This supplement contains the following items:

1. Original protocol submitted and approved by the FDA (version 3.0), current protocol submitted and approved by the FDA (version 8.0), and a table summarizing the changes.

2. Original statistical analysis plan submitted to the FDA, current statistical analysis plan approved by the FDA, and a table summarizing the changes.

Thoratec® Corporation

HeartMate® III

IDE Clinical Study Protocol

IDE # Pending IDE Submission

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REVISION HISTORY

Version	Date	Revision Summary	Originator	Release Date
1	3/6/2014	Original Protocol	Kelly Maslin	3/6/2014
2	4/22/2014	Update to Inclusion Criteria #6, update to functional status and independent assessor, clarification of pump log collection, modification to Modified Rankin Score timing, updated enrollment numbers, clarification of AE definitions; updated pager number; updated references	Kelly Maslin	4/24/2014
3	6/17/2014	Update to Exclusion Criteria #5, clarification to timeframe for randomization, clarification of x-ray collection, allow for collection of TEE post-implant, update number of study sites	Kelly Maslin	6/17/2014

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List of Abbreviations

6MWT .....Six-Minute Walk Test
AAA .....Abdominal Aortic Aneurysm
ACE .....Angiotensin Converting Enzyme
ADL.....Activities of Daily Living
AE.....Adverse Event
AHA .....American Heart Association
AI .....Aortic Insufficiency
AICD .....Automatic Internal Cardiac Defibrillator
AIMDD .....Active Implantable Medical Device Directive
ALT .....Alanine Aminotransferase
aPTT.....Activated Partial Thromboplastin Time
ARB .....Angiotensin Receptor Blocker
AST.....Aspartate Aminotransferase
AT .....As Treated
AV.....Aortic Valve
BNP .....B-type Natriuretic Peptide
BSA .....Body Surface Area
BTT.....Bridge to Cardiac Transplantation
BUN .....Blood Urea Nitrogen (Urea, blood)
CEC .....Clinical Events Committee
CFR .....Code of Federal Regulations
CI .....Cardiac Index
CIP.....Clinical Investigation Plan
CK.....Creatine Kinase
CNS .....Central Nervous System
COPD .....Chronic Obstructive Pulmonary Disease
CPB .....Cardiopulmonary Bypass
CRF .....Case Report Form
CRP .....C-reactive Protein
CRT .....Cardiac Resynchronization Therapy
CSA .....Clinical Study Agreement
CT.....Computed Tomography
CV.....Cardiovascular
CVP .....Central Venous Pressure
DT.....Destination Therapy
DSMB .....Data Safety Monitoring Board
ECG.....Electrocardiogram
eCRF .....Electronic Case Report Form
EDC .....Electronic Data Capture
EEG .....Electroencephalogram
eGFR .....Glomerular Filtration Rate
EQ-5D-5L.....EuroQol Health Utility Index
FDA .....U.S. Food and Drug Administration
FEV_1 .....Forced Expiratory Volume in One Second
FVC .....Forced Vital Capacity

List of Abbreviations

FWA.....Federal Wide Assurance
GI.....Gastrointestinal
GLP .....Good Laboratory Practices
H_0.....Null Hypothesis
H_A .....Alternative Hypothesis
HF.....Heart Failure
HIE.....Hypoxic-Ischemic Injury
HM II.....HeartMate II
HM III .....HeartMate III
HR .....Heart Rate
Hs-CRP.....High Sensitivity C-reactive Protein
IABP .....Intra Aortic Balloon Pump
IB .....Investigator's Brochure
ICD .....Internal Cardiac Defibrillator
ICH .....Intracranial Hemorrhage
ICF.....Informed Consent Form
ICU .....Intensive Care Unit
IDE.....Investigational Device Exemption
IFU.....Instructions For Use
INTERMACS.....Interagency Registry for Mechanically Assisted Circulatory Support
INR .....International Normalized Ratio
IRB.....Institutional Review Board
ITT .....Intent-to-treat
KCCQ .....Kansas City Cardiomyopathy Questionnaire
LDH .....Lactic Acid Dehydrogenase
LOS .....Length of Stay
LV .....Left Ventricle
LVAD .....Left Ventricular Assist Device
LVAS .....Left Ventricular Assist System
LVEDD.....Left Ventricular End Diastolic Diameter
LVEF.....Left Ventricular Ejection Fraction
LVESD.....Left Ventricular End Systolic Diameter
MB .....Myocardial Band
MCS.....Mechanical Circulatory Support
MCS.....Mechanical Circulatory Support Device
MPU.....Mobile Power Unit
MR.....Mitral Regurgitation
NT-ProBNP.....N terminal B-type natriuretic peptide
NYHA.....New York Heart Association
OMM.....Optimal Medical Management
PHgb.....Plasma Free Hemoglobin
PA.....Posterior-anterior
PI .....Principal Investigator
PMA .....Premarket Approval
PRBC.....Packed Red Blood Cells

List of Abbreviations

PT .....Prothrombin Time
PTT .....Partial Thromboplastin Time
PVD .....Peripheral Vascular Disease
PVR .....Pulmonary Vascular Resistance
RCT .....Randomized Controlled Trial
RV.....Right Ventricle
RVAD.....Right Ventricular Assist Device
SAE .....Serious Adverse Event
SBP .....Systolic Blood Pressure
SHFM .....Seattle Heart Failure Model
Thoratec.....Thoratec Corporation
tPA……..Tissue Plasminogen Activator
TR.....Tricuspid Regurgitation
UADE.....Unanticipated Adverse Device Effect
UNOS……United Network for Organ Sharing
VAD .....Ventricular Assist Device
VAS .....Visual Analogue Scale
WBC .....White Blood Cells
WMA.....World Medical Association

STUDY SYNOPSIS	
Device	HeartMate III (HM III) Left Ventricular Assist System (LVAS)
Indications for Use	The HM III LVAS is intended to provide hemodynamic support in patients with advanced, refractory left ventricular heart failure; either for short term support, such as a bridge to cardiac transplantation (BTT) or myocardial recovery, or as long term support, such as destination therapy (DT). The HM III is intended for use inside or outside the hospital.
Study Objective	The objective of the study is to evaluate the safety and effectiveness of the HM III LVAS by demonstrating non-inferiority to the HM II LVAS (HM II) when used for the treatment of advanced, refractory, left ventricular heart failure.
Study Population	Advanced Heart Failure New York Heart Association (NYHA) Class III patients with dyspnea upon mild physical activity, or NYHA Class IV who are refractory to advanced heart failure management.
Study Design	The study will be a prospective, multi-center, unblinded, randomized, controlled, non-inferiority study comparing the HM III LVAS to the HM II LVAS. The study will be conducted as a staged pivotal study that includes a pre-specified early assessment for safety. Other key elements include: – Up to 5 centers in the United States (U.S.) will be initiated to enroll up to 10 randomized HM III Subjects. A pre-specified analysis for safety will be performed after the first 10 randomized HM III Subjects have completed 30 days of follow-up. The results of this early safety analysis will be reviewed by the Data Safety Monitoring Board (DSMB), after which the DSMB report, along with supporting safety data from the HM III CE Mark study will be sent to FDA as an IDE supplement, with a request to gain full IDE approval to expand the study to up to a total of 60 centers in the U.S. The first 5 U.S. centers will continue enrollment during FDAs review of this IDE Supplement. – An adaptive design will be used, if required to adjust the sample size at a pre-specified time during the study. – **Primary Endpoint Analysis** – Perform an analysis and submit the Premarket Approval (PMA) when the specified number of Subjects complete 6 months of support for a short term indication – Perform an analysis and submit a PMA supplement when the specified number of Subjects complete 24 months of support for a long term indication – **Powered Secondary Endpoint Analysis** – Once the Subjects have been enrolled for the primary endpoint analysis, randomization will continue until sufficient Subjects have been enrolled to evaluate a pre-specified powered secondary endpoint. – Analysis of the pre-specified secondary endpoint will be used to update HM III labeling.
Control Group	The HM II will serve as the control group. Subjects will be randomized 1 HM III to 1 HM II.

