis rate and treatment comparison will be performed as described above. Bleeding: All subjects enrolled and randomized will be included in the analysis according to their randomization assignment. 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 primary endpoint analysis 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. For the ITT populations all bleeding events will be included through one year, including repeat bleeding events. 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.	
	12.	§2.3.3 (Page 11-12)	Rehospitalizations: The rehospitalization rate will be calculated based on the number of subjects who require a rehospitalization, for any cause, after randomization and initiation of the study treatment (14 or more days post implant), divided by the number of subjects in the primary endpoint analysis population. The number of rehospitalizations per treatment arm will also be presented as rehospitalizations per patient year of support using the As-Treated population. 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.	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.	Rehospitalizations will be analyzed with both the primary endpoint population and the ITT population.
	13.	§2.5 (Page 12)	The primary endpoint analysis will be performed, and the clinical report prepared when 482 subjects have data available to assess the primary endpoint.	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.	Updated to more clearly define the timing of the primary endpoint analysis.

Statistical Analysis Plan

Current Version	No.	SAP Section (Redline Version Page number)	Previous Version Content	Current Version Content	Comments/Rationales about the change
	14.	§2.7 (Page 12)	As described in Section 2.3.1.6, a sensitivity analysis will be performed to determine the effect on the primary endpoint of missing data. For subjects in the primary endpoint analysis population, the data points are unambiguous and missing data is not anticipated.	As described in Section 2.3.1.6, a tipping point analysis will be performed to evaluate the impact of missing data on the primary endpoint analysis result All other 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.	Updated to more clearly define which analyses will be evaluated for the impact of missing data.
	15.	§2.8 (Page 12)	This study includes a single primary endpoint and a non-powered secondary endpoint. Safety and descriptive endpoints are not intended to support labeling claims. Thus, multiplicity adjustment is not applicable.	This study includes a single primary endpoint. Thus, no Type I error adjustment is necessary.	Clarifies analysis multiplicity
	16.	§2.10 (Pages 12-13)	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. The data will be presented as the number and percentage of subjects 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 and relationship to the HeartMate 3.	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.	In response to FDA Design Consideration 5, clarifying how safety data for consented, non-randomized subjects will be summarized.
	17.	§2.13 (Page 13)	[No Current Text]	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.	This additional analysis was requested by the ARIES HM3 steering committee to examine any effects of pre-implant aspirin use.
	18.	APPENDIX B (Page 16)	[No Current Text]	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	This appendix is added in order to recognize the addition of a substudy to which the analysis details will be provided at a later date.

Statistical Analysis Plan

Current Version	No.	SAP Section (Redline Version Page number)	Previous Version Content	Current Version Content	Comments/Rationales about the change
				HeartMate 3 inflow cannula position. Validation will be performed by assessing: 1. The safety and feasibility of placing and visualizing the radiopaque marker; 2. The variation in cannula angulation relative to the radiopaque marker and cannula positional changes over time; 3. The relationship between the initial cannula angulation or its change over time with adverse clinical outcomes and functional capacity, as an exploratory analysis. The study is more fully described in Appendix VI of Version B of the ARIES HM3 CIP. Details of the substudy analysis plan will be provided in a future version of the SAP.	
C	1.	§2.1.1 (Page 7)	2.1.1 Primary Endpoint Analysis Population: The primary endpoint analysis population will include all randomized subjects with the following exception: 1. Subjects who experience a surgical adverse event, defined as ≤14 days post-implant, requiring investigator mandated antiplatelet therapy 2. Subjects who expire, are transplanted, or withdraw within 14 days of implant Subjects will be withdrawn at the time of an outcome (i.e. transplant, explant, exchange or study withdrawal). Non-surgically related major hemocompatibility related adverse events will only be analyzed up to the transition to open label. Subjects will be analyzed according to the treatment arm assigned at randomization.	2.1.1 Modified Intent to Treat Population (mITT) The mITT population will include all randomized subjects with the following exception: 1. Subjects who experience a surgical adverse event, defined as ≤14 days post-implant, requiring investigator mandated antiplatelet therapy 2. Subjects who expire, are transplanted, or withdraw within 14 days of implant Non-surgically related major hemocompatibility related adverse events will only be analyzed up to the transition to open label. Subjects will be analyzed according to the treatment arm assigned at randomization. The mITT population will be used for all analyses unless noted differently in one sensitivity analysis.	In response to FDA request to clarify the definitions of the study populations
	2.	§2.1.2 (Page 7)	All randomized subjects with the following exception: 1. Subjects who experience a surgical adverse event, defined as ≤14 days post-implant, requiring investigator mandated antiplatelet therapy. 2. Subjects who expire, are transplanted, or withdraw within 14 days of implant.	The ITT population will consist of all subjects randomized. Subjects will be analyzed according to the treatment arm assigned at randomization. The ITT population will only be used for one sensitivity analysis of the primary endpoint.	In response to FDA request to define ITT as all randomized subjects with no exclusions.

