Clinical Investigation Plan

[redacted]
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	[redacted]
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)	[redacted]
Abbott Medical Expert	[redacted]

[redacted]

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

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

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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.4 Treatment Arm Medication

2.4.1 Project Management

[redacted]

[redacted]

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. [redacted]

[redacted]

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 [redacted]

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

[redacted]

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.

[redacted]

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

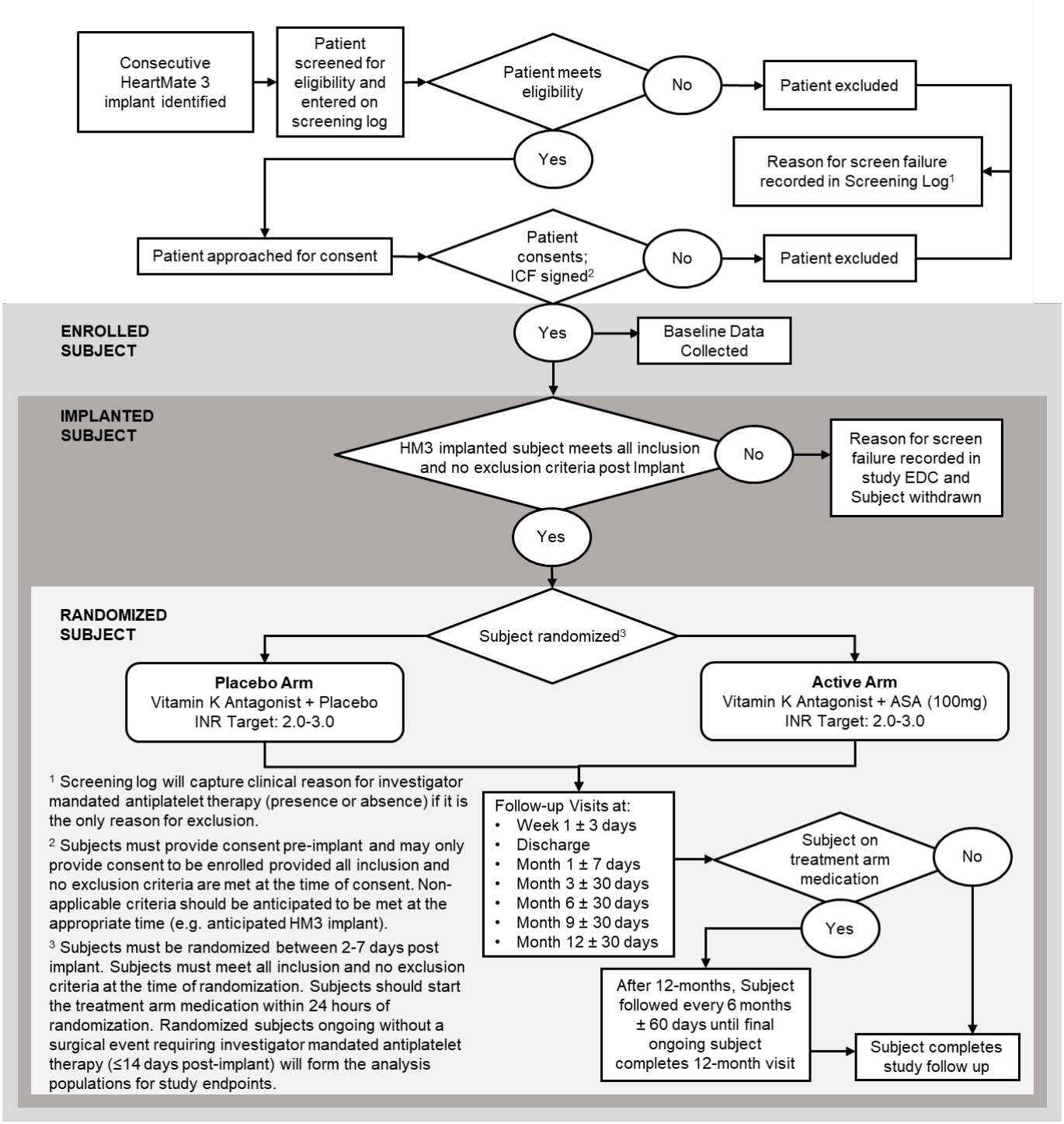

Figure 2 – Clinical Investigation Flow Chart

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.