STUDY SYNOPSIS	
Primary Study Endpoints	1. Short Term Indication: a. Composite of Survival to transplant, recovery or 6 months of LVAD support free of debilitating stroke (Modified Rankin Score > 3) or reoperation to replace the pump. 2. Long Term Indication: a. Composite of Survival to transplant, recovery or 24 months of LVAD support free of debilitating stroke (Modified Rankin Score > 3) or reoperation to replace the pump.
Secondary Study Endpoints	The following secondary objectives will be evaluated: 1. Quality of Life as measured by EuroQoL 5D-5L (EQ-5D-5L) and Kansas City Cardiomyopathy Questionnaire (KCCQ) 2. Functional status as measured by the 6-minute walk test (6MWT) and NYHA classification 3. Frequency and incidence of all re-operations 4. Frequency and incidence of all rehospitalizations 5. Frequency, incidence and rates of pre-defined anticipated adverse events. 6. Frequency and incidence of device malfunctions
Pre- Specified Powered Secondary Endpoint	In addition to powering the study on the primary endpoints for PMA approval, the study will pre-specify a powered secondary endpoint to evaluate incidence of pump replacements at 24 months.
Sample Size	Total sample size = 1028 (514 HM II/514 HM III Subjects, randomized 1:1).
Study Hypothesis and Sample Size	Short Term Indication Hypothesis: − HM III non-inferior to HM II at 6 months − Assumes 87% composite success rate for HM III and 85% for HM II at 6 months. − 294 Subjects (147 in each arm) provides 80% power to show non-inferiority when the margin of non-inferiority is 10% and alpha = 0.025. Sample size accounts for early transplants. Long Term Indication Hypothesis: − HM III non-inferior to HM II at 24 months − Assumes 55% composite success at 24 months for the HM III arm and 50% for the HM II arm − 366 Subjects (183 in each arm) provides 80% power to show non-inferiority when the margin of non-inferiority is 10% and alpha = 0.025. Sample size accounts for early transplants. Pre-Specified Secondary Analysis of Pump Replacements − When enrollment to evaluate the primary objective is complete, randomization will continue to enroll Subjects to determine if the pump replacement rate for HM III is superior to HM II at 24 months − The pump replacement rate for the HM II is about 7% at 24 months in the United States. − In order to determine if the rate of HM III pump replacements have been reduced to 3% at 24 months, 1028 Subjects (514 per arm) will be required (power=0.8; alpha = 0.05, two-sided). This will require the randomization of 662 additional Subjects.
Study Duration	All randomized Subjects will be followed for 24 months or to outcome (transplant, explant, or death), whichever occurs first.

STUDY SYNOPSIS	
Inclusion Criteria	1) Subject or legal representative has signed Informed Consent Form (ICF) 2) Age ≥ 18 years 3) BSA ≥ 1.2 m^2 4) NYHA Class III with dyspnea upon mild physical activity, or NYHA Class IV 5) LVEF ≤ 25% 6) a) Inotrope dependent OR b) CI < 2.2 L/min/m^2, while not on inotropes and subjects must also meet one of the following: • On Optimal Medical Management (OMM), based on current heart failure practice guidelines for at least 45 out of the last 60 days and are failing to respond • Advanced Heart Failure for at least 14 days AND dependent on intra-aortic balloon pump (IABP) for at least 7 days 7) Females of child bearing age must agree to use adequate contraception

STUDY SYNOPSIS	
Exclusion Criteria	1) Etiology of heart failure (HF) due to or associated with uncorrected thyroid disease, obstructive cardiomyopathy, pericardial disease, amyloidosis or restrictive cardiomyopathy 2) Technical obstacles which pose an inordinately high surgical risk, in the judgment of the investigator 3) Existence of ongoing mechanical circulatory support (MCS) other than IABP 4) Positive pregnancy test if of childbearing potential 5) Presence of mechanical aortic valve that will not be either converted to a bioprosthesis or oversewn at the time of LVAD implant 6) History of any organ transplant 7) Platelet count < 100,000 x 10^3/L (< 100,000/ml) 8) Psychiatric disease/disorder, irreversible cognitive dysfunction or psychosocial issues that are likely to impair compliance with the study protocol and LVAS management 9) History of confirmed, untreated AAA > 5 cm in diameter within 6 months of enrollment 10) Presence of an active, uncontrolled infection 11) Intolerance to anticoagulant or antiplatelet therapies or any other peri/post-operative therapy the investigator will require based upon the patients' health status 12) Presence of any one of the following risk factors for indications of severe end organ dysfunction or failure: a) An INR ≥ 2.0 not due to anticoagulation therapy b) Total bilirubin > 43 umol/L (2.5 mg/dl), shock liver, or biopsy proven liver cirrhosis c) History of severe chronic obstructive pulmonary disease (COPD) defined by $FEV_1/FVC < 0.7$, or FEV_1 <50% predicted d) Fixed pulmonary hypertension with a most recent PVR ≥ 8 Wood units that is unresponsive to pharmacologic intervention e) History of stroke within 90 days prior to enrollment, or a history of cerebrovascular disease with significant (> 80%) carotid stenosis f) Serum creatinine ≥ 221 umol/L (2.5 mg/dl) or the need for chronic renal replacement therapy g) Significant peripheral vascular disease (PVD) accompanied by rest pain or extremity ulceration 13) Patient has moderate to severe aortic insufficiency without plans for correction during pump implant 14) Pre albumin < 150 mg/L (15mg/dL), or Albumin < 30g/L (3 g/dL) 15) Planned Bi-VAD support prior to enrollment 16) Patient has known hypo or hyper coagulable states such as disseminated intravascular coagulation and heparin induced thrombocytopenia 17) Participation in any other clinical investigation that is likely to confound study results or affect the study 18) Any condition other than HF that could limit survival to less than 24 months
Study Follow-up Intervals	Screening, Baseline, Implant, Post-op Day 1, 1 week, Discharge, Month(s) 1, 3, 6, 12, 18 and 24.

