PREVENT II

PREVENTion of Non-Surgical Bleeding by Management of HeartMate II Patients without Antiplatelet Therapy

Clinical Investigation Plan (CIP)

Sponsor:	Abbott (formerly St. Jude Medical, Inc.) 23 Fourth Avenue Burlington, MA 01803 Tel: (781) 272-0139 Fax: (781) 852-8320
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Principal Investigator Signature Page

PREVENTion of Non-Surgical Bleeding by Management of HeartMate **II** Patients without Antiplatelet Therapy (PREVENT II)

Version A

Reference #: ABT-CIP-10353

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

Principal Investigator

Printed Name: _____

Signature: _____

Date: _____

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1 SYNOPSIS

Study Synopsis	
Title	**PREVENT**ion of Non-Surgical Bleeding by Management of HeartMate **II** Patients without Antiplatelet Therapy
Acronym	PREVENT II
Objectives	Reduce the incidence of non-surgical bleeding in HeartMate II (HM II) patients without increasing the risk of thromboembolic (TE) events
Primary Hypothesis	HM II patients managed with warfarin alone (Treatment Arm) have a lower rate of non-surgical bleeding and an equivalent rate of stroke and TE events compared to patients managed with warfarin + acetylsalicylic acid (aspirin, ASA) together (Control Arm)
Primary Endpoints	A comparison between the Treatment and Control Arms of: Primary Efficacy Endpoint (Superiority): Composite incidence of non-surgical bleeding at 6 months post initial implantation, including but not limited to gastrointestinal (GI), genitourinary (GU), epistaxis, subdural hematoma, and primary hemorrhagic stroke (not due to ischemic conversion, or to treatment of a hemolysis/suspected thrombosis event) Primary Safety Endpoint (Non-Inferiority): Composite incidence of pump thrombosis and TE stroke at 6 months post initial implantation, including ischemic stroke, or hemorrhagic stroke due to an ischemic conversion/treatment of an hemolysis/pump thrombosis event
Descriptive Endpoints	Comparison between the Treatment and Control Arms in the rates of: • Overall bleeding • GI bleeding • Suspected and confirmed pump thrombosis • Stroke (ischemic and hemorrhagic) • Hemolysis (major and minor) • As treated analysis of anticoagulation and antiplatelet medications • Survival • Assessment of adherence to the PREVENT study recommended practices

Study Synopsis	
Design	PREVENT II is a prospective, multi-center, randomized, double-blind placebo controlled study. The randomization scheme will be 1:1, with a total sample size of 350 subjects, with 175 subjects in the Treatment Arm and 175 subjects in the Control Arm defined as: • Treatment Arm: Warfarin (INR Target 2.0-2.5, median 2.25, per standard of patient care) + placebo (1 pill/day) • Control Arm: Warfarin (INR Target 2.0-2.5, median 2.25, per standard of patient care) + acetylsalicylic acid (ASA) therapy (81mg/day) Maximum follow-up duration per subject will be 12 months. Primary endpoints will be evaluated at 6 months. Individual components of the primary endpoints along with the descriptive endpoints will be evaluated at 12 months.

Study Synopsis	
Statistical Considerations	Primary Efficacy Endpoint Analysis – Reduction of Bleeding: The rate of non-surgical bleeding at 6 months will be compared between the Treatment and Control Arms utilizing the Fisher's Exact Test. The primary endpoint for efficacy will be assumed to be met if the p-value < 0.05. The assumption is that there will be a 15% rate reduction at 6 months. A sample size of 330 subjects (165 in each arm) with an alpha of 0.05 will provide 80% power to demonstrate a significant difference between the Treatment and Control Arms. Primary Safety Endpoint Analysis – Non-Inferiority of Stroke and Thrombus: The difference in the rates of the composite endpoint of stroke and pump thrombosis between Treatment and Control Arms and the 95% confidence limit of the difference will be evaluated. If the upper confidence limit of the difference is < 10% then the non-inferiority criterion will be considered to have been met. A sample size of 338 subjects (169 in each arm) will provide 80% power, with a target alpha of 0.025 (because this will be a one-sided test on the upper confidence limit) to demonstrate non-inferiority of the Treatment Arm to the Control Arm. A total study sample size of 350 subjects will provide enough statistical power to demonstrate both efficacy and safety of the warfarin only anticoagulation regimen in these patients. Both primary endpoints must be met for the study to be successful. Intermediate Safety Assessment: A safety assessment will be performed after 60 subjects have completed 3 months of follow-up. Both incidence of stroke and pump thrombosis will be analyzed and results will be presented to the Steering Committee. Additionally, after the initial 3-month safety review, an analysis of AEs associated with primary endpoints will be presented to the Steering Committee for continued safety assessment in regular 6-month intervals. The Steering Committee will review the findings and make a decision to proceed or stop the study due to safety concerns.
Devices Used	HM II Left Ventricular Assist Device (LVAD)
Research Drug	Aspirin (81mg – active ingredient: Acetylsalicylic acid (ASA); Enteric-Coated Low Dose Aspirin, Bayer Corporation, Whippany, NJ) will be blinded to a matching placebo (ALMAC Clinical Services, Souderton, PA)
Study Population	All patients undergoing HM II implantation per approved indications who meet inclusion/exclusion criteria may be considered for this study.

Study Synopsis	
Inclusion & Exclusion Criteria	Inclusion Criteria • Subject is receiving the HM II per standard of care (SOC) in accordance with the approved indications for use • Subject is ≥ 50 years of age • Subject is receiving the HM II as their first LVAD • Subject or legally authorized representative (LAR) has signed an informed consent form (ICF). Exclusion Criteria • Existence of ongoing mechanical circulatory support (MCS) other than intra-aortic balloon pump or Abiomed Impella® devices • Participation in any other clinical investigation(s) involving an MCS device, or an investigation(s) that is likely to confound study results or affect study outcome • Antiplatelet therapy is mandated for other conditions, in particular: a) recent coronary artery stenting (≤ 6 months), b) carotid artery disease, and c) other conditions where the investigator is not comfortable leaving subjects off-ASA or starting ASA post LVAD implantation. In situations where the investigator is uncertain, the Steering Committee can provide a recommendation to the investigator as needed. • Subjects in whom heart transplantation is expected in ≤ 6 months • Subjects with a known ASA allergy
Data Collection	Data will be collected on all subjects at the following time points: • Baseline • Implant • Week 1 post-implant (± 3 days) • Month 1 post-implant (± 7 days) • Month 3 post-implant (± 20 days) • Month 6 post-implant (± 20 days) • Month 9 post-implant (± 20 days) • Month 12 post-implant (± 20 days) Data will be collected for as occurs events, including initial discharge, adverse events, re-hospitalizations, operative events and outcomes. All changes to anticoagulant and antiplatelet therapies and all available values for INR and LDH will be collected during the follow-up period.

2 BACKGROUND AND JUSTIFICATION FOR CLINICAL STUDY

Over the last decade, mechanical circulatory support (MCS) with continuous-flow (CF) left ventricular assist devices (LVADs) has become the standard of care (SOC) treatment for patients with advanced stage heart failure. The HeartMate® II (HM II) LVAD is a commercially available, U.S. Food and Drug Administration (FDA) and Health Canada approved device. The HM II was approved for New York Heart Association Class (NYHA) IIIB/IV patients as a bridge to cardiac transplantation (BTT) by the FDA in April 2008 and Health Canada in May 2009. The HMII was approved for permanent destination therapy (DT) by the FDA in January 2010 and Health Canada in October 2010. Numerous publications have documented the success of the HM II in extending and improving the quality of life in patients with advanced heart failure (1-10). Over 22,000 patients have been implanted and treated with the HM II LVAD, and over 8,000 patients are currently supported by the HM II (*data on file*).

Patients with LVADs require adjunctive antithrombotic therapy, typically with warfarin +/- acetylsalicylic acid (aspirin, ASA). While ASA therapy, the research topic of this study, is suggested in the HM II IFU, the usage of ASA as SOC is variable. Some centers routinely utilize ASA while others do not (11, 12). Additionally, ASA therapy is usually discontinued when patients experience a serious bleeding event (13).

2.1 BLEEDING IN HM II PATIENTS

While overall outcomes with the HM II have steadily improved, bleeding and thromboembolic (TE) complications continue to persist (5, 8). In practice, clinicians must balance the risk of bleeding against that of thrombosis by managing patients on chronic antithrombotic therapy, which includes warfarin as well as ASA therapy (14). In HM II patients, the prevalence and incidence of bleeding, particularly gastro-intestinal (GI) bleeding, is elevated and is usually the leading cause of hospital readmissions post-LVAD implant (15, 16).

Antithrombotic therapy in CF-LVAD patients is complicated by the presence of acquired Von Willebrand Syndrome (AVWS) (17-19). In AVWS, patients present with a degradation of high molecular weight (HMW) multimers of Von Willebrand Factor (VWF) protein, which are necessary for platelet binding and normal hemostatic function of the coagulation system. The loss of HMW VWF reduces the ability of platelets to bind to each other, and predisposes patients to bleeding diatheses, including increased rates of GI bleeding (20).

Some investigators have hypothesized that ASA therapy in the presence of AVWS increases the risk of non-surgical bleeding in HM II patients (11). In a single center experience from France, the risk of TE events was not elevated when patients were managed on single antithrombotic therapy (Vitamin K antagonist – Fluindione only, target INR: 2.0-3.0)(11).

These observations led to the design of the TRACE study (Study of Reduced Anticoagulation/Antiplatelet Therapy in Patients with the HeartMate II Left Ventricular Assist System) (Clinical Trials.Gov: NCT01477528), a prospective, multi-center safety study of reduced antithrombotic therapy in HM II patients. TRACE enrolled 200 subjects across the United States and Europe, and demonstrated that HM II patients who were managed without ASA therapy did not experience an increased risk of TE events (12, 13).

The rate of bleeding in the TRACE EU cohort, in particular, appeared to be lower compared to published clinical experience (12, 21).

2.2 THROMBOSIS IN HM II PATIENTS

Despite bleeding being the more common adverse event, consequences of thrombosis can be far more serious. Early HM II clinical experience demonstrated a low rate of pump thrombosis and stroke (1, 2, 7, 14), but over time changes in management practices to address bleeding events have partially contributed to an increasing risk of pump thrombosis in HM II patients (22). Starling *et al.* reported an alarming increasing incidence of HM II pump thrombosis from 2.2% before 2011 to 8.4% after 2011 (23). Despite the alarming trend, there was significant disparity and center-to-center variability in the reported rates of pump thrombosis. For example, an analysis of clinical experience from 7 centers (24) showed that the risk of early pump thrombosis was found to be much lower (3.9%) compared to the published clinical experience (23, 25). In addition, subsequently published letters to the editor suggested that the increases in pump thrombosis rates observed in some centers were not evident at all HM II centers (26, 27).

Due to the variability in pump thrombosis rates and patient management practices, the PREVENT study (PREVENtion of HeartMate II Thrombosis through Clinical Management; ClinicalTrials.gov identifier: NCT02158403) was developed to investigate a set of recommended practices (**Appendix C**) based on the HM II instructions for use (IFU) with modifications derived from clinical practice (28). PREVENT evaluated the rate of pump thrombosis in HM II patients when the recommended practices were adopted across centers to minimize center-to-center variability and standardize clinical management.

Primary endpoint results from the PREVENT study were recently presented at the International Society of Heart and Lung Transplantation (ISHLT) 2016 annual meeting, where the rate of early (≤ 3 month) pump thrombosis was demonstrated to be 2.9% (significantly lower than the published rate of 8.4% at 3 months) (29). The reduction in the early risk of pump thrombosis associated with the adoption of consistent patient management techniques, has been confirmed by other studies (30, 31). Furthermore, an analysis of PREVENT data revealed that a sub-group of patients (~20% of the enrolled patient population) were not on ASA or any antiplatelet therapy; these patients did not experience any of the pump thrombosis events captured as part of the primary endpoint.

2.3 CLINICAL EQUIPOISE ON THE USE OF ASA IN HM II PATIENTS

The growing body of scientific evidence seems to suggest that ASA therapy in HM II patients may not have an impact on TE events, but may increase the risk of bleeding events in the presence of AVWS. This effect may be particularly accentuated in older patient populations who have higher risk of bleeding (21). The PREVENT recommendations, as well as the HM II IFU, recommend initiation of ASA therapy within 2-5 days post implant, with maintenance of ASA therapy throughout support. Despite these recommendations, clinical experiences from the US and EU cohorts of the TRACE study, as well as single-center experiences in Europe have indicated that ASA therapy may not be required in HM II LVAD patients. Furthermore, in a recent study, the use of high dose ASA therapy (325 mg) was associated with a significantly higher incidence of hemorrhagic events compared to low dose (81 mg) ASA therapy [54% vs. 22%, $p<0.004$] (32). These results suggest a clinical equipoise for the use of ASA therapy for

antithrombotic management of HM II patients, especially in older patients who are at higher risk of bleeding.