[redacted]

- 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.

[redacted]

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

[redacted]

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.

[redacted]

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.

[redacted]

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.

Clinical Investigation Plan

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

[redacted]

Clinical Investigation Plan

[redacted]

Clinical Investigation Plan

[redacted]

[redacted]

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.

[redacted]

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

[redacted]

[redacted]

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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.

[redacted]

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.

[redacted]

Clinical Investigation Plan

[redacted]

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

[redacted]

- > 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.

[redacted]

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

[redacted]

Clinical Safety Contact

[redacted]

[redacted]

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

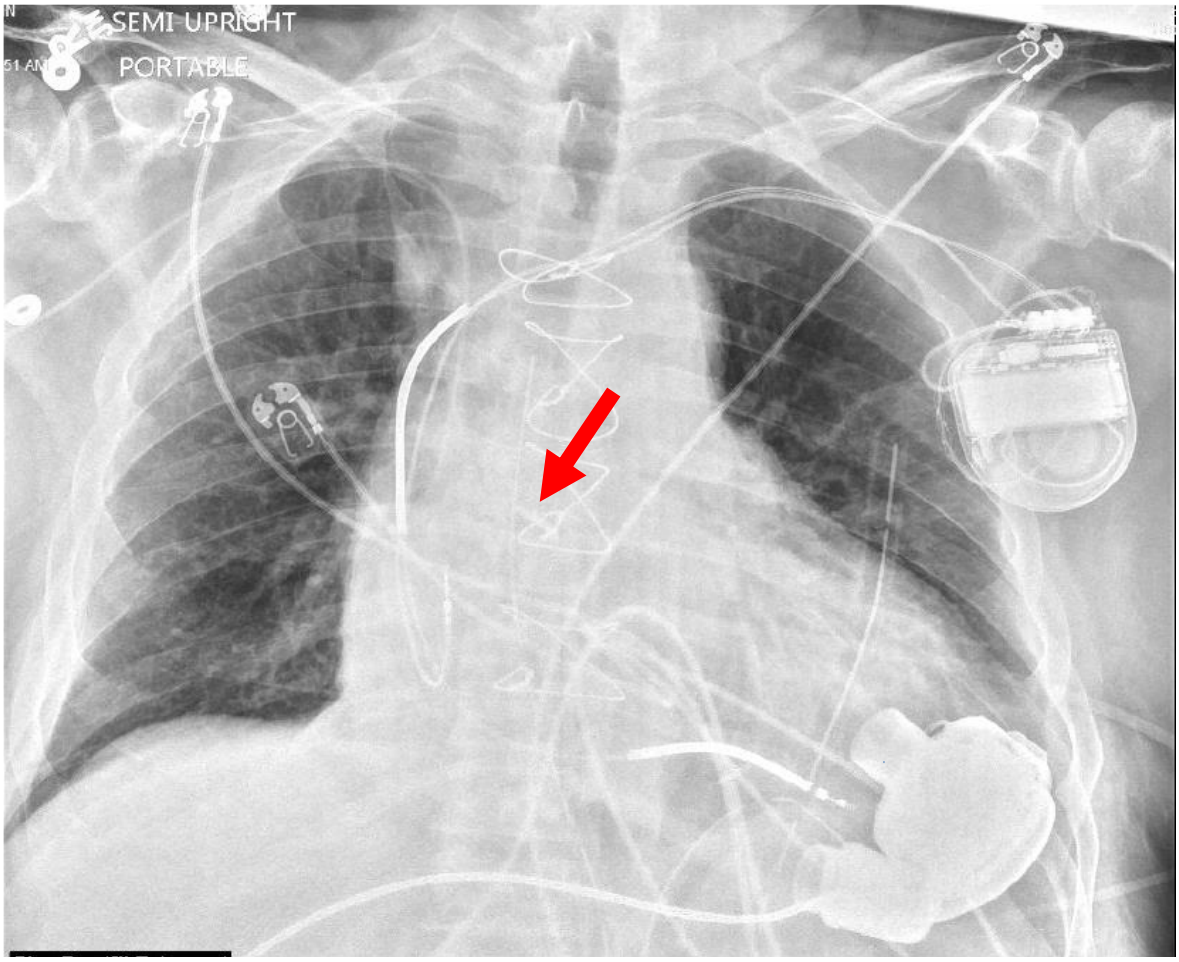
	The hypothesis of this sub-study is to develop and validate a surgical marker to serve as a consistent anatomical landmark to allow for accurate evaluation of the HeartMate 3 inflow canula position at the time of implant and subsequently, over time. We further hypothesize that differences in inflow canula 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.