STUDY SYNOPSIS	
Data Collection	A 21 CFR part 11 compliant Electronic Data Capture (EDC) system will be used to collect data.
Statistical Analysis	Baseline data will be analyzed using Fisher's exact test and unpaired t-tests as appropriate. The HM III will be considered non-inferior to the HM II for short term and long term indications if the lower 95% confidence limit of the difference between the success for the HM III and HM II is greater than the non-inferiority margin of -10%. Once non-inferiority is inferred, the data will be analyzed for superiority using closed testing methods. Differences in survival between treatment groups will be analyzed using the Kaplan-Meier product-limit method. Safety, including device malfunctions, will be reported as incidence and event rate per patient year of support. A time to event analysis will also be performed. Comparison of adjudicated adverse events between HM III and the HM II control group will be performed using Fisher's exact test or Poisson regression, as appropriate. Quality of Life and six minute walk data will be analyzed using mixed models. Subanalyses of the primary endpoints, survival, adverse events, and quality of life will also be performed and will include gender, ethnicity, age, VO2 Max, and intended use of the device at the time of implant as defined by INTERMACS. In addition to the primary outcome, the study will be powered to test if HM III pump reliability is superior to HM II by analyzing the incidence of pump replacement. The percentage of HM III pump replacements will be compared to HM II using Fisher's exact test.
Adverse Events	Anticipated adverse events will be captured using definitions described in this FDA approved protocol.
Adaptive Design	In case the assumptions of the study are incorrect, a pre-specified early look at the data will be performed by an independent statistician to determine if the study requires adjustment to the sample size. The adaptive design analysis will be performed to evaluate the conditional power.
Number of Investigational Sites	Up to 60 U.S. sites

1 INTRODUCTION

Over the last decade, mechanical circulatory support with left ventricular assist devices (LVADs) have become an important therapy for patients in advanced stage heart failure. The HeartMate® II (HM II) LVAD is a rotary axial-flow pump that has been approved by the U.S. Food and Drug Administration (FDA) for New York Heart Association Class (NYHA) IIIB/IV patients as a bridge to cardiac transplantation, and as permanent destination therapy. Numerous publications have documented the success of the HM II in extending and improving the quality of patient's lives[1, 2, 3, 9]. Adverse events associated with the HM II have included GI bleeding, pump thrombosis, and driveline issues which, in some cases, have resulted in pump replacement.

HeartMate III (HM III) Left Ventricular Assist System (LVAS) is the next generation of mechanical support device. The purpose of this study is to evaluate the safety and effectiveness of the HM III LVAS. This multicenter study is designed to determine if the HM III provides similar survival and quality of life benefits as the HM II by using a prospective, randomized, controlled, non-inferiority study design. Additional potential benefits of the HM III, such as reduced adverse events, will also be evaluated in a descriptive manner.

2 INDICATIONS FOR USE

The HM III LVAS is intended to provide hemodynamic support in patients with advanced refractory left ventricular heart failure; either for short term support, such as a bridge to cardiac transplantation (BTT) or myocardial recovery, or as long term support, such as destination therapy (DT). The HM III LVAS is intended for use inside or outside the hospital.

3 DEVICE DESCRIPTION AND THEORY OF OPERATION

The HeartMate III LVAS is a set of equipment and materials that together comprise a medical device designed to provide therapeutic benefit to those afflicted with advanced heart failure. In service, the LVAS assumes some or all of the workload of the left ventricle, thereby restoring the patient's systemic perfusion while palliating the underlying pathology. The LVAS features a Left Ventricular Assist Device (LVAD), a centrifugal magnetically levitated pump intended for long term implantation in such patients, an extracorporeal Controller, plus all of the features, controls, attachments, interfaces, power sources, supporting equipment, labeling, and tools required to achieve the desired therapeutic benefit.

The LVAS may be used in either of two configurations. First, line power may be utilized through the Power Module or Mobile Power Unit (MPU) to run the LVAD indefinitely, convenient for sedentary or sleeping periods. Second, portable Battery power may be utilized for limited periods, convenient for active periods. Due to the bifurcation of the Patient Cable, switching among these configurations or from one set of Batteries to another (as when one set has been depleted and a fully charged set is available) may be accomplished without interrupting LVAS function. Whenever the Power Module is used

a System Monitor may also be used as a means of viewing operating conditions, changing operating parameters, and manipulating stored data.

While Subjects are in the hospital, either the Power Module or MPU can be used with the system monitor. However, Subjects will be discharged from the hospital with the Power Module or MPU, without the system monitor, as their primary source of power.

The HeartMate III LVAD is part of the HeartMate III LVAS. See Figure 1. The LVAD is a blood pump intended for long term implantation in the thorax of patients with advanced heart failure. The LVAD is surgically connected to the patient's circulatory system via an Inflow Cannula placed into the left ventricular apex, and an Outflow Graft anastomosed to the ascending aorta. Detailed surgical, patient management and storage and handling instructions can be found in the HM III Instructions For Use (IFU).

Figure 1 – HeartMate III System during Battery-powered Operation

The HM III LVAD contains an Inflow Cannula, a Pump Cover, a Lower Housing, a Screw Ring to attach the Pump Cover to the Lower Housing, a Motor, the Outflow Graft, and a Pump Cable.

The HeartMate III Controller is also part of the HM III LVAS. The Controller is an extracorporeal interface device that receives power from the Power Module, Mobile

Power Unit, or portable Batteries, and appropriately delivers that power to the HM III LVAD. It is the primary user interface and has several important functions:

- Operating condition display,
- Source of audible and visible alarms,
- Communication link for transferring event/period log and alarm information, and
- Battery backup in the case of full power disconnection.

The HM III LVAD is assembled in Thoratec Corporation's manufacturing facility in Zurich, Switzerland. All other HM III components and accessories are manufactured at Thoratec Corporation's manufacturing facility in Pleasanton, California, U.S.A.

A complete list of HM III LVAS components and accessories, including model and/or serial/lot numbers is included in the HM III IFU.

For additional information about this product, including information about the biologically active materials used, please see the HM III Investigator's Brochure (IB).

4 DEVICE TESTING

4.1 Device Testing: Bench

The HeartMate III LVAD/LVAS is an implantable long term support device/system. As such, it has been designed in compliance with all applicable FDA and international standards[4,5,6,7]. The device/system has been subjected to a comprehensive verification and validation effort to ensure its safety including evaluation of biocompatibility, sterility and long term reliability. Please refer to the HeartMate III Investigator's Brochure for a more detailed description.

4.2 Device Testing: *In Vivo*

Extensive testing in animals has been done providing assurance to proceed with the use of the HM III LVAS in humans.

In vivo studies were conducted to evaluate the safety of the HeartMate III LVAS. The *in vivo* tests verified:

- Surgical human factors and usability data
- Device performance characterization
- Biological effects (thrombosis, hemolysis, bleeding)

Testing was conducted under Good Laboratory Practices (GLP) Guidelines[8]. Please reference the Investigator's Brochure for additional information.

5 STUDY DESIGN

The study will be prospective, multi-center, unblinded, randomized, controlled, non-inferiority study, comparing the HM III LVAS to the HM II LVAS. Short term use of the device will be evaluated when Subjects have been supported for 6 months. Long term use of the device will be evaluated when Subjects have been followed for 24 months.

Subjects who receive a device exchange to any device other than HM II or HM III, at any time during the study, will be withdrawn from the study and will not be followed.