2.4 STUDY JUSTIFICATION

The high rates of bleeding in HM II patients, presence of AVWS, uncertainty behind the clinical benefit of ASA therapy, and results from both PREVENT and TRACE studies form the basis of the design for the PREVENT II study. PREVENT II will be the first prospective, randomized, multi-center, double-blind, placebo-controlled clinical study conducted in the field of MCS therapy, comparing patients managed with warfarin alone to patients managed with warfarin + ASA therapy together. PREVENT II will set the precedent for future studies focused on developing evidence-driven best practices for improving outcomes in LVAD patients. Results of the study may not only impact the thousands of patients who will receive the HM II LVAD over the next few years, but also the thousands of patients who are currently supported by the HM II.

3 RISKS AND BENEFITS OF THE CLINICAL STUDY

The risks associated with the use of the HM II LVAD are anticipated to be comparable to those associated with the use of other currently available LVADs. Subjects participating in this study are indicated for an LVAD system as part of their standard medical management and are subject to the risks associated with the use of these devices. The study seeks to evaluate the safety and efficacy of eliminating ASA therapy in HM II patients. Subjects in the Treatment Arm of the study may have an increased risk for TE events due to the removal of ASA therapy.

3.1 ANTICIPATED CLINICAL BENEFITS

Commercially available MCS devices have been previously shown to provide safe and effective hemodynamic support in advanced heart failure subjects with clinically meaningful improvement in survival, quality of life and functional capacity when compared to optimal medical management (1-10, 33).

This study may or may not benefit the subjects involved, but it may help future subjects by increasing what we know about ways to care for subjects who are supported on LVADs.

3.2 ANTICIPATED ADVERSE EVENTS AND ADVERSE DEVICE EFFECTS

Adverse events potentially associated with LVAD therapy are documented in the HM II IFU.

3.3 POSSIBLE INTERACTIONS WITH CONCOMITANT MEDICAL TREATMENTS AND/OR CONCURRENT MEDICAL INTERVENTIONS

There are no known interactions of the HM II LVAD with concomitant medical treatment. Subjects experiencing an adverse event will be treated by their physician per SOC at the investigation site.

3.4 MITIGATION OF RISKS

Actions to control or mitigate risks will include the selection of qualified and experienced investigators and site personnel, and strict adherence to the clinical investigational plan (CIP). Investigators will be actively involved in the follow-up of all study subjects. Risks

will be minimized by careful assessment of each subject prior to, during, and at regular intervals throughout the study.

To address the risk of TE events in the Treatment Arm, the study design includes a safety assessment to be performed by the Steering Committee after 60 subjects reach 3 months of follow-up. If the Steering Committee determines that there are safety concerns, the study will be terminated. Furthermore, for continued safety assessment, after the initial safety assessment, an analysis of AEs associated with the primary endpoints will be performed at regular 6-month intervals by the Steering Committee.

4 STUDY DESIGN

4.1 PURPOSE

The purpose of this clinical study is to evaluate the safety and efficacy of managing HM II patients ≥50 years of age on warfarin (target INR 2.0-2.5, median: 2.25) alone, compared to HM II patients managed on warfarin (target INR 2.0-2.5, median: 2.25) and ASA (81 mg/day) together (11, 12)(13).

4.2 STUDY DESIGN AND SCOPE

This study is a prospective, multi-center, randomized, double-blind placebo-controlled study of subjects receiving the HM II LVAD as per currently approved indications for use. This is a post-market clinical study of HM II patient management practices to be conducted in the United States and Canada.

Subjects will be randomized in a 1:1 fashion to the following research drug groups:

1) Treatment Arm: Warfarin (INR target: 2.0-2.5, median: 2.25) + Placebo (1 pill/day)

2) Control Arm: Warfarin (INR target: 2.0-2.5, median: 2.25) + ASA Therapy (81mg/day)

The study will investigate if subjects in the Treatment Arm experience a reduced incidence of non-surgical bleeding, without an increased risk of TE events.

Once randomized, subjects will be placed on the research drug (ASA therapy or placebo) no later than post-operative day (POD) 5, provided bleeding has subsided and the subject is hemodynamically stable.

If the subject is experiencing bleeding or is not hemodynamically stable by POD 5, the subject must start the study drug as soon as bleeding has subsided and hemodynamic stability has been achieved, but no later than POD 15. If administration of the research drug has not begun by POD 15, the subject will be withdrawn from the study.

Withdrawn subjects will not be replaced.

4.3 STUDY BLINDING

The subjects and the investigators will be blinded to the subject's research drug assignment. Un-blinding will not be performed unless the subject is experiencing a major allergic reaction potentially attributable to the research drug. If a major allergic reaction occurs, the subject should be medically managed per standard of care. Un-blinding will occur only with approval from the Steering Committee and will be documented. Requests for unblinding will be answered within three business days of the request. If un-blinding occurs, the subject will be withdrawn from the study.

4.3.1 DESCRIPTION OF SUBJECT POPULATION

All subjects receiving a HM II implant in accordance with the approved indications for use (BTT or DT) will be considered for this study, regardless of gender, race, or ethnicity.

4.3.2 PREVENT RECOMMENDATIONS TO REDUCE PUMP THROMBUS

All subjects enrolled into this study will be implanted and managed in accordance with the PREVENT study recommended practices to reduce pump thrombosis with the exception of the use of antiplatelet therapy, which is the research topic of this study. Refer to **Appendix C** for full details of the PREVENT study recommended practices.

4.3.3 NUMBER OF SUBJECTS REQUIRED TO BE INCLUDED IN THE STUDY

A total sample size of up to 350 subjects will be enrolled. Subjects enrolled into the study will be randomized in a 1:1 fashion and randomization will be stratified by study site and blocked to maintain a 1:1 ratio over time.

Subjects will be followed up to 12 months with the primary endpoints evaluated at 6 months. The study will be conducted at up to 45 sites, and up to 45 subjects may be enrolled at any site. An enrollment increase may be requested by individual sites, and approval will be granted at the discretion of the Sponsor.

4.3.4 ESTIMATED TIME NEEDED TO ENROLL SUBJECT POPULATION

Based on the anticipated enrollment rate, the estimated time needed to enroll this subject population is approximately 2.75 years.

4.4 OBJECTIVE

The primary objective of the study is to reduce the incidence of non-surgical bleeding in HM II patients, without increasing the risk of TE events, by eliminating ASA therapy from the antithrombotic management regimen for HM II patients. The primary objective will be accomplished by a comparison of non-surgical bleeding and TE events at 6 months post initial implantation between the Treatment and Control Arms.

4.5 ENDPOINTS

4.5.1 PRIMARY ENDPOINTS

There are two primary endpoints of this study:

Efficacy Endpoint (Superiority): Composite incidence of non-surgical bleeding at 6 months post initial implantation, including but not limited to GI, GU, epistaxis, subdural hematoma, and primary hemorrhagic stroke (not due to ischemic conversion, or due to the treatment of a hemolysis/suspected thrombosis event).

Safety Endpoint (Non-Inferiority): Composite incidence of pump thrombosis and TE stroke at 6 months post initial implantation, including ischemic stroke, or hemorrhagic stroke due to an ischemic conversion/treatment of hemolysis/pump thrombosis event.

4.5.2 DESCRIPTIVE ENDPOINTS

The descriptive endpoints will involve a comparison between the Treatment and Control Arms in the rates of:

- Overall bleeding
- GI bleeding
- Suspected and confirmed pump thrombosis
- Stroke (both ischemic and hemorrhagic)
- Hemolysis (major and minor)
- As treated analysis of anticoagulation and antiplatelet medications
- Survival
- Assessment of adherence to the PREVENT study recommended practices.

4.6 INCLUSION AND EXCLUSION CRITERIA

To qualify for inclusion in the study, subjects must meet all eligibility criteria listed below.

4.6.1 INCLUSION CRITERIA

- Subject is receiving the HM II per SOC in accordance with the approved indications for use
- Subject is ≥ 50 years of age
- Subject is receiving the HM II as their first LVAD
- Subject or legally authorized representative (LAR) has signed an informed consent form (ICF).

4.6.2 EXCLUSION CRITERIA

- Existence of ongoing mechanical circulatory support (MCS) other than intra-aortic balloon pump or Abiomed Impella® devices.
- Participation in any other clinical investigation(s) involving an MCS device, or an investigation(s) that is likely to confound study results or affect study outcome.
- Antiplatelet therapy is mandated by treating physician for other conditions, in particular: a) recent coronary artery stenting (≤ 6 months), b) carotid artery disease, and c) other conditions where the investigator is not comfortable leaving subjects off ASA or starting ASA post LVAD implantation. In situations where the investigator is uncertain, the Steering Committee can provide a recommendation to the investigator as needed.
- Subjects in whom heart transplantation is expected in ≤ 6 months.
- Subjects with a known ASA allergy.

4.7 SUBJECT POPULATION

All patients undergoing HM II implantation approved indications for use who meet inclusion/exclusion criteria may be considered for this study.

4.8 SUBJECT SCREENING

The Principal Investigator (PI) or designated site personnel will screen all subjects receiving a HM II LVAD per SOC. Subjects who do not meet inclusion/exclusion criteria will not qualify to participate in this study. The reason for ineligibility will be documented.

Refer to **Section 6.3** for a description of the screening process.

4.9 INFORMED CONSENT PROCESS

Prior to participation in the study or any study-specific procedures, all subjects will be consented as required by applicable regulations and the applicable institutional review board (IRB). The subject will be provided with the informed consent form written in a language that is understandable to the subject. The informed consent form must be approved by the Sponsor and applicable IRB prior to use.

The PI or an authorized designee will conduct the Informed Consent Process. This process will include a verbal discussion with the subject (or designated LAR) on all aspects of the study relevant to the subject's decision to participate in the study. Written consent must be signed and dated by the subject (or designated LAR), and by the designated site personnel obtaining the consent.

A copy of the fully executed informed consent form must be given to the subject at the time of signature, and the original signed confirmed form will be filed in the site research files. A consent note, which documents the complete Informed Consent Process, will be entered into the subject's hospital record with a copy of the fully executed consent form.

Failure to obtain informed consent from a subject prior to study enrollment should be reported to the Sponsor within 5 working days, and to the applicable IRB consistent with the applicable reporting requirements.

4.10 POINT OF ENROLLMENT

Subjects are considered enrolled in the study when subject consent has been provided, the HM II LVAD implant has been successfully completed, and the subject has been randomized to a research drug arm. Enrollment reporting and randomization must occur immediately when the subject leaves the operating room or no later than 48 hours following implant. An enrollment is reported to the Sponsor upon submission of the Implant and Randomization CRFs in the EDC. The follow-up assessment schedule is based on Day 1 being the date that the implant was completed.

5 DEVICE USED AND RESEARCH DRUG TREATMENT

5.1 DEVICE DESCRIPTION

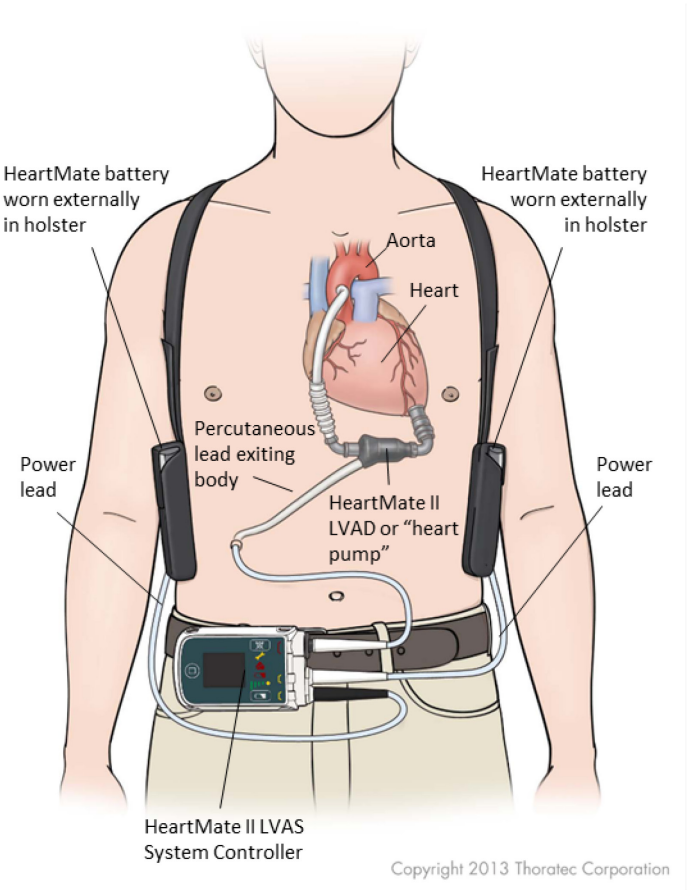
The HM II Left Ventricular Assist System (LVAS) utilizes a rotary axial-flow pump that weighs 290 grams and has a displacement volume of 63 milliliters. A microprocessor-based system controller provides power, control and monitoring of the implanted pump. Control and power to pump are through a percutaneous lead connected to the external controller and power supply. External system components include batteries, battery charger, power supply, and system monitor. Batteries are used in pairs to power the pump during ambulatory operation. A power module provides AC electrical power to the system during tethered operation. The battery charger charges, tests, and calibrates the14 volt Li-

Ion or 12-volt NiMH batteries. The system monitor displays pump operating parameters and provides an interface for the operator.