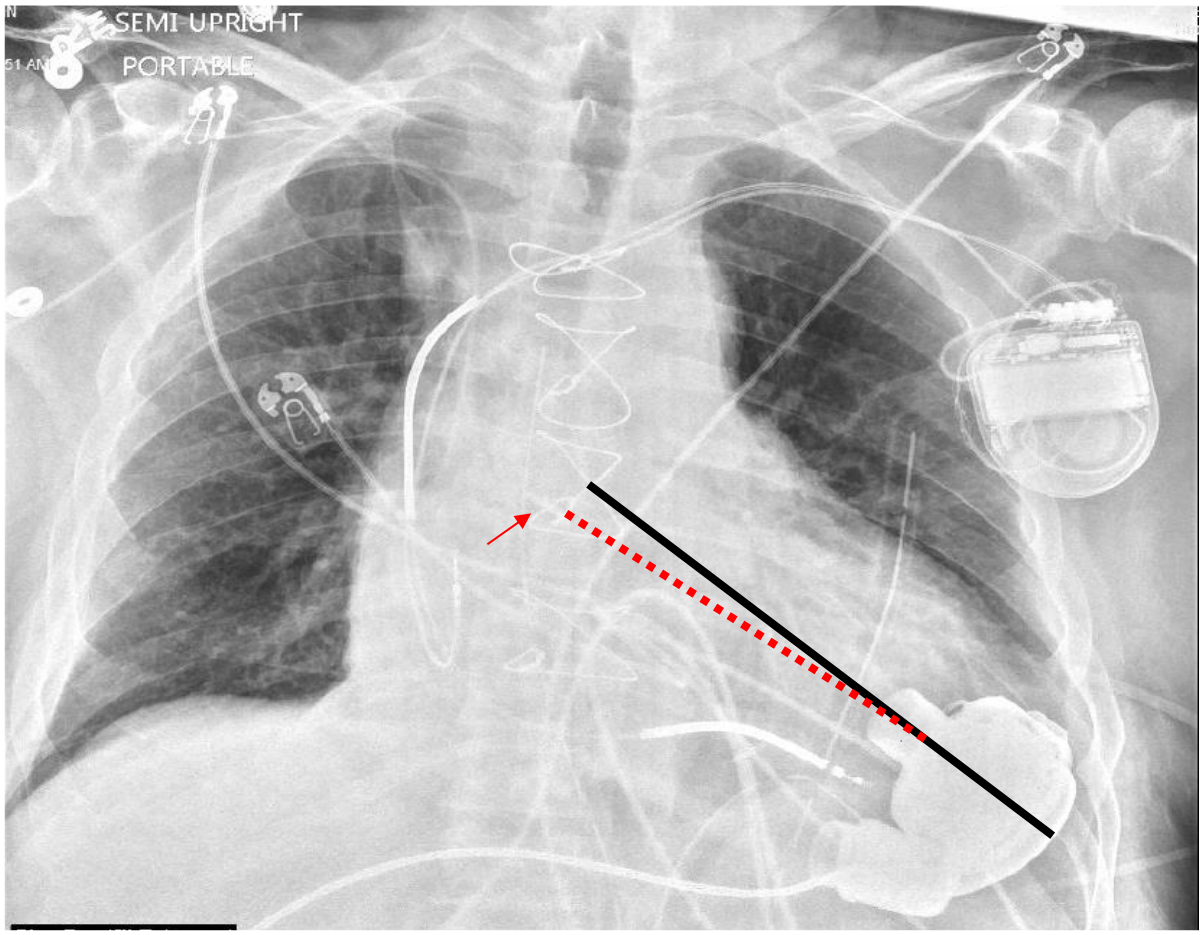
Clinical Investigation Plan

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.