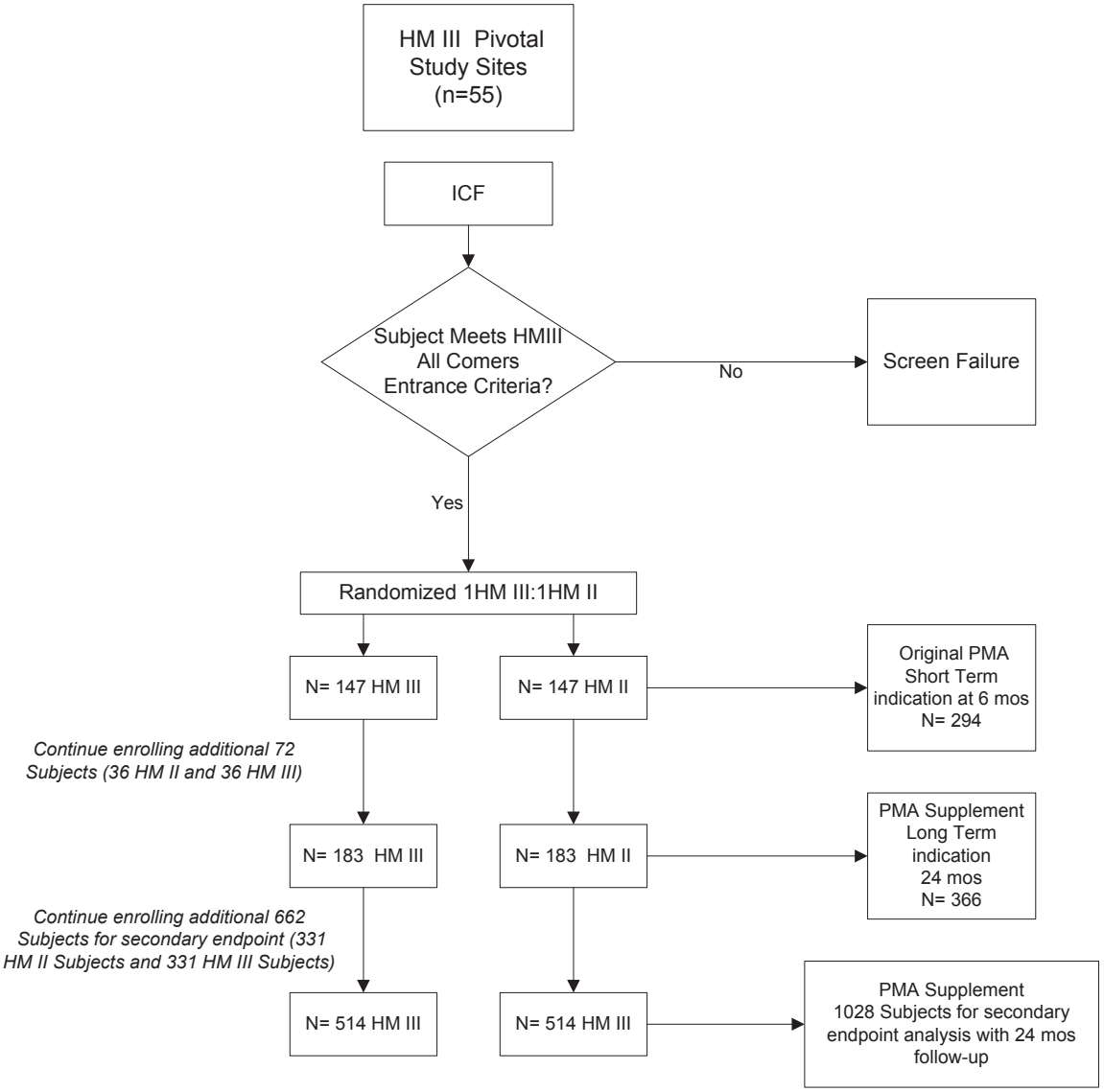
This study will be conducted as a staged pivotal study that includes a pre-specified early assessment for safety that is consistent with FDA's new Guidance for staged approval process, and in accordance with applicable local and federal regulations as specified in 21 CFR part 812.

During the early safety phase of the pivotal study, up to 5 centers in the United States (U.S.) will be initiated to enroll up to 10 randomized HM III Subjects. A pre-specified analysis for safety will be performed after the first 10 randomized HM III Subjects have completed 30 day follow-up. The results of this early safety analysis will be reviewed by the Data Safety Monitoring Board (DSMB), after which the DSMB report, along with supporting safety data from the HM III CE Mark study will be sent to FDA as an IDE supplement, with a request to gain full IDE approval to expand the study to up to a total of 60 centers in the U.S. The first 5 U.S. centers will continue enrollment during FDA's review of this IDE Supplement.

The study will include an adaptive design which will be used, if required to adjust the sample size at a pre-specified time during the study.

In addition to the primary study endpoint, the study will include a powered secondary endpoint to provide supplemental data for HM III labeling.

Figure 2 – HeartMate III IDE Study Flow



Total sample size = 1028 (514 HM II/514 HM III Subjects, randomized 1:1).

6 STUDY POPULATION

Advanced heart failure NYHA Class III patients with dyspnea upon mild physical activity, or NYHA Class IV patients who are refractory to advanced heart failure management.

7 NUMBER OF CLINICAL SITES AND SUBJECTS

The study will be conducted in up to 60 clinical sites. The total sample size for this study is 1028 Subjects. Three hundred and sixty-six (366) Subjects (183 HM III and 183 HM II) will be enrolled and randomized to evaluate the primary endpoint. The data from the Subjects randomized for the primary endpoint will be used for PMA submission for the Short Term and Long Term indications. An additional 662 Subjects will be randomized to achieve 1028 Subjects needed for the powered secondary endpoint analysis. The data from the powered secondary endpoint will be used to update labeling under a Supplemental PMA. Refer to Figure 2.

8 STUDY DURATION

It is anticipated that it will take approximately 6 months to complete the early safety assessment phase of the study. After that, the first 5 U.S. centers will continue to enroll while the IDE Supplement is under review with the FDA for full IDE approval to expand the study to 60 centers.

It is anticipated that it will take approximately 42 months to complete enrollment and follow up for the primary endpoint analysis of the study for the short and long term evaluation of the device. All randomized Subjects needed for the primary endpoint analysis will be followed for 24 months or to outcome (transplant, explant, or death), whichever occurs first.

It is anticipated that it will take approximately 13 additional months to enroll the randomized Subjects for the powered secondary endpoint. All randomized Subjects that are not required for the primary endpoint analysis will be followed for 24 months or to outcome, whichever occurs first.

9 STUDY OBJECTIVES

9.1 Primary Study Objective

The primary objective of the study is to evaluate the safety and effectiveness of the HM III LVAS by demonstrating non-inferiority to the HM II LVAS when used for the treatment of advanced, refractory, left ventricular heart failure.

9.2 Secondary Study Objectives

Secondary objectives include:

- Assessment of adverse events
- Assessment of rehospitalizations and re-operations
- Assessment of quality of life and functional status
- Assessment of clinical reliability, device malfunctions, and device failures

10 CLINICAL STUDY ENDPOINTS

10.1 Primary Study Endpoints

- Composite of survival to transplant, recovery or 6 months of LVAD support free of debilitating stroke (Modified Rankin Score > 3) or reoperation to replace the pump
- Composite of survival to transplant, recovery or 24 months of LVAD support free of debilitating stroke (Modified Rankin Score > 3) or reoperation to replace the pump

The 6 month composite data will be submitted for the short term indication and the 24 month composite data will be submitted for the long term indication.