Statistical Analysis Plan

Current Version	No.	SAP Section (Redline Version Page number)	Previous Version Content	Current Version Content	Comments/Rationales about the change
			Subjects will only be withdrawn at the time of a patient outcome (i.e. transplant, explant, exchange or study withdrawal). Non-surgically related hemocompatibility related adverse events will continue to be analyzed beyond the time of open label.		
	3.	§2.3.1 (Page 8)	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. lost-to-follow up, transitioned to open label, transplanted, or withdrawn) 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. A subject will not be included in the primary endpoint analysis if: • the subject expires during the 14 day blanking period • the subject experiences a surgically related hemocompatibility related adverse event during the14 day blanking period.	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	In response to FDA request to remove subjects who are lost to follow-up, transition to open label or withdraw prior to 12 months visit that have not reported a non-surgical hemocompatibility related adverse event from the definition of success. Also adjusted wording to agree with new population definitions.

Statistical Analysis Plan

Current Version	No.	SAP Section (Redline Version Page number)	Previous Version Content	Current Version Content	Comments/Rationales about the change
	4.	§2.3.1.3 (Page 9)	The primary endpoint composite success rate will be calculated for each treatment arm based on the number of subjects who successfully meet the primary endpoint divided by the total number of subjects in the primary endpoint analysis population (refer to section 2.1.1). The Farrington-Manning test for the difference of proportions will be performed at the 2.5% significance level. The null hypothesis will be rejected, and the placebo arm considered non-inferior to the aspirin arm, if the lower boundary of the one-sided 97.5% confidence limit of the difference in the composite success between treatment arms (Placebo-arm minus Aspirin-arm) is greater than the non-inferiority margin (10%).	The primary endpoint composite success rate will be calculated for each treatment arm based on the number of subjects who successfully meet the primary endpoint divided by the total number of subjects in the mITT population (refer to section 2.1.1). Subjects who terminate the study prematurely (e.g. lost to follow-up or withdrawn) without experiencing any primary endpoint events prior to 12 month visit will be excluded in in the denominator for the calculation of the composite success rate. The Farrington-Manning test for the difference of proportions will be performed at the 2.5% significance level. The null hypothesis will be rejected, and the placebo arm considered non-inferior to the aspirin arm, if the lower boundary of the one-sided 97.5% confidence limit of the difference in the composite success between treatment arms (Placebo-arm minus Aspirin-arm) is greater than the non-inferiority margin (10%).	Section changed to reflect how the patients who terminate the study prematurely without experiencing a primary endpoint event will be addressed in the primary endpoint analysis.
	5.	§2.3.1.6 (Page 10)	To demonstrate robustness with respect to missing data, a tipping point analysis will be performed for the primary composite endpoint. This will involve imputing all possible combinations of outcomes for the primary endpoint among subjects who terminate the study prematurely without experiencing any primary endpoint events. In order to assess if the adequacy of anticoagulation or compliance with prescribed anticoagulation is confounding the primary endpoint result, the time in therapeutic (TTR) range will be assessed using the Rosendaal method. Time in therapeutic range will be compared between treatment groups using a Wilcoxon rank sum test. If it is determined there is a difference in TTR between treatment groups, a sensitivity analysis of the primary endpoint will be performed by stratifying the subjects by TTR. Poor anticoagulation control will be defined as a TTR less than 65%. Stratification will include subjects with TTR < 65% vs subjects with TTR ≥ 65%. Sensitivity analysis of the primary endpoint will also be performed based on the time to the first primary endpoint event using the Kaplan-Meier product-limit method. Treatment arms will be tested for non-inferiority with a NIM = 10% using Com-Nougue method [3].	The following sensitivity analyses of the primary endpoint will be performed in the mITT population: 1. To demonstrate robustness with respect to missing data, a tipping point analysis will be performed for the primary composite endpoint. This will involve imputing all possible combinations of outcomes for the primary endpoint among subjects who terminate the study prematurely without experiencing any primary endpoint events. 2. In order to assess if the adequacy of anticoagulation or compliance with prescribed anticoagulation is confounding the primary endpoint result, the time in therapeutic (TTR) range will be assessed using the Rosendaal method. Time in therapeutic range will be compared between treatment groups using a Wilcoxon rank sum test. If it is determined there is a difference in TTR between treatment groups, a sensitivity analysis of the primary endpoint will be performed by stratifying the subjects by TTR. Poor anticoagulation control will be defined as a TTR less than 65%. Stratification will include subjects with TTR < 65% vs subjects with TTR ≥ 65%.	Sensitivity analysis was reorganized to clarify the population to be used and the analyses proposed. The ITT sensitivity was changed to a Kaplan-Meier analysis to account for patients who leave study prematurely.