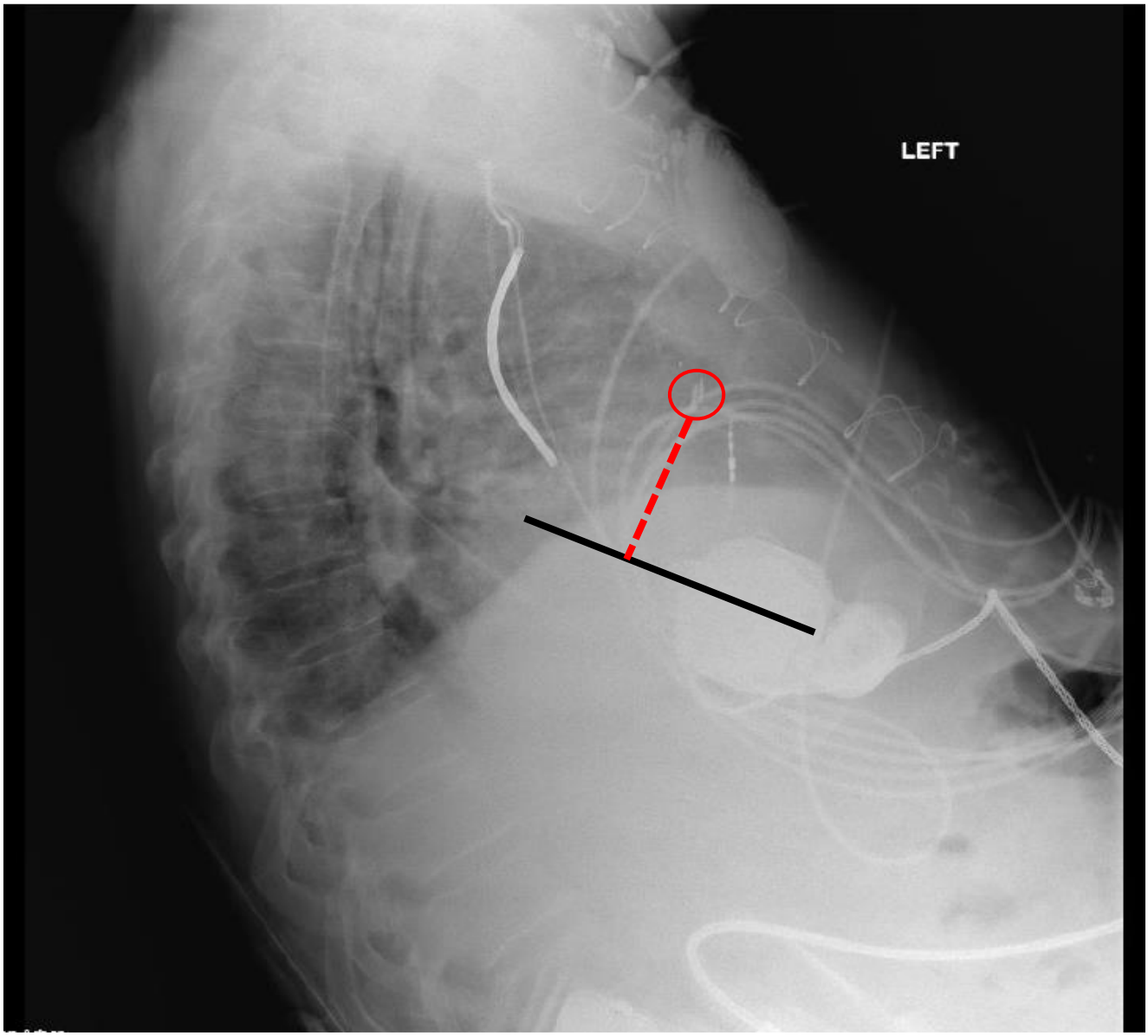
Clinical Investigation Plan

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).