The HM II pump contains a single moving component, the rotor. Vanes on the rotor move the blood through the pump in the range of 3 to 10 liters per minute. The pump does not have valves and venting is not required. The inflow conduit and outflow elbow are textured with titanium microspheres to promote cellular adhesion and the development of a thromboresistant tissue lining. The remaining internal blood-contacting components have smooth, polished titanium surfaces. The rotor is suspended between the inlet and outlet stators with ball-and-cup bearings.

The pump is implanted just below the left hemidiaphragm with the inflow attached to the apex of the left ventricle and the outflow graft anastomosed to the ascending aorta. Blood is pumped continuously throughout the cardiac cycle from the left ventricle to the aorta. The percutaneous lead is tunneled subcutaneously across the abdomen and exits the abdominal wall in the right or left upper quadrant.

Figure 1 – The HeartMate II Left Ventricular Device



The HM II Left Ventricular Assist Device is implanted below the heart and is connected by a percutaneous lead to a controller and batteries worn by the patient. Blood is pumped continuously throughout systole and diastole from a cannula inserted into the left ventricular apex with flow redirected to the ascending aorta.

5.2 DEVICE ACCOUNTABILITY

Because the HM II is commercially available and approved, device accountability is not required for this study; however, the standard commercial practices for device accountability and reporting to the Sponsor should be followed. Refer to **Section 7.2** for complaints reporting.

5.3 RESEARCH DRUG

5.3.1 PROJECT MANAGEMENT

ALMAC Clinical Services will manage manufacturing and distribution logistics of the research drug at their facility at 25 Fretz Road, Souderton, PA 18964.

ALMAC Clinical Services will manage the WebEZ system and drug accountability at their facility at 4228 Technology Drive, Durham, NC 27704.

ALMAC Clinical Services is a part of ALMAC Group Limited headquartered at ALMAC House, 20 Seagoe Industrial Estate, Craigavon, BT63 5QD, Northern Ireland (Reg. No: NI 41905).

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

- Research drug blinding and matching placebo manufacture, including packaging and labelling (due to country-specific requirements research drug labels may vary)
- Dispensing research drug to sites
- Providing support dispensing to study subjects via the ALMAC WebEZ system
- Research drug accountability

5.3.2 RESEARCH DRUG BLINDING

ALMAC Clinical Services will blind the Control Arm research drug (81mg ASA; Enteric-Coated Low Dose Aspirin, Bayer Corporation, Whippany, NJ) to a matching placebo, the Treatment Arm research drug.

5.3.3 RESEARCH DRUG DISPENSING

Initial dispensing of the research drug will occur after randomization, which will be performed immediately after the patient has been successfully implanted with the HM II. Resupply dispensing will occur at Month 3, Month 6, and Month 9 follow-up visits. Dispensing will be controlled at the sites with the use of ALMAC Clinical Services' WebEZ system. At each dispensing time point, the designated site personnel will log on to the WebEZ system, enter information required for randomization or resupply, and requisition a bottle to dispense to the subject from the on-site stock.

Each bottle of research drug will be tracked by bottle number. The WebEZ system will provide sites with the bottle number to be dispensed to a given subject. Site supply and resupply shipments will be automatically controlled by ALMAC Clinical Services.

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

Subjects should always be sufficiently supplied with research drug until their next resupply visit. Each bottle will contain 110 days of research drug, which is a sufficient supply for the period leading up to the subject's next visit, including the acceptable visit windows.

5.3.4 RESEARCH DRUG DOSING

The research drug will be taken once daily by mouth. Warfarin therapy will be per SOC with a target INR of 2.0-2.5.

5.3.5 RESEARCH DRUG ACCOUNTABILITY

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

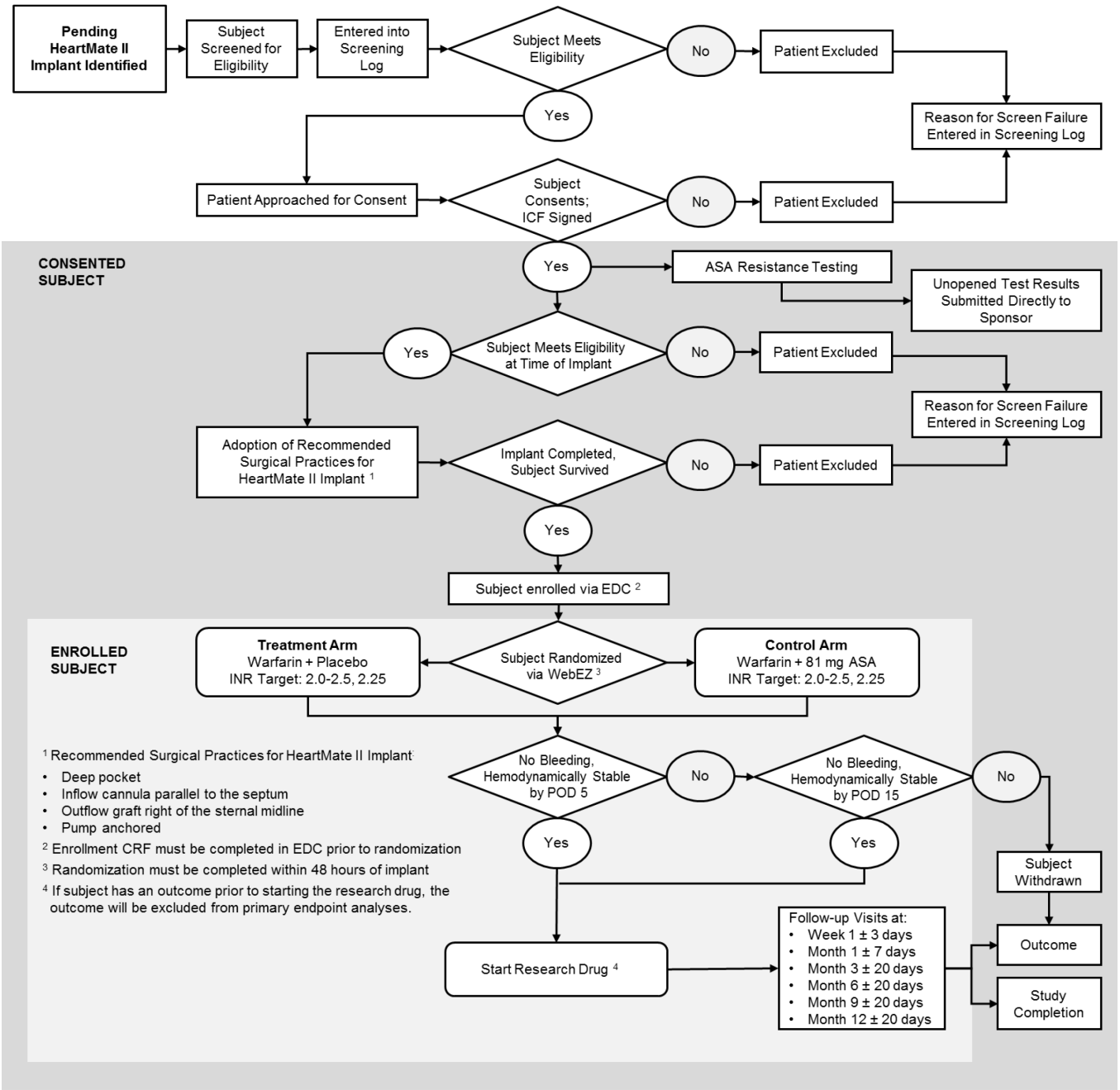
The research drug bottles and unused portions will be shipped (at the Sponsor's expense) per country-specific Drug Return Instructions (DRI).

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. Drug return instructions (DRI) will be provided during training.

6 PROCEDURES

6.1 STUDY FLOW CHART

Figure 2 – Study Overview



6.2 STUDY ACTIVITIES AND PROCEDURES

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

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

Table 1 – Schedule of Assessments

Assessment	Baseline	Implant	Week 1 (± 3 days)	Month 1[1] (± 7 days)	Month 3[1] (± 20 days)	Month 6[1] (± 20 days)	Month 9[1] (± 20 Days)	Month 12[1] (± 20 days)	As Occurs/ Unscheduled
Inclusion/ Exclusion	X								
Informed Consent	X								
Demographics	X								
General and Cardiac Medical History	X								
Coagulation Assessment	X[2]								
Right Heart Catheterization	X[2]								X[4]
Vital Signs	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
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	
ASA Resistance Testing	X								
Implant Data		X							X[6]
Enrollment		X[7]							
Randomization		X							
Adherence to Recommended Practices		X	X	X	X	X	X	X	
Pump Parameters		X	X	X	X	X	X	X	X[5]
Bottle Assignment via WebEZ		X			X	X	X		
Research Drug Bottle Dispensing and Dispensing Log		X			X	X	X		X
Bridging Therapy Log		X	X						X[8]
Anti-Factor Xa Assay Log		X	X						X[8]
Initial Discharge Data									X
Subject Status			X	X	X	X	X	X	
Cardiac Arrhythmias			X	X	X	X	X	X	
INR & LDH Log			X	X	X	X	X	X	X
Chest/Abdominal X-Ray				X[9]					X[5]
Return Bottle with Remaining Test Drug to ALMAC Clinical for Accountability					X	X	X	X	
Death									X
Withdrawal (early termination)									X
Rehospitalizations			X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X
Operative Procedures			X	X	X	X	X	X	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: Implant Data and Recommended Practices.*
[7] *Subject is considered enrolled when inclusion/exclusion criteria are met; has been successfully implanted with a HM II LVAD; and has been randomized to a research drug arm (Treatment or Control).*
[8] *Within the first 21 days post implant.*
[9] *Best view available between Implant and Month 1 visit.*

6.2.1 ANTIPLATELET TESTING AND PLATELET FUNCTION TESTING

Subjects in both the Treatment and Control Arms will receive ASA resistance testing (e.g. TEG® PlateletMapping®, VerifyNow®, etc.) at the baseline visit. After obtaining informed consent, testing will be performed prior to implantation, and may require a brief administration of ASA (recommended 3-5 days) to subjects who are not currently on ASA therapy. Testing should be timed adequately prior to surgery so as not to effect subjects' ability to reach post-operative hemodynamic stability.

To retain investigator and patient blinding to the test results, all site labs should be directed to return de-identified (patient screening ID only) ASA resistance test results at the Sponsor's expense to the Sponsor. Results will not be entered into the subject's hospital record to protect blinding.

While the subject is on the research drug, antiplatelet testing or platelet function testing should not be performed, as it may result in un-blinding of the subject or the investigator. Un-blinding of the subject or investigator will be considered a CIP deviation and the subject will be withdrawn from the study.

6.2.2 AVOIDANCE OF ADDITIONAL ANTIPLATELET MEDICATIONS

Investigators should not prescribe or administer additional antiplatelet medications to subjects, except in the instance in which the subject has met the primary study endpoints.

6.3 SCREENING AND ENROLLMENT

All patients who are screened for eligibility will be documented in the PREVENT II Screening Log and assigned a Screening ID number. To protect patient privacy, no identifying information will be recorded.

The Sponsor may request copies of the Screening Log throughout the study, but the ongoing log will be maintained on site.

Patients who qualify to participate in the study will be approached to discuss the study, consider voluntary participation, and, if applicable, provide informed consent. For patients who do not qualify to participate in this study, the reason for ineligibility will be entered in the screening log. For enrolled subjects, the assigned Subject ID number will be entered in the screening log. Patients with an Impella® device must have the device removed during HMII implant to be enrolled into the study.