10.2 Secondary Study Endpoints

- Quality of Life: Quality of Life as measured by the EuroQoL-5D-5L (EQ-5D-5L) and the Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Functional Status: Functional status as measured by the Six Minute Walk Test (6MWT) and by NYHA Classification.
- Adverse Events: Frequency, incidence and rates of pre-defined anticipated adverse events
- Device Malfunctions: Frequency and incidence of device malfunctions
- Reoperations: Frequency and incidence of all reoperations
- Rehospitalizations: Frequency and incidence of all rehospitalizations

10.3 Powered Secondary Endpoint

- Incidence of pump replacements at 24 months

11 INCLUSION CRITERIA

1) Subject or legal representative has signed Informed Consent Form (ICF)
2) Age ≥ 18 years
3) BSA ≥ 1.2 m^2
4) NYHA Class III with dyspnea upon mild physical activity or NYHA Class IV
5) LVEF ≤ 25%
6) a) Inotrope dependent

   OR

   b) CI < 2.2 L/min/m^2, while not on inotropes and subjects must also meet one of the following:

   - On optimal medical management (OMM), based on current heart failure practice guidelines for at least 45 out of the last 60 days and are failing to respond
   - Advanced heart failure for at least 14 days AND dependent on intra-aortic balloon pump (IABP) for at least 7 days,

7) Females of child bearing age must agree to use adequate contraception

12 EXCLUSION CRITERIA

1) Etiology of HF due to or associated with uncorrected thyroid disease, obstructive cardiomyopathy, pericardial disease, amyloidosis, or restrictive cardiomyopathy
2) Technical obstacles which pose an inordinately high surgical risk, in the judgment of the investigator
3) Existence of ongoing mechanical circulatory support (MCS) other than IABP
4) Positive pregnancy test if of childbearing potential
5) Presence of mechanical aortic cardiac valve that will not be either converted to a bioprosthesis or oversewn at the time of LVAD implant
6) History of any organ transplant
7) Platelet count < 100,000 x 10^3/L (< 100,000/ml)
8) Psychiatric disease/disorder, irreversible cognitive dysfunction or psychosocial issues that are likely to impair compliance with the study protocol and LVAS management
9) History of confirmed, untreated Abdominal Aortic Aneurysm (AAA) > 5 cm in diameter within 6 months of enrollment
10) Presence of an active, uncontrolled infection
11) Intolerance to anticoagulant or antiplatelet therapies or any other peri/post-operative therapy that the investigator will require based upon the patients' health status
12) Presence of any one of the following risk factors for indications of severe end organ dysfunction or failure:
    a) An INR ≥ 2.0 not due to anticoagulation therapy
    b) Total bilirubin > 43 umol/L (2.5 mg/dl), shock liver, or biopsy proven liver cirrhosis
    c) History of severe chronic obstructive pulmonary disease (COPD) defined by $FEV_1/FVC < 0.7$, or FEV_1 <50% predicted
    d) Fixed pulmonary hypertension with a most recent PVR ≥ 8 Wood units that is unresponsive to pharmacologic intervention
    e) History of stroke within 90 days prior to enrollment, or a history of cerebrovascular disease with significant (> 80%) carotid artery stenosis
    f) Serum Creatinine ≥ 221umol/L (2.5 mg/dl) or the need for chronic renal replacement therapy
    g) Significant peripheral vascular disease (PVD) accompanied by rest pain or extremity ulceration
13) Patient has moderate to severe aortic insufficiency without plans for correction during pump implant
14) Pre albumin < 150 mg/L (15mg/dL), or Albumin < 30g/L (3 g/dL)
15) Planned Bi-VAD support prior to enrollment
16) Patient has known hypo or hyper coagulable states such as disseminated intravascular coagulation and heparin induced thrombocytopenia
17) Participation in any other clinical investigation that is likely to confound study results or affect the study
18) Any condition other than HF that could limit survival to less than 24 months

13 DATA ANALYSIS AND STATISTICAL ISSUES/JUSTIFICATION FOR STUDY DESIGN

13.1 General Statistical Analysis Plan:

The HM III IDE study will investigate the safety and effectiveness of the HM III LVAS for short term hemodynamic support, such as a bridge to cardiac transplantation (BTT) or myocardial recovery, or as long term support, such as destination therapy (DT). The HM III IDE study is a prospective, multicenter, unblinded, randomized, controlled, non-inferiority study comparing the HM III LVAS to the HM II LVAS.

In general, continuous data will be presented as the number of Subjects, mean with standard deviation, median, and minimum and maximum values. Categorical data will be reported as frequencies and percentages. Adverse events will also be reported as rates per patient year. Only adverse events that occur after the start of the implant procedure will be analyzed. Survival data will be presented using the Kaplan-Meier product limit method.

Data will be analyzed using the intent-to-treat method (ITT) defined as all randomized Subjects. Every effort will be made to avoid cross-over but in the event they occur, data will also be analyzed “as randomized” for efficacy analysis and “as treated” for safety analysis and all other secondary endpoints.

Every effort will be made to collect all required data. Missing primary endpoints will be imputed using multiple imputation techniques. Missing secondary endpoints will not be imputed, except as described below. 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.

Statistical analysis will be performed using SAS version 9.1 or higher.

13.2 Analysis Populations

13.2.1 Intent-to-treat: All Randomized Subjects

This is the primary analysis population for the primary endpoint. Subjects are analyzed under the treatment to which they were randomized.

13.2.2 As Treated: All Treated Subjects

This is the primary analysis population for the secondary endpoints. Subjects are analyzed under the treatment they received.

13.3 Study Hypothesis

13.3.1 Short Term Support:

The short term study endpoint is a composite of survival to transplant, myocardial recovery or 6 months of support (whichever occurs first) free of a debilitating stroke (modified Rankin Score > 3) or reoperation to replace the original pump. A Subject will be considered a success if they are:

- Electively transplanted or explanted for myocardial recovery prior to 6 months or
- Alive at 6 months, and
  - Have not experienced a stroke with a modified Rankin Score > 3, and
  - Have not received a device replacement or exchange, and
  - Have not received an urgent transplant due to a LVAS malfunction.

A Subject will be considered a failure if they:

- Expire prior to 6 months, or
- Experience a stroke with a modified Rankin Score > 3 prior to 6 months, or
- Have a device replaced or exchanged or deactivated for reasons other than myocardial recovery prior to 6 months, or
- Have received an urgent transplant due to a LVAS malfunction prior to 6 months, or
- Have withdrawn from the study for any reason prior to 6 months

HM III short term success rate will be compared to that of the HM II control in a non-inferiority manner. The null and alternative hypotheses are:

H_o: $\pi_{HM\ III} \leq \pi_{HM\ II} - \Delta$
H_A: $\pi_{HM\ III} > \pi_{HM\ II} - \Delta$

where $\pi_{HM\ III}$ and $\pi_{HM\ II}$ are the short term success rates of HM III and HM II, respectively, and where Δ is the non-inferiority margin.

13.3.2 Long Term Support:

The long term study endpoint is a composite of survival to transplant, myocardial recovery or 24 months of support (whichever occurs first) free of a debilitating stroke (modified Rankin Score > 3) or reoperation to replace the original pump. A Subject will be considered a success if they are:

- Electively transplanted or explanted for myocardial recovery prior to 24 months or
- Alive at 24 months, and
  - Have not experienced a stroke with a modified Rankin Score > 3, and
  - Have not received a device replacement or exchange, and
  - Have not received an urgent transplant due to a device malfunction.

A Subject will be considered a failure if they:

- Expire prior to 24 months, or
- Experience a stroke with a modified Rankin Score > 3 prior to 24 months, or
- Have a device replaced or exchanged or deactivated for any reason other than myocardial recovery prior to 24 months, or

- Have received an urgent transplant due to a LVAS malfunction prior to 24 months, or
- Have withdrawn from the study for any reason prior to 24 months

The 24 month success rate of the HM III Subjects will be compared to the HM II control. The null and alternative hypotheses are:

H_o: $\pi_{HM\ III} \leq \pi_{HM\ II} - \Delta$
H_A: $\pi_{HM\ III} > \pi_{HM\ II} - \Delta$

where $\pi_{HM\ III}$ and $\pi_{HM\ II}$ are the long term success rates of HM III and HM II, respectively, and where Δ is the non-inferiority margin.