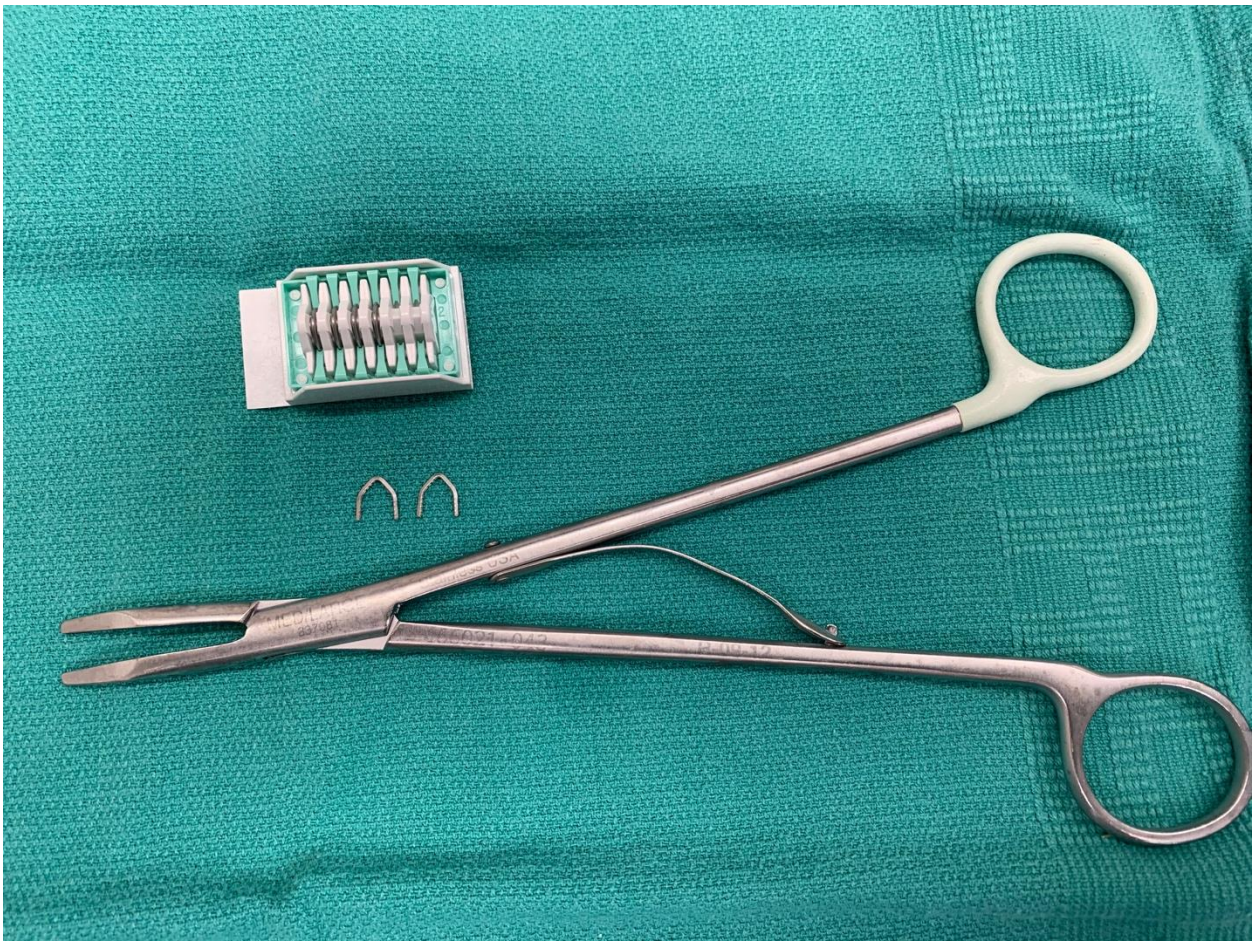
Clinical Investigation Plan

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).