Qualified subjects who have provided consent will be entered in the appropriate EDC CRF, which must be submitted to the Sponsor after the patient has been screened and prior to enrollment, or no later than 48 hours post implantation. Notification of enrollment to the Sponsor will only take place when the consented subject has been entered in the EDC. Enrollment information (name of the study, date of consent, and inclusion/exclusion criteria) will be recorded in the subject's hospital records.

If a consented subject does not meet all eligibility criteria at the time of implant; does not receive a HM II LVAD; experiences a serious adverse event in the perioperative period that the investigator feels would compromise the patient's participation in the trial (e.g., debilitating stroke); or expires during the implant procedure, then the subject will not be enrolled or contribute to the study endpoints. The reason for ineligibility at the time of

implant will be recorded in the screening log. The subject is enrolled upon successful implantation of the HM II and randomization per **Section 4.10**.

6.4 BASELINE VISIT

The following baseline assessments will be performed:

Table 2 – Baseline Data Collection

Study Activity	Data Collection
Informed Consent	Informed consent details
Inclusion/Exclusion	Subject's eligibility details
Demographics	Age, gender, ethnicity, race, blood type, INTERMACS profile, and NYHA class
General and Cardiac Medical History	Etiology of HF, duration of HF, indication (BTT/DT), arrhythmias, prosthetic valve(s), stroke, diabetes, smoking, history of bleeding (diverticular disease, diagnosed arteriovenous malformations (AVMs), GI ulcer(s), anemia, and/orerythropoietin 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, CardioMEMS, and HIV
Vital Signs	Height, weight, blood pressure, and heart rate
Anticoagulation/Antiplatelet Medications	Warfarin, clopidogrel, dipyridamole, other anticoagulation agents, other vitamin K antagonists, direct thrombin inhibitors, etc (including research drug). *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 Warfarin/Coumadin. Only the start and stop dates will be collected for Warfarin/Coumadin*
Other Medications	ACE inhibitors, inotropes, ARBs, beta blockers, antiarrhythmics, statins, nitrates, allopurinol, aldosterone blockers, antibiotics, diuretics, insulin and antidiabetic medications, and other cardiovascular medications
[1] Laboratory Assessments	Hemoglobin (Hgb), Hematocrit (Hct), White Blood Cell Count (WBC), Platelets (PLT), Creatinine (Cr), Estimated Glomerular Filtration Rate (eGFR), LDH and INR. For diabetic patients: HbA1c, and fasting glucose Collected only if SOC: Activated Partial Thromboplastin Time (aPTT), Partial Thromboplastin Time (PTT), Plasma free Hgb (PHgb), liver function tests (AST, ALT, total bilirubin, albumin, pre-albumin), blood urea nitrogen (BUN), D-Dimers, P Selectin, and fibrinogen
ASA Resistance Testing	ASA resistance testing (e.g. TEG® PlateletMapping®, VerifyNow®, etc.) *Note: To protect blinding of the study, platelet function testing (including ASA resistance testing) should be avoided during the course of the study except where indicated by the CIP.*
[2] Coagulation Assessment	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
[2] Right Heart Catheterization	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)
[2] Echocardiogram	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, including percent AV area opening, and AV opening time

[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 following data will be collected for each subject's HM II implant procedure.

Table 3 – Implant Procedure Data Collection

Study Activity	Data Collection
HM II System Information	VAD serial number, reference number and date of implant of entire implanted system
Implant Data	Signs of infection prior to implant, location of outflow anastomosis, apical cuff attachment method, driveline location and positioning, percutaneous driveline exit type, initial pump parameters, presence of LV or LA 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 completion time
Adherence to PREVENT Recommended Practices	Pump pocket size, pump pocket location (inferiorly deep and lateral), inflow cannula position, outflow graft position, pump position, pump fixation, pump speed management, post-operative anticoagulation/antiplatelet management (including Heparin bridging) and blood pressure management
Pump Parameters	Pump Speed, Pump Flow, Pulsatility Index, and Pump Power
Randomization	Confirmation of randomization, date of randomization, and date that research drug was started following implant
Research Drug Bottle Dispensing	Bottle number of the research drug dispensed and date dispensed.

6.6 SCHEDULED FOLLOW-UP VISITS

The required assessments, follow-up schedule, and associated visit windows are generally aligned with INTERMACS, a national MCS registry. All follow-up visits are based on the initial implant date, even if a pump exchange occurs while the subject is being followed on the study. The windows for each follow-up visit are as follows:

Table 4 – Follow-Up Visit Windows

Baseline	Implant	Visit 1	Visit 2	[1] Visit 3	[1] Visit 4	[1] Visit 5	[1] Visit 6
-	-	Week 1 ± 3 days	Month 1 ± 7 days	Month 3 ± 20 days	Month 6 ± 20 days	Month 9 ± 20 days	Month 12 ± 20 days

[1] Note that the window for these visits have been shortened to ± 20 days from the original INTERMACS ± 30 days window.

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 CIP deviation. The Sponsor understands that some lab results may be received several days after the visit has occurred.

At the completion of the Month 12 visit, the subject has completed 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 not collected by the date of the final visit will be considered a protocol deviation.

Table 5 – Scheduled Follow-Up Visit Data Collection

Study Activity	Definition
Subject Status	Initial discharge status, and visit completion
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 Warfarin/Coumadin. Only the start and stop dates will be collected for Warfarin/Coumadin*
Other Medications	ACE inhibitors, inotropes, ARBs, beta blockers, antiarrhythmics, statins, nitrates, allopurinol, aldosterone blockers, antibiotics, diuretics, insulin and antidiabetic medications, and other cardiovascular medications
Bottle Dispensing	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 and Unused Research Drug Return	Bottle status and shipping information. All bottles and unused doses must be returned to ALMAC Clinical upon receipt from subject.
Laboratory Assessments	Hemoglobin (Hgb), Hematocrit (Hct), White Blood Cell Count (WBC), Platelets (PLT), Creatinine (Cr), Estimated Glomerular Filtration Rate (eGFR), LDH and INR. For diabetic patients: HbA1c, and fasting glucose Collected only if SOC: Activated Partial Thromboplastin Time (aPTT), Partial Thromboplastin Time (PTT), Plasma free Hgb (PHgb), liver function tests (AST, ALT, total bilirubin, albumin, pre-albumin), blood urea nitrogen (BUN), D-Dimers, P Selectin, fibrinogen, and Anti Factor Xa Assay (Heparin Assay). *Note: To protect blinding of the study, platelet function testing (including ASA resistance testing) should be avoided during the course of the study except where indicated by the CIP.*
Adherence to PREVENT Recommended Practices	Blood pressure management, INR goals, and pump speed management
Chest/Abdominal X-Ray	PA and lateral chest/abdominal X-rays (that show the entire pump relative to major cardiac/anatomical structures) will be submitted to Sponsor for independent analysis of pump position *Note: Collected between Implant and Month 1 visits, or at pump thrombosis or pump exchange events*
[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, including percent AV area opening, and AV opening time

[1] *If collected per SOC.*

6.7 UNSCHEDULED VISITS

6.7.1 OPERATIVE PROCEDURES

Data related to any cardiac or non-cardiac operative procedures occurring after enrollment will be collected. Operative procedures must be reported to the Sponsor through the EDC system immediately upon discovery of the event or, at the latest, if the operation is unknown to the implanting site (i.e. at another facility), during the next follow-up visit.

For pump exchanges (HM II to HM II only), additional Pump Exchange data will be collected, including exchange status, implant data, PREVENT recommended practices and Chest/Abdominal X-ray. In the event of a pump exchange, the follow-up visit schedule will continue to be based on the initial implant date.

6.7.2 REHOSPITALIZATIONS

All hospitalizations extending over 24 hours 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. Rehospitalizations must be reported to the Sponsor through the EDC system immediately upon discovery of the event or, at the latest, if the rehospitalization is unknown to the implanting site (i.e. at another facility), during the next follow-up visit.

6.7.3 OUTCOMES

Subjects will be followed for 12 months or until an outcome is reached, whichever occurs first. Outcomes include death, heart transplantation, explant (except in cases of HM II to HM II pump exchange), and withdrawal from the study. Outcomes must be reported to the Sponsor through the EDC system immediately upon discovery of the event.

If a subject receives a pump exchange (HM II to non-HM II) during the follow-up period, this event will be considered an explant outcome. If a subject receives a pump exchange (HM II to HM II) during the follow-up period, the subject will remain in the study on the original follow-up schedule.

If a subject has a device explanted for confirmed or suspected pump thrombosis, the pump will be returned to the Sponsor for analysis. Standard commercial processes should be used for pump return.

6.8 SUBJECT STUDY COMPLETION

When the subject has completed the study, the physician will resume management per SOC. To preserve blinding for investigators and remaining enrolled subjects, the research drug arm assignments of individual subjects will not be disclosed until all subjects at the respective site have completed the study.

6.9 CRITERIA AND PROCEDURES FOR SUBJECT WITHDRAWAL

Subjects will be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the subject is otherwise entitled. Withdrawal from the study will not jeopardize their future medical care or

relationship with the investigator. Subjects will be asked to specify the reason for the termination, but have the right not to answer.

The investigator may decide to withdraw a subject from the study at any time with reasonable rationale. The subject's future care will not be influenced by a withdrawal, voluntary or otherwise, from the study. All reasonable efforts should be made to retain the subject in the clinical study until completion of the study.

Reasons for subject's withdrawal may include, but are not limited to:

- Subject refuses to continue participating in the study
- Research drug is not initiated by post-operative day 15
- Subject non-compliance
- Subject participation is terminated by the investigator, as participation is no longer medically appropriate, even though the subject has provided consent
- Subject is lost to follow-up, or can no longer be tracked for data collection at a participating center. This does not apply to missed visits. Site personnel should at all times make all reasonable efforts to locate and communicate with the subject in order to achieve subject compliance to the scheduled follow-up visits:
  - The subject will be considered lost to follow-up after missing two consecutive visits; however, the PI or designated site personnel must document a minimum of two phone calls over a period of two consecutive weeks to demonstrate efforts to communicate with the subject. These phone calls will be documented in the subject's hospital records.
  - If these attempts are unsuccessful, a letter will be sent to the subject's last known address or general practitioner (GP) and a copy of the letter will be maintained in the subject's hospital records.

Note: If a subject does not attend a scheduled follow-up visit within the visit window, this will be considered a missed visit. The subject should attend the next scheduled visit and will not be excluded from the study.

If a subject withdraws from the study, the reason for withdrawal will be documented if available.

If subject withdrawal is due to an adverse event, the subject will be followed until resolution of the event or a determination has been made that the subject's condition is stable. The status of the subject's condition will be documented at the time of withdrawal.

When a subject is withdrawn for any reason, there are no withdrawal procedures to be performed, but all follow-up visits, study assessments, and research drug will be immediately stopped. The physician will resume management according to SOC. Withdrawn subjects should return all remaining research drug to the site. Refer to **Section 5.3.5** for the return of unused study drug.

7 ADVERSE EVENT AND COMPLAINT REPORTING

7.1 DEFINITIONS

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, users or other persons, whether or not related to the investigational medical device.

This definition includes AEs related to the medical device, the research drug, and study procedures.

For this study, data for specified AEs will be collected as follows:

- Neurological Dysfunction, including hemorrhagic stroke, ischemic stroke, and/or TIA
- Pump Thrombosis
- Major Bleeding
- Hemolysis
- Major Infection
- Right Heart Failure

Refer to **Appendix D** for a detailed description of each type of AE.

7.1.2 SERIOUS ADVERSE EVENT

A serious adverse event (SAE) is an adverse event that:

- Led to death
- Led to serious deterioration in the health of the subject, that either resulted in**:**
  - A life-threatening illness or injury, or
  - A permanent impairment of a body structure or a body function, or
  - In-patient or prolonged hospitalization, or
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- Led to fetal distress, fetal death or a congenital abnormality or birth defect.

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

7.1.3 PROCEDURE FOR ASSESSING, RECORDING, AND REPORTING ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Investigators are responsible for the safety surveillance and reporting for the study. Safety surveillance begins at implant and after-the-fact reporting for all enrolled subjects will occur at the time enrollment and will continue until the subject has been withdrawn, experienced an outcome, or completed the study.

Investigators are responsible for reporting AEs to the Sponsor in a timely manner through the EDC, as well as for reporting applicable AEs to their IRB in accordance with their institutional requirements, national and local laws and regulations.

AEs will be followed until they are adequately resolved. Records relating to the subject's subsequent medical course must be maintained until the event has subsided, or until the event stabilizes and the overall clinical outcome is determined. The Sponsor may request de-identified source documentation as applicable.

There are known and anticipated AEs associated with LVAD therapy. These AEs along with detailed definitions can be found in the HM II IFU.

All suspected and confirmed pump thrombosis events will be adjudicated by an independent committee.