13.4 Randomization

Subjects will be randomized in a 1:1 fashion (1 HM III: 1 HM II). The randomization will be stratified by study center and blocked to maintain the 1:1 ratio over time. Randomization will be implemented through the Electronic Data Capture (EDC) system. Study centers will be allowed a maximum of 50 randomized Subjects. Subjects will be considered enrolled in the study upon randomization and will be included in the intent-to-treat analysis.

13.5 Sample Size

13.5.1 Assumptions

- Larger gap between the rotor and pump housing in the HM III may result in less thrombus than HM II
- Larger gap between the rotor and pump housing in the HM III may result in less pump replacement due to ingested thrombus than HM II
- HM III modular driveline may reduce pump replacements due to driveline damage or fatigue.

13.5.2 Short Term Indication

Based on a review of recent INTERMACS and Thoratec data, it is assumed that the HM II will achieve a composite success rate of 85% at 6 months. It is also assumed that the HM III will have a composite success rate of 87% due to less pump replacements at 6 months caused by thrombus or driveline issues. It will take 138 HM III and 138 HM II Subjects (276 total Subjects) to achieve 80% power to prove the HM III 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.

INTERMACS HM II data from 26 sites likely to participate in the HM III IDE study was reviewed. Eight hundred and twenty (820) patients were implanted with the HM II in 2012 at these sites and 52 (6%) received a transplant or explant due to myocardial recovery prior to 6 months. In order to have sufficient data to evaluate the 6 month success rate, an additional 9 Subjects will be randomized per arm (6% of 138) to account for these early outcomes. This results in a total of 147 Subjects randomized in each arm (294 total Subjects).

13.5.3 Long Term Indication

Based on the results from the HM II Destination Therapy IDE study, it is assumed that 50% of the HM II Subjects will successfully achieve the composite primary endpoint. It is also assumed that the HM III will have a composite success rate of 55% due to less pump replacements at 24 months caused by thrombus or driveline issues. It will take 174 HM III and 174 HM II Subjects (348 total Subjects) to achieve 80% power to prove the HM III is non-inferior to HM II when the margin of non-inferiority (=Δ in the above null and alternative hypotheses) is -10% using the Farrington-Manning risk difference approach to non-inferiority at a one-sided alpha = 0.025.

INTERMACS HM II data from 26 sites likely to participate in the HM III IDE study was reviewed. Eight hundred and twenty (820) patients were implanted with the HM II in 2012 at these sites and 52 (6%) received a transplant or explant due to myocardial recovery prior to 6 months. In order to have sufficient data to evaluate the 24 month success rate, an additional 9 Subjects will be randomized per arm (6% of 138) to account for these early outcomes. This results in a total of 183 Subjects randomized in each arm (366 total Subjects).

13.6 Early Safety Assessment

The HM III IDE study will include an early safety assessment in lieu of a feasibility study. The first 10 HM III Subjects enrolled in the study will be included and their data analyzed when they have achieved 30 days of support. A table describing the 30 days status of the Subjects will be prepared. Adverse events will be presented as the percentage of Subjects who experience the event, the number of events and the event rate per 30 days. The data will be presented to the DSMB and FDA for a recommendation to continue the study and to expand to remaining study centers. All Subjects included in the early safety assessment will continue to be followed per protocol and will be included in the final Short Term and Long Term analysis.

13.7 Analysis of Primary Endpoint

The HM III will be considered non-inferior to the HM II for both short and long term indications if the lower two-sided 95% confidence limit of the risk difference in the composite success between treatment arms (HM III minus HM II) is greater than -10% (“negative 10%”, where 10% is the non-inferiority Δ in the above null and alternative hypotheses). Once non-inferiority is inferred, the data will be analyzed for superiority at a one-sided 0.025 level of significance using closed testing methods via the z-test of proportions using the normal approximation to the binomial distribution. Since the short term and long term evaluations are two distinct endpoints, no adjustment for multiple comparisons is required.

13.7.1 Primary Endpoint Stratified by Components of the Composite Endpoint

Differences in success rates between HM III and HM II will be performed for each component of the composite endpoint to evaluate if a single component is influencing the outcome. Specifically, for each component, two-sided 95% confidence intervals of the differences and a z-test of proportions will be generated using the normal approximation to the binomial distribution.

13.7.2 Effect of Site Bias on the Primary Endpoint

In order to determine if a few superior investigational sites are influencing the primary endpoint results, a comparison of results across sites will be performed. Specifically, for each of the short term and long term outcomes, the significance of the treatment-by-site interaction effect will be assessed using logistic regression with the main effects for treatment and site, and with a treatment-by-site interaction effect. The treatment-by-site interaction effect will be tested at the 0.10 level of significance. A non-significant interaction or an interaction that is significant but only quantitative and not qualitative in nature will support the pooling of Subjects across sites for the primary analyses. Given that a number of sites will contribute only small numbers of Subjects, we will pool sites with less than 5 Subjects for the analysis.

13.7.3 Unblinded Interim Efficacy Analysis (Adaptive Design)

After 50% of Subjects are treated and followed for 6 months, an interim unblinded analysis comparing treatments on the 6-month short term outcome will be carried out. There will be no provision to stop the study at interim stage for overwhelming effectiveness and hence no adjustment of the significance level for the final analysis. The first purpose of the interim analysis is to calculate the power for non-inferiority, conditioned on the interim short term outcome rates in each treatment and on the non-inferiority margin of 10%. If conditional power is <50% or >80%, the study will continue as is; if conditional power is between 50-80%, the sample size will be re-estimated to maintain conditional power of 80% for the 6-month short term endpoint, controlling Type I error following the method in Wang et al[10]. Any sample size increase will then be applied to the long term endpoint.

13.8 Subgroup Analysis

Once the analyses comparing the treatment arms are complete, a series of subgroup analyses will be performed, assessing treatment difference within each subgroup. Each subgroup will be evaluated for the primary composite endpoint, survival, adverse events, device malfunction, quality of life and functional status, as described above. Subgroups will include but may not be limited to:

- Gender: Males vs Females
- Race: Caucasian/White vs African-American/ Black vs Other
- Age: 18 – 59 vs 60 – 75 vs > 75 years
- Intended Use at implant as defined by Appendix 6
- VO2 max

The purpose of the subgroup analyses is not to reach a statistically significant result within each subgroup, but rather to assess consistency of treatment difference across subgroups.

13.9 Analysis of Survival and Subject Outcome

Overall survival will be assessed for each of the two treatments using the Kaplan-Meier product-limit method. Differences between treatments in survival distributions will be

analyzed using a logrank test. Subjects surviving will be censored at last known follow-up time point.

A competing outcome graph will be prepared at 6 months for short term results and 24 months for long term results.

13.10 Analysis of Adverse Events

All pre-defined adverse events will be captured. Tables will be created for HM III and HM II AEs that show the by-treatment incidences of all adverse events and the by-treatment event rate per patient year of support. Serious adverse events (SAEs) will be analyzed in a similar manner as AEs. Differences in event rates between the treatment arms will be analyzed using Fisher's Exact test or Poisson regression, as appropriate.