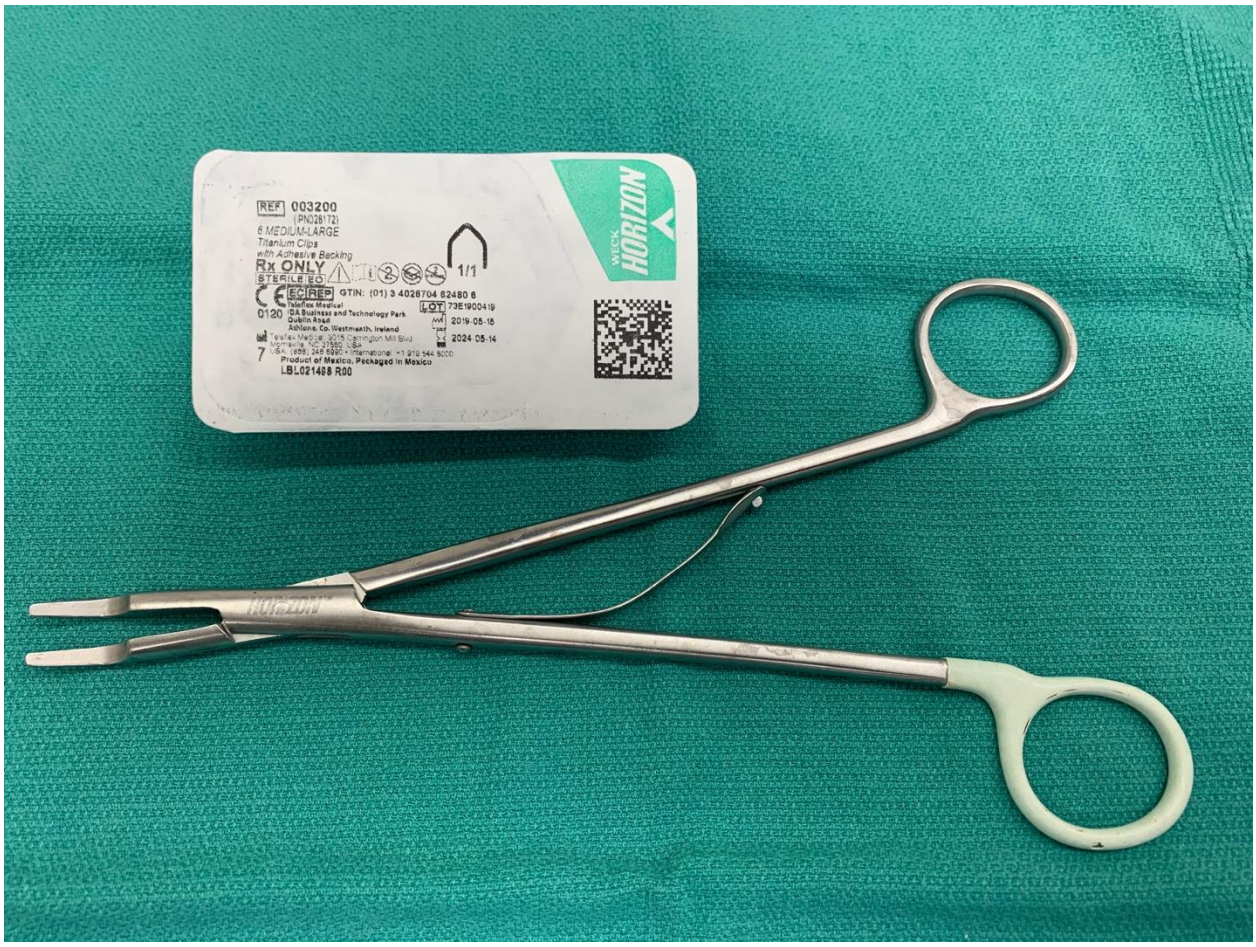
Clinical Investigation Plan

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
[redacted]				

[redacted]

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

[redacted]

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	[redacted]

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

[redacted]

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

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