The Sponsor will ensure that all events are reported to the relevant authorities in accordance with applicable regulations.

7.1.4 SUBJECT DEATH

All subject deaths will be documented and reported to the Sponsor in a timely manner after the investigator becomes aware of the event.

The Sponsor may request de-identified source documentation as applicable. Additional information may be requested, when required, by the Sponsor in order to support the reporting of deaths to regulatory authorities.

The PI or designated site personnel must notify the IRB, if appropriate, of the deaths reported to the Sponsor in accordance with national and local laws and regulations.

7.2 COMPLAINTS

During the study, the investigator will be responsible for reporting all complaints. A complaint means any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution.

If the complaint does not involve an AE, the investigator must notify the Abbott Post-market Surveillance Department by entering complaints information into the Thoratec® Connect™ System or by calling the HeartLine™ at 1-800-456-1477 as soon as possible after becoming aware of the complaint. Please contact the local Abbott representative to coordinate product returns as applicable. This information will not be collected on a CRF for the study.

If the complaint involves an AE, the investigator must complete an AE Case Report Form (CRF) including the information on the complaint and report to Abbott as soon as possible.

Should a subject death be caused by the Abbott device or the device contributed to the death, the investigator should complete a Form 3500A (MedWatch) and submit to Abbott and the FDA within 10 days after becoming aware of the event.

8 COMPLIANCE TO CIP

8.1 STATEMENTS OF COMPLIANCE

The investigator will not begin subject enrollment or request informed consent from any subject prior to obtaining IRB approval and authorization from the Sponsor in writing for the study.

In case additional requirements are imposed by the IRB, those requirements will be followed, if appropriate. If any action is taken by the IRB, and regulatory requirements with respect to the study, that information will be forwarded to the Sponsor.

8.2 ADHERENCE TO THE CLINICAL INVESTIGATION PLAN

A deviation is defined as an event in which the investigator, site personnel, Sponsor or Sponsor representative did not conduct the study in accordance with the CIP, IRB requirements, or the Investigator Agreement. The investigator is not allowed to deviate from the CIP, which includes inclusion/exclusion criteria and protection of subject safety, except as specified under emergency circumstances. Investigators and sites agreeing to participate in the study must believe that there is equipoise for randomization, and must be willing to be blinded for the duration of the study at their site. Un-blinding will not be performed unless subject is experiencing a major allergic reaction potentially attributable to the research drug, and will require Steering Committee approval. If the study drug is un-blinded, then the subject will be withdrawn from the study.

8.2.1 REPEATED AND SERIOUS NON-COMPLIANCE

In the event of repeated non-compliance or one-time serious non-compliance (as determined by the Sponsor), a Clinical Research Associate or clinical representative will attempt to secure compliance by one or more of the following actions:

- Visiting the investigator
- Contacting the investigator by telephone
- Contacting the investigator in writing
- Retraining of the investigator and/or site personnel
- Corrective and Preventive Action (CAPA)

If an investigator is found to be repeatedly non-compliant with the CIP, research contract, or any other conditions of the study, the Sponsor will either secure compliance or, at its sole discretion, suspend or terminate the investigator's participation in the clinical study.

9 DATA MANAGEMENT

Overall, the Sponsor will be responsible for the data handling. The Sponsor and/or its affiliates will be responsible for compiling and submitting all required reports to governmental agencies.

Data will be analyzed by the Sponsor and may be transferred to the Sponsor's locations or regulatory authorities worldwide in support of a market-approval application.

The PI or institution will provide direct access to source data during and after the clinical study for monitoring, audits, IRB review and regulatory authority inspections. As required, the PI or institution will obtain permission for direct access to source documents from the subject, hospital administration, and national regulatory authorities before starting the clinical study.

9.1 DATA MANAGEMENT PLAN

A detailed Data Management Plan (DMP) will be established to ensure consistency of the data. This document will include procedures used for data review, database cleaning, and the issuance and resolution of data queries. If appropriate, the DMP may be updated throughout the study. All revisions will be tracked and document controlled.

CRF data will be captured in a validated electronic database management system hosted by the Sponsor. Only specially trained designated site personnel will be permitted to enter the CRF data through the EDC system. An electronic audit trail will be used to track any subsequent changes of the entered data.

9.2 DOCUMENT AND DATA CONTROL

9.2.1 TRACEABILITY OF DOCUMENTS AND DATA

The PI will ensure accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor on the CRFs and in all required reports.

9.2.2 RECORDING DATA

Original documentation supporting the data recorded in the CRFs must be maintained, including clinical charts, medical records, laboratory reports, physician referral or consultation letters, X-ray reports, etc. AEs, which are managed at a health care facility other than the study site, must be reported to the Sponsor and every attempt must be made to obtain source documentation from that facility.

The EDC CRFs will be electronically validated by the designated site personnel. Any change or correction to data will be recorded in the EDC system's audit trail.

10 MONITORING

It is the responsibility of the Sponsor to ensure that the study is conducted, recorded, and reported in accordance with the approved CIP, subsequent amendment(s), applicable regulations, and guidance documents.

Prior to beginning the study, the Sponsor will contact the PI and designated site personnel to discuss the study and data requirements.

Centralized monitoring will occur through routine internal data review. This monitoring is designed to identify missing and inconsistent data, data outliers, and potential CIP deviations that may be indicative of site non-compliance. Remote monitoring will be performed. On-site monitoring may occur in lieu of remote monitoring at the discretion of the sponsor. A Sponsor monitor may periodically review the subject records and associated source documents. The PI will make subject and study records available to the clinical monitor for monitoring.

11 REGULATORY INSPECTIONS

The PI or designated site personnel should contact the Sponsor immediately upon notification of a governmental agency inspection at the site. A clinical monitor or designee will assist the site in preparing for the audit.

An investigator who has authority to grant access, will permit authorized governmental agency employees, at reasonable times and in reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are used or where records or results are kept).

An investigator, or designated site personnel, will permit authorized governmental agency employees, at reasonable times and in reasonable manner, to inspect and copy all records relating to the study.

An investigator will permit authorized governmental agency employees to inspect and copy records that identify subjects, upon notice that governmental agency has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator, to the Sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading.

12 STATISTICAL CONSIDERATIONS

PREVENT II is a prospective, multi-center, randomized, double-blinded, placebo-controlled study evaluating the risk of subjects over 50 years of age being managed on warfarin therapy alone compared to warfarin and ASA therapy together. The two groups in the study are as follows:

1) Treatment Arm: Warfarin (INR target: 2.0-2.5, median: 2.25) + Placebo (1 pill/day)
2) Control Arm: Warfarin (INR target: 2.0-2.5, median: 2.25) + ASA therapy (81mg/day)

In general, continuous data will be presented as the number of subjects, mean with standard deviation, median, minimum, and maximum values. Categorical data will be reported as frequencies and percentages. Adverse events will additionally be reported as events per subject year, with only those events that start after implantation of the HM II analyzed. The adverse events will be compared between the two arms of the study using risk ratios (Poisson's regression). Survival data will be presented and analyzed using the Kaplan-Meier method.

The primary endpoints will be analyzed per protocol method as defined in **Section 12.1**. Every effort will be made to avoid crossovers, but in such instances, analysis will be performed in accordance with **Section 12.1**. The study will be conducted in a double-blinded fashion with neither the investigator, nor the subject having the knowledge of whether the subject is in the Treatment or the Control Arm. Only the primary statistician from the Sponsor will have knowledge of the specific groups, and all other parties will be blinded.

Every effort will be made to collect all required data. A one-sided 0.025 level of significance or two-sided 0.05 level of significance will be used to declare statistical significance as outlined below. Multiplicity adjustments will not be made unless specified below. A sensitivity analysis will be performed to account for any bias that may have been introduced by subjects withdrawing from the study or being removed from the study.

12.1 STATISTICAL DESIGN, HYPOTHESES, METHOD AND ANALYTICAL PROCEDURES

Subjects will be block randomized per site on a 1:1 ratio into the Treatment and Control Arms. The study is designed to satisfy two primary endpoints. Both primary endpoints must be met for the study to be successful.

12.1.1 PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint is the incidence of non-surgical bleeding within the first 6 months of support. If a subject experiences any non-surgical bleeding including GI bleeding, epistaxis, subdural hematoma, or a primary hemorrhagic stroke (not due to an ischemic conversion or due to a treatment of a hemolysis/suspected thrombosis event), then the subject will be counted as having reached the primary efficacy endpoint. The determination of whether a hemorrhagic stroke is due to ischemic conversion or due to treatment of a hemolysis/suspected thrombosis event or is a primary hemorrhagic stroke will be made by the Clinical Events Committee (CEC).

The incidence of non-surgical bleeding will be compared between the Treatment and Control Arms using the following null and alternative hypotheses as follows:

$$H_o: \pi_{TREATMENT} \geq \pi_{CONTROL}$$

$$H_A: \pi_{TREATMENT} < \pi_{CONTROL}$$

where $\pi_{TREATMENT}$ and $\pi_{CONTROL}$ are the incidence rates of non-surgical bleeding in the Treatment and Control Arms, respectively.

12.1.2 PRIMARY SAFETY ENDPOINT

The primary safety endpoint is the composite incidence of TE events within the first 6 months of HM II support. If a subject experiences any TE event, including pump thrombosis, ischemic stroke, or hemorrhagic stroke as a result of treatment of a suspected thrombosis/hemolysis event, then the subject will be counted as having reached the primary safety endpoint. The determination of whether a hemorrhagic stroke is due to ischemic conversion or due to treatment of a hemolysis/suspected thrombosis event or is a primary hemorrhagic stroke will be made by the Clinical Events Committee (CEC).

The incidence of TE events in the Treatment Arm will be compared to the Control Arm in a non-inferiority manner. The null and alternative hypotheses are as follows:

$$H_o: \pi_{TREATMENT} \leq \pi_{CONTROL} + \Delta$$

$$H_A: \pi_{TREATMENT} > \pi_{CONTROL} + \Delta$$

where $\pi_{TREATMENT}$ and $\pi_{CONTROL}$ are the incidence rates of TE events in the Treatment and Control Arms respectively, and where Δ is the non-inferiority margin.

12.1.3 SAMPLE SIZE

A total sample size of up to 350 subjects will provide adequate power to satisfy both the primary efficacy and the safety endpoints respectively. The assumptions and rationale are provided in the sections below.

12.1.4 PRIMARY EFFICACY ENDPOINT

Assumptions: Based on the analysis of the first 100 subjects enrolled in the PREVENT study (Data on file), the anticipated incidence of non-surgical bleeding in the Control Arm at 6 months is 40%. The assumption for PREVENT II is that there will at least be a 15% reduction in the incidence of non-surgical bleeding in the Treatment Arm compared to the Control Arm.

The comparison of Treatment and Control Arms will be made using the Fishers Exact Test. The primary endpoint for efficacy will be considered to be met if the p-value ≤ 0.05. A sample size of 330 subjects (165 in each of the Treatment and Control Arms) with an alpha of 0.05 will provide 80% power to demonstrate a significant difference between the Treatment and Control Arms.

12.1.5 PRIMARY SAFETY ENDPOINT

Assumptions: Based on the analysis of the first 100 subjects enrolled in the PREVENT study (Data on file), the anticipated composite incidence of TE events in the Control Arm at 6 months is expected to be 8%. The assumption for PREVENT II is that the Treatment Arm will experience an incidence of TE events of no more than 9% at 6 months. The Treatment Arm will be considered non-inferior to the Control Arm if the upper one-sided 95% confidence limit of the risk difference in the 6 month TE rate between research drug arms (Treatment - Control) is less than +10% (“positive 10%”, where 10% is the non-inferiority Δ in the above null and alternative hypotheses).

A sample size of 338 subjects (169 each in the Treatment and Control Arms) will achieve 80% power to prove the Treatment Arm is non-inferior to HM II when the margin of non-inferiority is 10% (=Δ in the above null and alternative hypotheses) using the Farrington-Manning risk difference approach to non-inferiority at a one-sided alpha = 0.025.