13.11 Analysis of Device Malfunctions

All suspected HM III device malfunctions will be reported. Thoratec will ask that all explanted devices be returned for analysis. Data on device malfunctions will be analyzed and tables will be created that report the following:

- Events that are confirmed by analysis of the device by Thoratec engineers
- The component of the device involved
- Days to the malfunction
- Action taken in response to the malfunction
- Reoperations due to malfunction
- Death due to malfunction

13.12 Analysis of Pre-Implant Data

Tables will be created to define the study population at baseline. Tables will include demographics, all laboratory assessments, all hemodynamic assessment, cardiac history, INTERMACS profile, and concurrent interventions (Cardiac Resynchronization Therapy (CRT), Automatic Internal Cardiac Defibrillator (AICD), IABP, Inotropes, etc). The intended use of the device at implant will also be collected, as defined by INTERMACS (Appendix 6). Baseline data will be compared between treatment groups using unpaired t-tests or Fisher's exact test as appropriate.

13.13 Analysis of Implant and Discharge Data

Time on cardiopulmonary bypass during implant surgery will be collected and reported as a median, quartiles and range. All concurrent procedures carried out during implant surgery will be reported. Length of Stay (LOS) will be defined as the time from implant to discharge. LOS will be reported as a mean with standard deviation, median, quartiles and range. The time on cardiopulmonary bypass and LOS will be compared between treatment groups using the Wilcoxon Rank Sum test.

13.14 Analysis of Secondary Endpoints

Secondary endpoints will each be tested at the two-sided 0.05 level of significance. There will be no adjustment for multiple comparisons across the secondary endpoints. There will be no imputation of missing data for the secondary endpoints.

13.14.1 Pump Hemodynamics

The mean flow and pump index (flow/BSA) with standard deviation for the HM III and HM II Subjects will be plotted over time. At each time point, treatments will be compared using the unpaired t-test.

13.14.2 Laboratory values

Mean laboratory values with standard deviations for HM III and HM II Subjects will be plotted over time. At each time point, treatments will be compared using the unpaired t-test.

13.14.3 Rehospitalization

Time to rehospitalization and the reason for rehospitalization will be reported. Time in and out of the hospital will be reported for the HM III and HM II Subjects. Treatments will be compared on time to re-hospitalization using the log-rank test. Subjects not re-hospitalized will be censored at last known follow-up.

13.14.4 Reoperations

Time to reoperation, frequency of reoperation, and the reason for the surgery will be reported for HM III and HM II Subjects. Treatments will be compared on time to re-operation using the log-rank test. Subjects not re-operated will be censored at last known follow-up.

13.15 Analysis of Functional Status

13.15.1 NYHA

The Subjects NYHA Functional Status will be assessed by an independent assessor at baseline and then at 3, 6, 12, 18, and 24 months. At each visit, treatments will be compared on NYHA functional status and on the change from baseline functional status using the Wilcoxon Rank Sum test. The Short Term indication will be limited to the 3 and 6 month assessments. The Long Term indication will include all assessments until 24 months or outcome, whichever occurs first.

13.15.2 Six Minute Walk Test

Subjects may not be able to walk due to heart failure, especially at baseline. Subjects unable to walk due to heart failure will receive a score of 0 meters. For all other reasons for missing data the score will remain missing and not be included in the analysis. The Six Minute Walk test will be conducted at baseline and then at months 3, 6, 12, 18 and 24 post implant. Data will be analyzed using mixed modeling by comparing the distances walked over time to the baseline distance. The Short Term indication will be limited to the 3 and 6 month assessment. The long term indication will include all assessments until 24 months or outcome, whichever occurs first.

13.16 Analysis of Quality of Life

Quality of Life will be measured using the EuroQol (EQ-5D-5L) and the Kansas City Cardiomyopathy Questionnaire (KCCQ).

13.16.1 EQ-5D-5L

The EQ-5D-5L VAS and total score will be assessed at baseline and then at 3, 6, 12, 18, and 24 months. Data will be analyzed using mixed modeling by comparing the EQ-5D-5L score at each assessment interval to the baseline score. The Short Term indication will be limited to the 3 and 6 month assessments. The Long Term indication will include all assessments until 24 months or outcome, whichever occurs first. In addition, the percentage of each component of the EQ-5D-5L will be graphically presented over time.

13.16.2 KCCQ

The KCCQ score will be assessed at baseline and then at 3, 6, 12, 18, and 24 months. Data will be analyzed using mixed modeling by comparing the KCCQ score at each assessment interval to the baseline score. The Short Term indication will be limited to the 3 and 6 month assessments. The Long Term indication will include all assessments until 24 months or outcome, whichever occurs first.

13.17 Powered secondary analysis:

In addition to the primary outcome, the study will be powered to test if HM III pump reliability is superior to HM II by analyzing the incidence of pump replacements. Randomization described in Section 13.4 will continue beyond the Subjects needed to power the primary endpoint until a sufficient sample size has been enrolled to test the secondary endpoint. The null and alternative hypotheses are:

H_o: $\pi_{HM\ III} \geq \pi_{HM\ II}$
H_A: $\pi_{HM\ III} < \pi_{HM\ II}$

where $\pi_{HM\ III}$ is the HM III pump replacement rate and $\pi_{HM\ II}$ is the HM II pump replacement rate.

Based on data contained in Thoratec's device tracking database, 7% of the HM II Subjects receive a pump replacement by 24 months. If we assume that HM III pump replacements will be reduced to 3% at 24 months, then 1028 Subjects (514 per arm) will be needed to prove superiority with a power of 80% and alpha = 0.05 (2-sided).

Once the 366 Subjects needed for the long term indication are enrolled, Thoratec will continue to randomize 662 more Subjects (331 HM III and 331 HM II) for this secondary analysis. Data for this secondary analysis is not needed for the short or long term indications, but rather will be used to provide additional labeling information.

The Subjects will be followed for 24 months or to outcome, whichever occurs first, and analyzed using the Fisher's exact test. Treatments will also be compared on time-to-pump replacement using the log-rank test where Subjects without a replacement are censored at last known follow-up. Otherwise, there will be no imputation of missing data for this analysis.

14 ADVERSE EVENTS (AE)

14.1 Adverse Events

Adverse Events are any unfavorable and unintended sign (including abnormal labs), or symptom or disease temporally associated with the investigational product and whether or not related to the use of the investigational product. Investigators are responsible for reporting required pre-defined AEs to the Study Sponsor in a timely manner by submitting AEs through the EDC, and for reporting AEs to their Institutional Review Board (IRB) as required.

All pre-defined, anticipated AEs, including those occurring after discharge, will be reported and will be categorized as related to the device or not.

All anticipated AE definitions can be found in Appendix 1.

14.2 Serious Adverse Event (SAE)

Serious adverse events are defined as those adverse events causing death, or congenital abnormality or birth defect, or a life-threatening illness or injury that results in permanent disability, requires hospitalization, or prolongs a hospitalization, and/or requires intervention to prevent permanent injury or damage. Investigators are responsible for reporting SAEs to the Study Sponsor in a timely manner (but no later than 24 hours after becoming aware of an SAE) by submitting SAEs through the EDC, and for reporting SAEs to the IRB as required.

All SAEs will be reported and will be categorized as related to the device or not.