Statistical Analysis Plan

Current Version	No.	SAP Section (Redline Version Page number)	Previous Version Content	Current Version Content	Comments/Rationales about the change
				3. Sensitivity analysis of the primary endpoint will also be performed based on the time to the first primary endpoint event using the Kaplan-Meier product-limit method. Treatment arms will be tested for non-inferiority with a NIM = 10% using Com-Nougue method [3]. 4. To assess the impact of transition to open label, a sensitivity analysis will be performed to include non-surgical major hemocompatibility related adverse events beyond the time of transition to open label. The following sensitivity analysis will be performed on the ITT population: 5. The primary endpoint will be analyzed based on the time to the first primary endpoint event using the Kaplan-Meier product-limit method in ITT population. Treatment arms will be tested for non-inferiority with a NIM = 10% using Com-Nougue method. Subjects who experience a surgical adverse event requiring investigator mandated antiplatelet therapy, transplanted, or withdraw within 14 days of implant, withdraw or are lost-to-follow-up without experiencing an endpoint event prior to 12 month visit will be censored on the date of withdrawal/loss-to-follow-up.	
	6.	§2.3.2 (Page 11)		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.	Sentence added to include secondary endpoint analyses beyond transition to open label in mITT population.
	7.	§2.7 (Page 12)	As described in Section 2.3.1.6, a tipping point analysis will be performed to evaluate the impact of missing data on the primary endpoint analysis result All other 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.	As described in Section 2.3.1.6, a tipping point analysis will be performed to evaluate the impact of missing data on the primary endpoint analysis result in mITT population. Any unused or spurious data will be noted as appropriate in the final report.	Sensitivity analyses and some secondary analyses include observations with missing data.
D	1.	§2.1.3 (Page 6)		2.1.3 Per Protocol (PP) Population The Per-Protocol (PP) population will consist of all randomized subjects within the mITT population excluding: • Subjects with protocol deviations for the following:	Added Per Protocol population in order to account for subjects with specific protocol deviations and those terminating the study early with no endpoint events.