12.2 ADDRESSING CLINICAL SCENARIOS IN WHICH CHANGES TO ANTIPLATELET THERAPY MAY BE REQUIRED

Subjects should be maintained on both Warfarin (with a target INR: 2.0-2.5) and the research drug (ASA or placebo) for the entire duration of the study. Changes in therapies are only accepted under the following scenarios:

Figure 3 – Treatment of Non-Surgical Bleeding Events

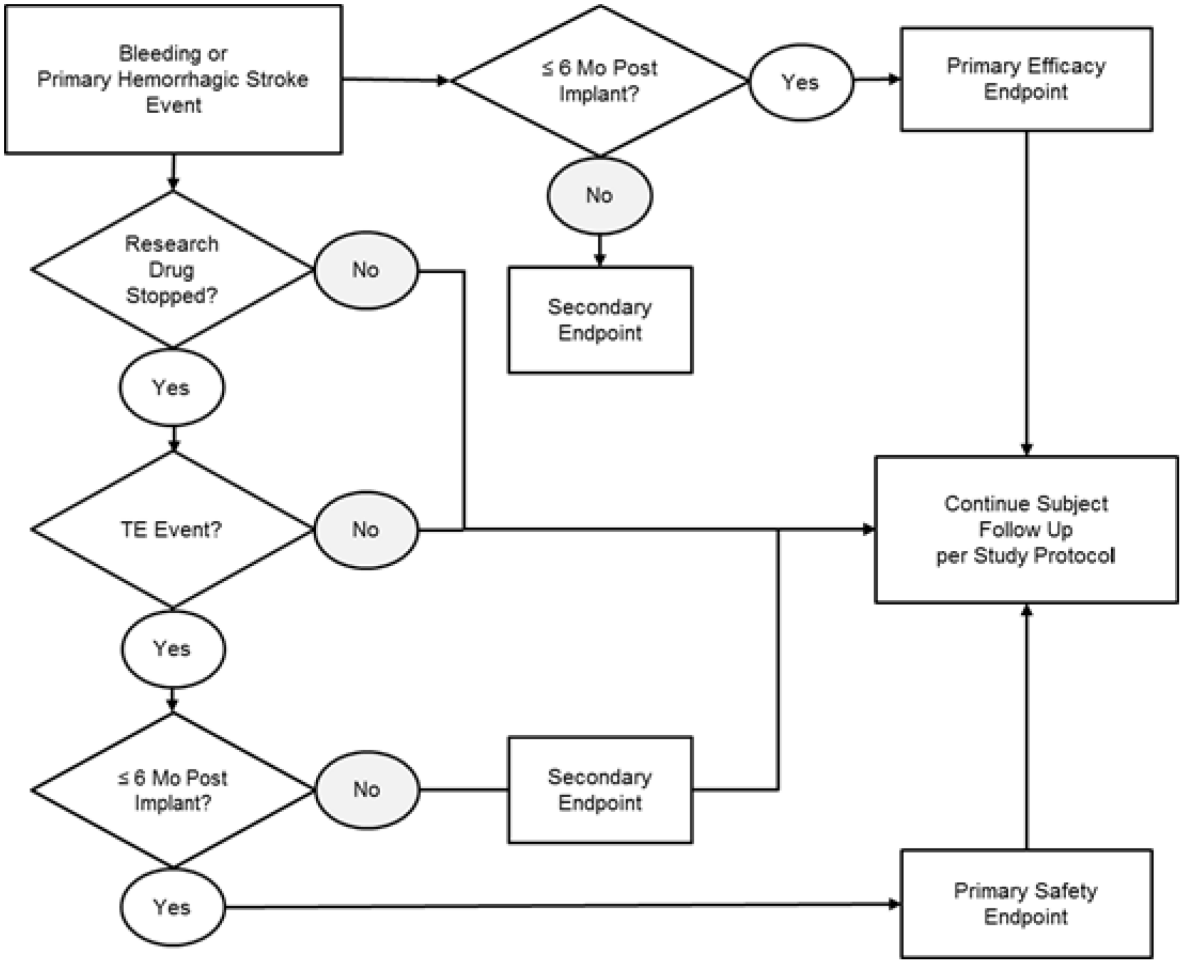


Figure 4 – Treatment of Thromboembolic Events

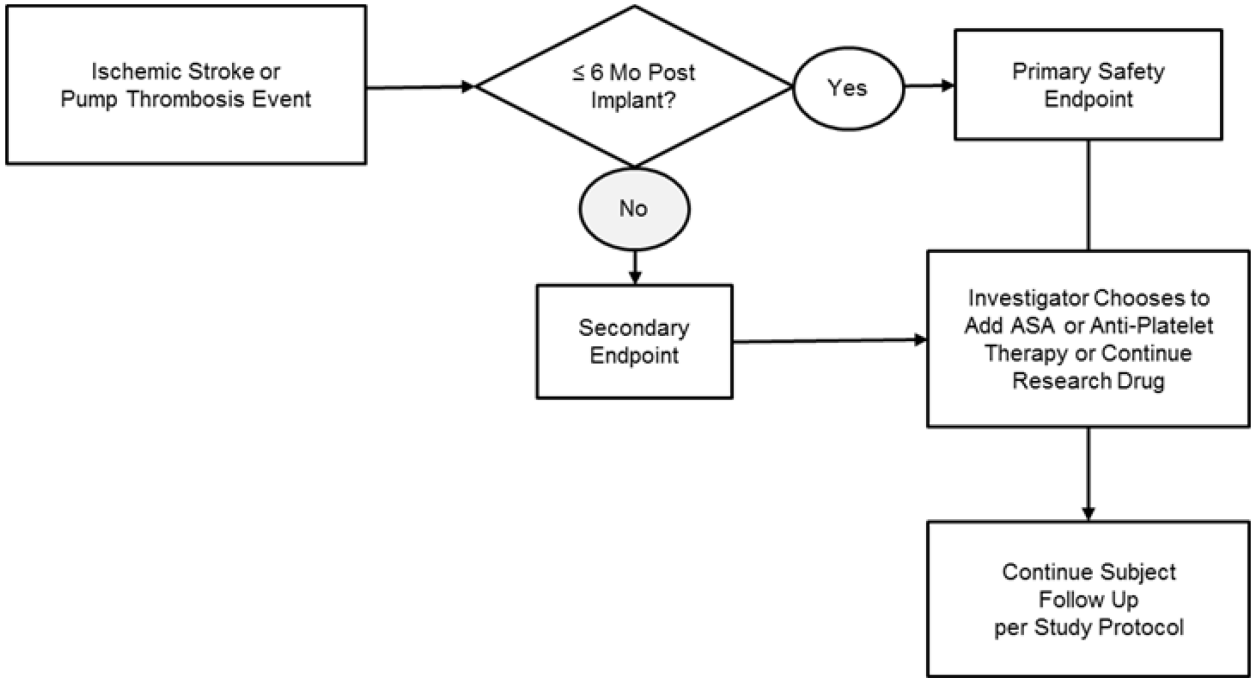


Figure 5 – Treatment of Hemolysis Events

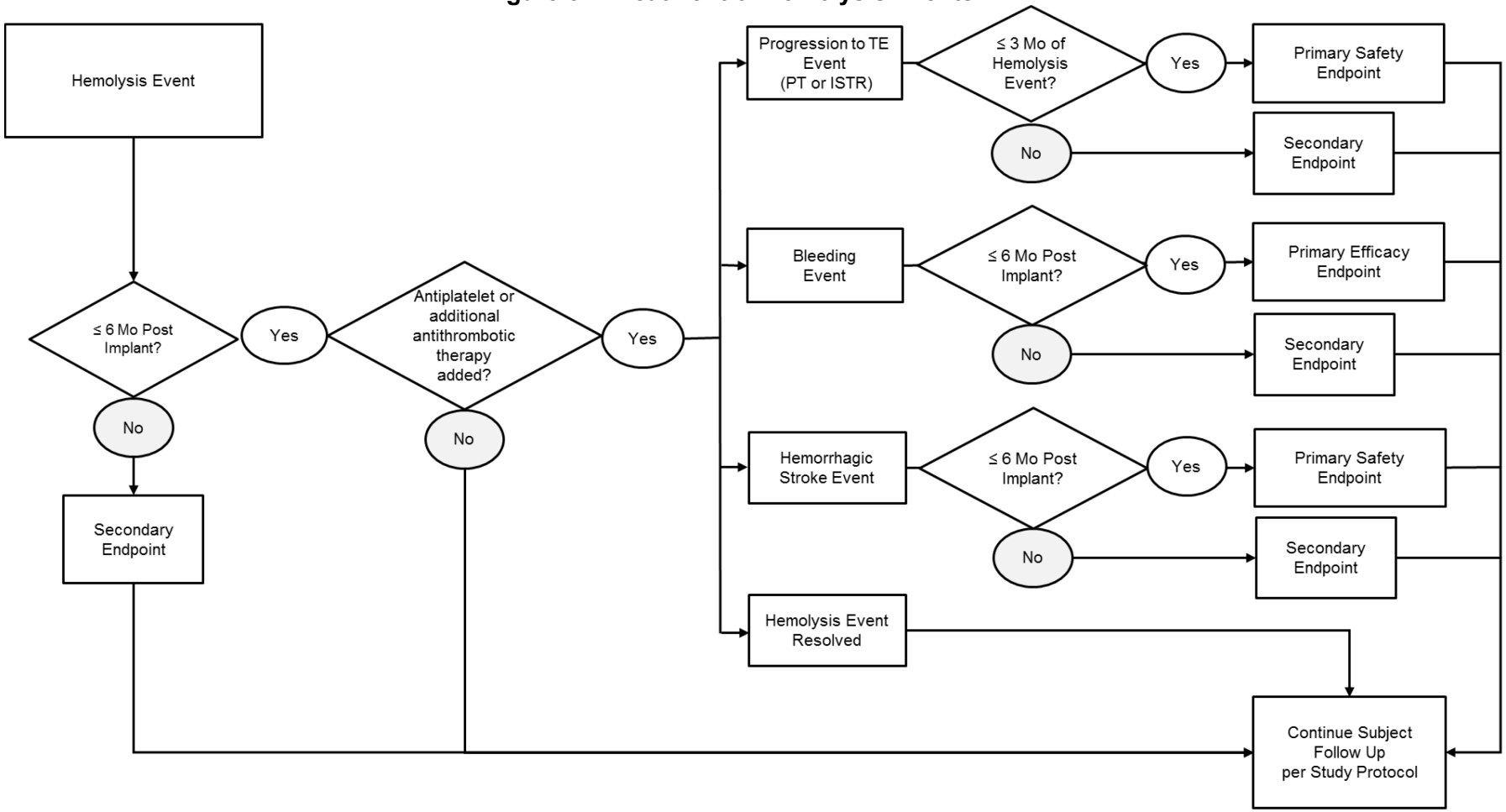
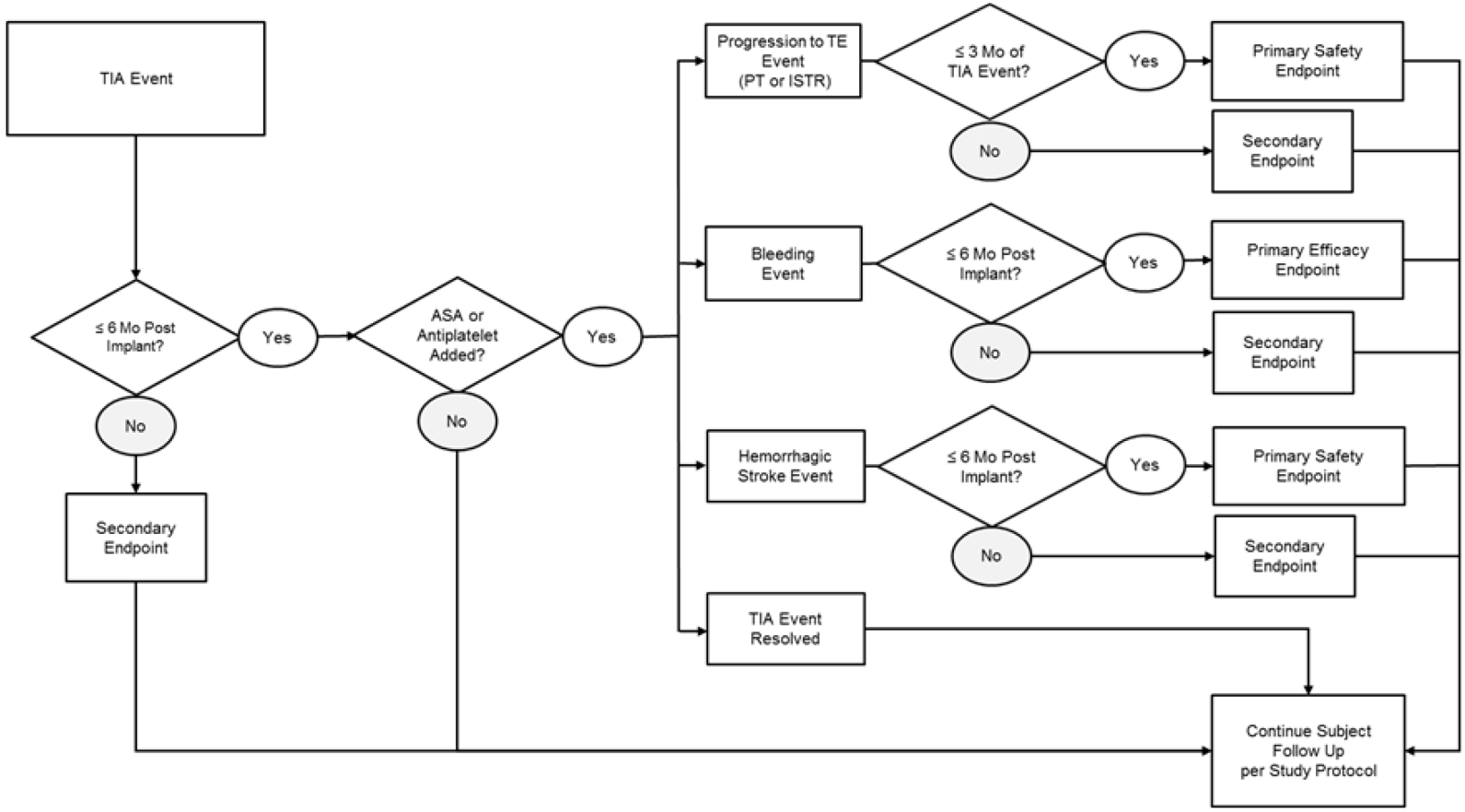


Figure 6 – Treatment of Transient Ischemic Attack Events



12.2.1 PERSISTENT CHANGES TO ANTIPLATELET THERAPY

If the investigator persistently deviates from the CIP by deliberately changing antiplatelet therapy outside of the scenarios outlined above, the subject will be censored from that point onwards. Follow-up will continue, but the data will not contribute to the primary endpoints. This will be considered a CIP deviation and may result in site disqualification. The deviation and details about therapy changes will be recorded on the appropriate CRF.