Statistical Analysis Plan

Current Version	No.	SAP Section (Redline Version Page number)	Previous Version Content	Current Version Content	Comments/Rationales about the change
				o Randomized subjects who do not meet eligibility requirements o Unblinding of subject or investigator prior to completion of study including possible unblinding by platelet function testing o Withdrawal of the treatment arm antithrombotic regimen without clinical reason o Additional antiplatelet medications added to the treatment arm antithrombotic regimen • Subjects who transition to open label without experiencing any primary endpoint events • Subjects who terminate the study prematurely without experiencing any primary endpoint events prior to 12 month visit The PP population will only be used for one sensitivity analysis of the primary endpoint.	
	2.	§2.3.1.6 (Page 10)	The following sensitivity analysis will be performed on the ITT population: 5. The primary endpoint will be analyzed based on the time to the first primary endpoint event using the Kaplan-Meier product-limit method in ITT population. Treatment arms will be tested for non-inferiority with a NIM = 10% using Com-Nougue method.	The following sensitivity analysis will be performed on the ITT and PP populations: 5. The primary endpoint will be analyzed based on the time to the first primary endpoint event using the Kaplan-Meier product-limit method. Treatment arms will be tested for non-inferiority with a NIM = 10% using Com-Nougue method.	Added Per Protocol Population to sensitivity analysis using Kaplan-Meier method.
E	1.	§2.3.1.3 (Page 8)	Subjects who terminate the study prematurely (e.g. lost to follow-up or withdrawn) without experiencing any primary endpoint events prior to 12 month visit will be excluded in in the denominator for the calculation of the composite success rate.	Subjects who terminate the study prematurely (e.g. lost to follow-up or withdrawn) or transition to open label without experiencing any primary endpoint events prior to 12 month visit will be excluded in the denominator for the calculation of the composite success rate.	Directly stating subjects transitioning to open label without prior endpoint event will be removed from the primary endpoint analysis denominator.
	2.	§2.3.1.5.2 (Page 9)	Analysis will be performed by pooling data across study sites. The trial will have up to 50 sites globally. Subject enrollment is capped at 96 per site (15% of the total number of enrollments assuming dropouts).	Analysis will be performed by pooling data across study sites. The trial will have up to 50 sites globally. Subject randomization is capped at 94 per site (15% of the total number of randomized subjects assuming dropouts).	Updated language to align with CIP.
	3.	§2.3.4 (Page 11 & 12)		2.1.2 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	Added a new section of COVID-19 Sensitivity Analyses as determined by the steering committee.

Statistical Analysis Plan

Current Version	No.	SAP Section (Redline Version Page number)	Previous Version Content	Current Version Content	Comments/Rationales about the change
				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.	
	4.	APPENDIX B (Page 17 & 18)	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. Validation will be performed by assessing: 1. The safety and feasibility of placing and visualizing the radiopaque marker; 2. The variation in cannula angulation relative to the radiopaque marker and cannula positional changes over time; 3. The relationship between the initial cannula angulation or its change over time with adverse clinical outcomes and functional capacity, as an exploratory analysis.	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	Added analysis method details to the substudy description.

Statistical Analysis Plan

Current Version	No.	SAP Section (Redline Version Page number)	Previous Version Content	Current Version Content	Comments/Rationales about the change

			The study is more fully described in Appendix VI of Version B of the ARIES HM3 CIP. Details of the substudy analysis plan will be provided in a future version of the SAP.	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	

Statistical Analysis Plan

Current Version	No.	SAP Section (Redline Version Page number)	Previous Version Content	Current Version Content	Comments/Rationales about the change
				• 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.	
F	1.	§2.3.1.3 (Page 8)	Subjects who terminate the study prematurely (e.g. lost to follow-up or withdrawn) or transition to open label without experiencing any primary endpoint events prior to 12 month visit will be excluded in the denominator for the calculation of the composite success rate.	Subjects who terminate the study prematurely (e.g. lost to follow-up or withdrawn) without experiencing any primary endpoint events prior to 12 month visit will be excluded in in the denominator for the calculation of the composite success rate.	After FDA review, it was suggested that the SAP maintain it's original language regarding transition to open label subjects. This revision reverses the change made in Version E, leaving transition to open label subjects in the denominator of the primary endpoint analysis.