12.3 SAFETY ASSESSMENT

A safety assessment will be performed after 60 subjects have completed 3 months of follow-up. Both incidence of stroke and pump thrombosis will be analyzed. Results will be presented to the Steering Committee, which will review the findings and make a decision to proceed or stop the study due to safety concerns. Enrollment will continue during this review process. Additionally, after the initial 3-month safety review, an analysis of AEs associated with the primary endpoints will be presented to the Steering Committee for continued safety assessment at regular 6-month intervals. The Steering Committee will review the findings and make a recommendation to proceed or stop the study due to safety concerns.

12.4 RANDOMIZATION APPROACH

Subjects will be randomized in a 1:1 fashion (one Treatment Arm subject to one Control Arm subject). The randomization will be stratified by study site and blocked to maintain the 1:1 ratio over time. The Sponsor will implement randomization through ALMAC Clinical's WebEZ system. Randomization will occur after the subject is successfully implanted with the HM II, and must be completed within 48 hours of implant.

13 DOCUMENT MANAGEMENT AND RETENTION

13.1 REGULATORY DOCUMENTATION

The following study documents will be maintained by the study site and copies of site-specific documents sent to Sponsor (including but not limited to):

- Research Agreement and amendments
- Approved Protocol and amendments
- Protocol signature page
- IRB approved ICF templates
- IRB Submissions and Approval(s)
- IRB Membership Roster(s) or Federal wide Assurance (FWA) number
- Pertinent IRB Correspondence
- Delegation of Authority Log
- Training Log
- Financial Disclosure(s)
- Curriculum Vitae(s)
- Medical License(s)
- Laboratory Certifications and Normals
- Screening Log
- Aspirin Resistance Testing Instructions
- WebEZ Instructions
- Drug Return Instructions (DRI)
- Research Drug Shipping/Receiving Receipts
- Submission of Media Instructions
- Media Shipping/Receiving Receipts
- Monitoring Log
- Sponsor Correspondence

- Source documentation (such as subject clinic charts, medical records, laboratory records)
- Notes to File

13.2 RETENTION OF RECORDS

The PI will maintain all study documents from prior, during, and (as specified) after the clinical study on file at the site for a minimum of 15 years after the termination of this study, or longer as per local laws, or when it is no longer needed to support a marketing application, whichever is later.

The PI must contact the Sponsor prior to destroying or archiving off-site any records and reports pertaining to this study to ensure that they no longer need to be retained on site.

All original subject files must be stored for the longest possible time permitted by the regulations at the hospital, research institute, or practice in question. If archiving can no longer be maintained at the site, or if the responsibility of retention transfers to a different individual, the investigator will notify the Sponsor.

All data and documents will be made available on request of the relevant authorities in case of an audit. In the event of an audit by the FDA or other regulatory authority, the PI must notify the Sponsor.

The Sponsor will archive and retain all essential clinical study documents from prior, during and (as specified) after the clinical study as per requirements.

14 STUDY COMMITTEES

At least two committees will be established as part of this study: the Steering Committee and the Clinical Events Committee (CEC).

The Steering Committee will oversee the conduct and execution of the study. The Steering Committee, already established, is comprised of three cardiologists and two cardiovascular surgeons, who are each leaders in the field of MCS therapy for advanced heart failure. The Steering Committee will meet regularly to discuss study progress and proceedings of the meetings will be documented. See Section 12.3 for additional information on the Steering Committee's safety assessment of trial progress. The responsibilities of the Steering Committee may include, but are not limited to:

- Reviewing and providing input to the study design, and the study protocol
- Providing assessment of perceived evidence gaps and opinions of the medical community regarding study design and execution
- Providing guidance on study execution including study eligibility questions, data analysis, presentation/publication of study results, patient safety, and address any study-related issues (e.g. recruitment and compliance to study protocol)
- Provide recommendations for the selection of other committee members, including the Publication Committee, the CEC, and other sub-committees

The CEC will be responsible for the adjudication process for adverse events that are related to bleeding and thromboembolic events. The CEC will be established prior to study

initiation, and will meet regularly to ensure that adverse events reported as part of the study are adequately adjudicated.

15 OUTSOURCING OF DUTIES AND FUNCTIONS

The Sponsor may transfer any or all of the duties and functions related to the clinical study, including monitoring, to an external organization (such as a CRO or individual contractor), but the ultimate responsibility for the quality and integrity of the clinical study will reside with the Sponsor. All requirements applying to the Sponsor will also apply to the external organization inasmuch as this organization assumes the clinical study related duties and functions of the Sponsor.

16 INVESTIGATION SUSPENSION OR TERMINATION

16.1 PREMATURE TERMINATION OF THE WHOLE STUDY OR THE STUDY AT ONE OR MORE INVESTIGATIONAL SITES

The Sponsor reserves the right to stop the study at any stage, with appropriate written notice to the PI. Possible reasons for early termination of the study by the Sponsor, either at a local or national level, may include, but are not limited to:

- The device / therapy fails to perform as intended
- Sponsor's decision
- Recommendation from Steering committee to Sponsor
- Request of IRB(s)
- Concern for subject safety and welfare
- Failure to secure subject Informed Consent prior to any investigational activity
- Failure to report unanticipated adverse device effects within 72 hours to Abbott
- Repeated non-compliance with the CIP or the Clinical Trial Agreement
- Inability to successfully implement the CIP
- Violation of applicable national or local laws and regulations
- Falsification of data, or any other breach of ethics or scientific principles.

The investigator may discontinue participation in the study with appropriate written notice to the Sponsor.

If the investigator or Sponsor terminates site participation, the investigator will return all documents to the Sponsor, provide a written statement as to why the premature termination has taken place, and notify the IRB and/or regulatory authority (if applicable). Follow-up for all enrolled subjects will be as per CIP requirements.

A PI, IRB, or regulatory authority may suspend or prematurely terminate participation in a clinical study at the investigational sites for which they are responsible.

If suspicion of an unacceptable risk to subjects arises during the study or when so instructed by the IRB or regulatory authority, the Sponsor may suspend the clinical study

as appropriate while the risk is assessed. The Sponsor will terminate the clinical study if an unacceptable risk is confirmed.

If suspension or premature termination occurs, the terminating party will justify its decision in writing and promptly inform the other parties with whom they are in direct communication. The PI and the Sponsor will keep each other informed of any communication received from IRB or regulatory authority.

If for any reason the Sponsor suspends or prematurely terminates the study at an individual investigational site, the Sponsor will inform the responsible regulatory authority, as appropriate, and ensure that the IRB is notified, either by the PI or by the Sponsor. If the suspension or premature termination was in the interest of subject safety, the Sponsor will inform all other PIs.

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 up the subjects enrolled in the clinical study, and the PI or authorized designee will promptly inform the enrolled subjects at his/her investigational site, if appropriate.

16.2 STUDY CONCLUSION

The study will be concluded when:

- All sites are closed, **AND**
- The Final Report generated by the Sponsor has been provided all participating to sites or the Sponsor has provided formal documentation of study closure.

17 PUBLICATION POLICY

The results of the clinical study, whether positive or negative, will be submitted for publication. The Steering Committee will oversee the development of a Publication Committee, as well as the development of study publication policy in close collaboration with the Sponsor. Publication Committee membership may consist of Steering Committee members, site PIs who have provided significant contributions (e.g. enrollment, scientific contribution), and three representatives from the Sponsor. The Publication Committee will be responsible for identifying, selecting, and approving publication proposals and determining authorship according to the publication policy.

For more information on publication guidelines, please refer to the International Committee of Medical Journal Editors (ICMJE) on www.icmje.org.

This study will be posted on ClinicalTrials.gov and results will be posted on ClinicalTrials.gov as required.

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Appendix A: Abbreviations

Abbreviation	Term
ACE	Angiotensin-converting Enzyme
AC	Alternating Current
AE	Adverse Event
AI	Aortic Insufficiency
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
ARBs	Angiotensin II Receptor Blockers
ASA	Acetylsalicylic Acid (aspirin)
AST	Aspartate Aminotransferase
AVMs	Arteriovenous Malformations
AVWS	Acquired von Willebrand Syndrome
BTT	Bridge-to-Transplantation
BUN	Blood Urea Nitrogen
CABG	Coronary Artery Bypass Graft
CAPA	Corrective and Preventative Action
CEC	Clinical Events Committee
CF-LVAD	Continuous Flow Left Ventricular Assist Device
CI	Cardiac Index
CIP	Clinical Investigational Plan
CNS	Central Nervous System
CO	Cardiac Output
CPB	Cardiopulmonary Bypass
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
CVP	Central Venous Pressure
DMP	Data Management Plan
DRI	Drug Return Instructions
DT	Destination Therapy
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EU	European Union
FDA	Food and Drug Administration
FFP	Fresh Frozen Plasma
GI	Gastrointestinal
GP	General Practitioner
GU	Genitourinary
HbA1c	Hemoglobin A1c
Hct	Hematocrit
HF	Heart Failure
Hgb	Hemoglobin
HIT	Heparin Induced Thrombocytopenia

Abbreviation	Term
HIV	Human Immunodeficiency Virus
HM II	HeartMate II
HMW	High Molecular Weight
ICF	Informed Consent Form
ICH	Intracranial Hemorrhage
ICMJE	International Committee of Medical Journal Editors
ID	Identification
IFU	Instructions for Use
INR	International Normalized Ratio
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
IRB	Institutional Review Board
ISHLT	International Society for Heart & Lung Transplantation
LA	Left Atrium
LAR	Legally Authorized Representative
LDH	Lactate Dehydrogenase
LMWH	Low Molecular Weight Heparin
LV	Left Ventricle
LVAD	Left Ventricular Assist Device
LVAS	Left Ventricular Assist System
LVEF	Left Ventricular Ejection Fraction
LVEDD	Left Ventricular End Diastolic Diameter
LVESD	Left Ventricular End Systolic Diameter
MAP	Mean Arterial Pressure
MCS	Mechanical Circulatory Support
MCSD	Mechanical Circulatory Support Device
MI	Myocardial Infarction
mmHg	Millimeters of Mercury
MO	Month
MR	Mitral Regurgitation
MRI	Magnetic Resonance Imaging
NA	Not Applicable
NC	North Carolina
NJ	New Jersey
NYHA	New York Heart Association Class
PA	Pennsylvania
PAD	Diastolic Pulmonary Artery Pressure
PAM	Mean Pulmonary Artery Pressure
PAS	Systolic Pulmonary Artery Pressure
PCPW	Pulmonary Capillary Wedge Pressure
PHgb	Plasma Free Hemoglobin
PI	Principal Investigator
PLT	Platelet Count
POD	Post-Operative Day
PR	Pulmonary Regurgitation

Abbreviation	Term
PRBC	Packed Red Blood Cells
PT	Pump Thrombosis
PTT	Partial Thromboplastin Time
PVAD	Paracorporeal Ventricular Assist Device
RAP	Right Atrial Pressure
REV	Revision
RPM	Revolutions Per Minute
SAE	Serious Adverse Event
SOC	Standard of Care
TE	Thromboembolic
TEG	Thromboelastography
TIA	Transient Ischemic Attack
tPA	Tissue Plaminogen Activator
TR	Tricuspid Regurgitation
UNOS	United Network for Organ Sharing
US	United States
VAD	Ventricular Assist Device
VER	Version
VT	Ventricular Tachycardia
VWF	Von Willebrand Factor
WBC	White Blood Cell Count

Appendix B: CIP Revision History

Revision History				
Amendment Number	Version	Date	Rationale	Details
N/A	A	13JUN2016	First release of CIP	N/A
1.0	B	25JUL2016	Clarification of multiple sections	Additional detail/edits added to sections on blinding, assessments, screening and complaints
2.0	C	17APR2017	Addition of geographical region; increase in number of subjects; addition of patients with Impella® devices; rebranding, clarification of multiple sections	Canada added as an additional geography; maximum number of subjects was increased from 40 to 45; patients with an Impella® device may now be considered; branding has changed from SJM to Abbott, and additional detail was added to Appendix C, treatment guidelines, safety assessment and on stroke determination.
3.0	D	09OCT2017	Updated language for consistency between sections, updated inclusion criteria; updated study contacts	Updated language in section 3.4 to be consistent with other sections regarding safety assessment; updated inclusion criteria and study description to include subjects 50 years or older; updated study contacts
4.0	ABT-CIP-10353 Rev. A	16JUL2020	Redacted for clinicaltrials.gov posting	• Contact information of study personnel was removed from page 13. • Since the document was redacted for submission to clinicaltrials.gov, a new document number (ABT-CIP-10353 Rev. A) was issued by our QMS, but apart from the redacted information, the CIP is the same as SJM-CIP-10134 Rev. D

Appendix C: PREVENT Recommended Practices to Reduce the Risk of Pump Thrombosis

The PREVENT recommended practices outlined are aimed at maximizing flow through the LVAD, reducing risk of cannula malposition, and ensuring that the patient is adequately anticoagulated while on LVAD support. These recommendations are similar to what is published in the HM II IFU with modifications derived from clinical practice. Additional recommendations have also been provided regarding the HM II implantation technique itself, as recent publications have highlighted that pump migration and cannula obstruction can increase the risk of device thrombosis (34, 35).

It is anticipated that adoption of these patient management practices will ultimately lower the risk of pump thrombosis, while maintaining an acceptable rate of bleeding; however, it is understood that deviation from these recommendations may be necessary in certain clinical scenarios.

Summary of Recommended Practices

Implantation Technique

- Create an adequately sized pump pocket, located inferiorly deep and lateral.
- Position the inflow cannula parallel to the septum, oriented to the central LV.
- Position the outflow graft right of sternal midline to avoid compression of RV.
- Position the pump below the diaphragm.
- Fixate the pump (e.g., to the diaphragm or chest wall) to prevent migration.

Anticoagulation/Antiplatelet Management

- In patients without persistent bleeding, begin bridging with unfractionated heparin or LMWH within 48 hours of device implant with a goal PTT of 40-45 sec in the first 48 hours, followed by titration up to PTT 50–60 by 96 hours. If heparin is contraindicated, consider other alternatives including argatroban, intravenous warfarin, and bivalirudin.
- Initiate warfarin within 48 hours to obtain a goal INR of 2.0-2.5 by POD 5-7, at which time heparin therapy may be discontinued.
- Once there is no evidence of bleeding, initiate research drug within 5 days post HM II implantation.
- Maintain the patient throughout LVAD support on the research drug and Warfarin with a goal INR of 2.0-2.5.

Pump Speed Management

- Run pump speeds above 9000 rpm when possible.
- Avoid pump speeds below 8600 rpm when possible.
- Adjust pump speed to permit intermittent aortic valve opening only after the above goals are achieved.

Blood Pressure Management

- Maintain a mean arterial pressure (MAP) < 90 mm Hg

Implantation Technique

Proper implantation of the HM II helps to maximize flow and reduce the incidence of adverse events. The goals are intuitive: unobstructed inflow cannula, unobstructed outflow graft with avoidance of right ventricular compression, and prevention of pump migration. The basic principles summarized above address these objectives and include recommendations for pocket size and location, pump position and anchoring.

Anticoagulation Management

The recommended anticoagulation strategy is divided into early anticoagulation therapy and long term anti-thrombotic therapy.

Heparin Bridging (Early Anticoagulation Therapy)

The HM II IFU calls for perioperative intravenous heparin as a bridge to warfarin therapy. However, over time, the use of heparin bridging in clinical practice has gone down in order to reduce the risk of post-operative bleeding (14, 36). Although bleeding rates have decreased since the clinical trial (5, 8), this may have contributed to an increased incidence of pump thrombosis. As such, the recommended practices outlined here include a return to heparin bridging as outlined originally in the HM II IFU.

Warfarin Anticoagulation (Early and Long-Term Therapy)

The recommendation regarding warfarin anticoagulation is to obtain a goal INR of 2.0-2.5 by post-operative day 5-7 and to maintain this goal throughout the duration of LVAD support. This INR target is within the management guidance outlined in the HM II IFU. In the HM II DT trial, the median discharge INR was 2.1 (7). In general, the risk of thrombotic events increases with INR < 1.5 and the risk of hemorrhagic stroke increases with INR > 2.5 (37).

Administration of Research Drug

Once bleeding has subsided and the patient is hemodynamically stable (typically PODs 2-5), begin administering a single pill of the research drug daily. Maintain the subject on the research drug and warfarin throughout the duration of support.

Pump Speed Management

Recent studies have indicated that a decreased frequency of aortic valve opening post LVAD implantation is associated with an increased risk of TE events (32). As such, there has been a gradual trend of reducing pump speeds in order to increase the frequency of aortic valve opening to reduce the risk of aortic insufficiency and increase flow pulsatility. However, low pump speeds may result in low flow through the pump, especially in situations when the patient is hypertensive. Pump speed optimization is critical to ensure that there is adequate flow through the pump.

Pump speeds coming out of the operating room should be optimized. Pump speeds that are too high may adversely impact the right ventricle or septal position; those that are too low may result in low flow and increase risk of pump thrombosis or insufficient circulatory support. Recommendations for pump speed have been established based on observations from the HM II

clinical trial (14). Average speed in the HM II clinical was 9150 ± 495 rpm on day 1, and 9405 ± 448 rpm on day 180 (data on file). Specifically, the recommendation is to run pump speeds greater than 9000 rpm for most patients and to avoid pump speeds less than 8600 rpm.

Blood Pressure Management

Post-implantation hypertension should be treated at the discretion of the attending physician. Per the HM II IFU, any therapy that consistently maintains mean arterial blood pressure (MAP) less than 90 mm Hg should be considered adequate. Manual auscultation with a Doppler is recommended.

Appendix D: Adverse Event Definitions

The following definitions will be utilized for this study:

Neurological Dysfunction (Modified INTERMACS Definition)

Any new, temporary or permanent, focal or global neurologic dysfunction 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 a cerebrovascular event as defined below or as a non-vascular acute neurologic event. A neurologic event may be recognized by a clinically evident sign or symptom, or by clinically-silent electrographic seizure activity, or as a clinically silent lesion detected by surveillance neuroimaging.

Each neurologic event should be classified by the clinical provider following complete neurologic assessment as **one** of the following event types:

- Transient Ischemic Attack (TIA): An acute transient neurologic 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. Ischemic stroke should be specified as due to arterial-distribution ischemia or venous thrombosis.
- Acute Symptomatic Intracranial Hemorrhage: A new acute neurologic deficit attributable to intracranial hemorrhage (ICH). ICH subtype should be specified as one or a combination of the following types: subarachnoid, intraventricular, parenchymal, or subdural.
- Other: Neurological dysfunction events that do not satisfy the criteria for a hemorrhagic or ischemic stroke such as hypoxic-ischemic encephalopathy (such as signs and symptoms of subclinical electrographic seizures), new encephalopathy due to other causes (such as meningitis, toxic-metabolic, or drug-related processes).

Pump Thrombus (Modified INTERMACS Definition)

Pump Thrombus represents a special case of major device malfunction and will be classified as either suspected or confirmed pump thrombus.

Suspected Pump Thrombus: A pump-related malfunction in which clinical or MCSD parameters suggest thrombus on the blood contacting components of the pump, cannulae, or grafts.

Signs and symptoms for suspected pump thrombus should include the following:

1) **Both** of the following criteria:

- Major Hemolysis: A hemolysis event occurring after the first 72 hours post-implant and associated with clinical symptoms or findings of hemolysis such as hemoglobinuria, anemia, and/or hyperbilirubinemia, with one of the following:
    - Plasma-free hemoglobin value greater than 20 mg/dl
    - A serum lactate dehydrogenase (LDH) level greater than two and one-half times (2.5x) the upper limits of the normal range at the implanting center

- Hemoglobinuria
- Presence of heart failure not explained by structural heart disease, an abnormal ramp test, or abnormal pump parameters

AND

2) An event or intervention, including **one or more** of the following:

- 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 Pump Thrombus: A major pump-related malfunction in which thrombus is confirmed within the blood contacting surfaces of device inflow cannula or outflow conduit or grafts. This can 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.

If a Suspected Pump Thrombus event is ultimately confirmed through visual inspection following pump replacement, urgent transplantation or upon autopsy following death, the event will be adjudicated by the CEC for reclassification to Confirmed Pump Thrombus.

Major Bleeding (INTERMACS Definition)

An episode of suspected internal or external bleeding that results in **one or more** of the following:

- Death
- Re-operation
- Hospitalization
- Transfusion of red blood cells as follows:
  - During first 7 days post implant
    - ≥ 50 kg: ≥ 4U packed red blood cells (PRBC) within any 24-hour period during first 7 days post implant.
    - < 50 kg: ≥ 20 cc/kg packed red blood cells (PRBC) within any 24-hour period during first 7 days post implant.
  - After 7 days post implant
    - A transfusion of packed red blood cells (PRBC) after 7 days following implant with the investigator recording the number of units given. (Record number of units given per 24-hour period.)

Note: Hemorrhagic stroke is considered a Neurological Dysfunction and not a separate bleeding event.

Hemolysis (Modified INTERMACS Definition)

Minor Hemolysis: A hemolysis event occurring after the first 72 hours post-implant in the absence of clinical symptoms or findings of hemolysis or abnormal pump function, with **one** of the following:

- Plasma-free hemoglobin value greater than 20 mg/dl
- A serum lactate dehydrogenase (LDH) level greater than two and one-half time (2.5x) the upper limits of the normal range at the implanting center.

Major Hemolysis: A hemolysis event occurring after the first 72 hours post-implant and associated with clinical symptoms or findings of hemolysis such as hemoglobinuria, anemia, and/or hyperbilirubinemia, with **one** of the following:

- Plasma-free hemoglobin value greater than 20 mg/dl
- A serum lactate dehydrogenase (LDH) level greater than two and one-half times (2.5x) the upper limits of the normal range at the implanting center.

Major Infection (INTERMACs Definition)

A clinical infection accompanied by pain, fever, drainage and/or leukocytosis that is treated by non-prophylactic anti-microbial agents. 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 Pocket Infection: A positive culture from the skin and/or tissue surrounding the driveline or from the tissue surrounding the external housing of a pump implanted within the body, coupled with the need to treat with anti-microbial 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. (There should be a separate data field for paracorporeal pump that describes infection at the percutaneous cannula site, e.g. Thoratec PVAD).

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

Right Heart Failure (INTERMACS Definition)

Symptoms or findings of persistent right ventricular failure characterized by **both** of the following:

1) Elevated central venous pressure (CVP) documented by **one or more** of the following:
    - Direct measurement (e.g., right heart catheterization) with evidence of a central venous pressure (CVP) or right atrial pressure (RAP) > 16 mmHg
    - Findings of significantly dilated inferior vena cava with absence of inspiratory variation by echocardiography

- Clinical findings of elevated jugular venous distension at least half way up the neck in an upright patient.

AND

2) Elevated central venous pressure manifestation characterized by **one or more** of the following:

- Clinical findings of peripheral edema (>2+ either new or unresolved)
- Presence of ascites or palpable hepatomegaly on physical examination (unmistakable abdominal contour) or by diagnostic imaging
- Laboratory evidence of worsening hepatic (total bilirubin > 2.0) or renal dysfunction (creatinine > 2.0).

Appendix E: Case Report Forms

Study-specific Case Report Forms (CRFs) will be provided separately.

Appendix F: Sample Informed Consent

A sample informed consent will be provided separately.