15 UNANTICIPATED ADVERSE DEVICE EFFECTS (UADE)

An unanticipated adverse device effect includes any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence. A UADE may also include any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of Subjects. Investigators are responsible for reporting any UADEs to Thoratec by telephone, email, or fax, and through the EDC as soon as the study site personnel are made aware of an event, but no later than 24 hours of becoming aware. Thoratec will review all malfunctions and determine if they are UADEs. Thoratec will report all such effects to the FDA, in accordance with regulatory requirements.

In addition to reporting UADEs to the Study Sponsor, Investigators must report UADEs to their IRB as required.

16 STUDY PROCEDURES AND ASSESSMENTS

Participating centers will utilize their own local laboratories for protocol required laboratory assessments, and will be instructed to follow their institution's requirements for maintenance and/or calibration of laboratory equipment.

16.1 Screening and Enrollment

1. Sign written informed consent
2. Determine if the Subject is eligible: meets all inclusion and no exclusion criteria
3. Subjects who sign informed consent but do not meet inclusion or exclusion criteria, or who are not randomized will be considered screen failures and reasons for failing screening will be documented
4. Only Subjects who have signed informed consent and have met the eligibility criteria and who have a scheduled implant date will be randomized through the EDC system. Subjects will be considered enrolled on the day they are randomized. Randomization should occur as close as possible to the implant date; if possible, within 72 hours.
5. Demographics: age, gender, ethnicity, race
6. Intended Use as defined by INTERMACS (Appendix 6)

16.2 Baseline Assessments

The following baseline assessments will be performed within 30 days prior to enrollment (refer to Section 34, Table 2 for the Study Visit Schedule):

1. Medical History, including cardiovascular history with etiology of HF and duration of HF
2. Physical Exam, including height, weight and vital signs
3. Current Medications (total daily dose): anticoagulation/anti platelet, antibiotics, and cardiovascular medications including ACE inhibitors, ARBs, beta blockers, statins, nitrates, allopurinol, aldosterone blockers, and diuretics including metolazone, hydrochlorothiazide and furosemide
4. Laboratory Assessments:
   a. Hematology: hemoglobin, hematocrit, percent lymphocytes, platelet count, WBC, PHgb, Bleeding/Coagulation: INR, aPTT/PTT, PT
   b. Chemistry: Potassium, Blood Urea Nitrogen (BUN), creatinine, uric acid, sodium, eGFR (calculated), serum BNP or NT-proBNP, total protein, albumin, pre-albumin, CRP (hs-CRP if available)
   c. Lipids: cholesterol
   d. Liver Enzymes: LDH, AST, ALT, total bilirubin
5. Hemodynamic Measurements
6. Echocardiogram: LVEF, LVEDD, LVESD, AV opening, AI, MR, TR including severity and/or grade.
7. Electrocardiogram (ECG): Heart Rate, QRS duration, Arrhythmias
8. 6 Minute Walk Test (6MWT) (if Subject is able; reason must be provided if not performed)
9. EQ-5D-5L
10. Kansas City Cardiomyopathy Questionnaire (KCCQ)
11. VO2 Max (if Subject is able; reason must be provided if not performed)
12. Functional/clinical status using the following:
    a. Modified Rankin Score
    b. NYHA Classification (as determined by an independent assessor; defined as an advanced practice practitioner other than the treating investigator)
    c. INTERMACS Patient Profile (refer to Appendix 2 for definitions)

16.3 Implant

1. Current Medications (total daily dose): anticoagulation/anti platelet, antibiotics, and cardiovascular medications including ACE inhibitors, ARBs, beta blockers, statins, nitrates, allopurinol, aldosterone blockers, and diuretics including metolazone, hydrochlorothiazide and furosemide
2. Implant data/Total CPB time/Blood Product use
3. Pump Parameters (HM II and HM III)
4. HM III Pump Log files (pump period log, pump event log, controller period log, and controller event log) will be submitted to Thoratec
5. Concurrent Procedures
6. Occurrence of AEs (date of adverse event, determination of seriousness and/or relation to the device, resolution of the adverse event)
7. Device Malfunctions
8. Modified Rankin Score (only if a stroke has occurred and 60 days post-stroke)
9. HM II Pump Log files will be submitted to Thoratec (only if a pump-related AE or malfunction has occurred)

16.4 Post Op Day 1

1. HM III Pump Log files (pump period log, pump event log, controller period log, and controller event log) will be submitted to Thoratec
2. AP chest x-ray for HM III subjects; AP feeding tube view x-ray for HM II subjects
3. Echocardiogram or transesophageal echocardiogram (TEE): LVEF, LVEDD, LVESD, AV opening, AI, MR, TR including severity and/or grade (can be perfomed on post-operative day 0 (post-implant) +2 days)
4. HM II Pump Log files will be submitted to Thoratec (only if a pump-related AE or malfunction has occurred)

16.5 1 Week Post-implant (+/- 1 Day)

1. Current Subject Status: whether or not the Subject is ongoing on VAD support
2. Subject Outcome: whether or not the Subject has been transplanted or explanted
3. Current Medications (total daily dose): anticoagulation/anti platelet, antibiotics, and cardiovascular medications including ACE inhibitors, ARBs, beta blockers, statins, nitrates, allopurinol, aldosterone blockers, and diuretics including metolazone hydrochlorothiazide and furosemide
4. Vital Signs
5. Laboratory Assessments:
   a. Hematology: hemoglobin, hematocrit, percent lymphocytes, platelet count, WBC, PHgb, Bleeding/Coagulation: INR, aPTT/PTT, PT
   b. Chemistry: Potassium, BUN, creatinine, uric acid, sodium, eGFR (calculated), serum BNP or NT-proBNP, total protein, albumin, pre-albumin, CRP (hs-CRP if available)
   c. Lipids: cholesterol
   d. Liver Enzymes: LDH, AST, ALT, total bilirubin
6. Echocardiogram: LVEF, LVEDD, LVESD, AV opening, AI, MR, TR including severity and/or grade.
7. Pump Parameters (HM II and HM III)
8. HM III Pump Log files (pump period log, pump event log, controller period log, and controller event log) will be submitted to Thoratec.

9. Occurrence of AEs (date of adverse event, determination of seriousness and/or relation to the device, resolution of the event)
10. Device Malfunctions
11. Reoperations/Operative procedures
12. Pump Replacements/Explants/Device Exchanges
13. Driveline Management Assessment
14. Modified Rankin Score (only if a stroke has occurred and 60 days post-stroke)
15. HM II Pump Log files will be submitted to Thoratec (only if a pump-related AE or malfunction has occurred)

16.6 Discharge (-1 day)

Subjects and his or her family member or caregiver (as applies) must be trained on the operation and care of their LVAS and its components, prior to discharge. Information related to required Subject and caregiver training can be found in the HM II or HM III Instructions for Use and Patient Handbook. Training documentation will be required to show compliance to the required training.

1. Current Subject Status: whether or not the Subject is ongoing on VAD support
2. Subject Outcome: whether or not the Subject has been transplanted, or explanted
3. Current medications (total daily dose): anticoagulation/anti platelet, antibiotics, and cardiovascular medications including ACE inhibitors, ARBs, beta blockers, statins, nitrates, allopurinol, aldosterone blockers, and diuretics including metolazone, hydrochlorothiazide and furosemide
4. Number of days in ICU
5. Vital Signs
6. Laboratory Assessments:
   a. Hematology: hemoglobin, hematocrit, percent lymphocytes, platelet count, WBC, PHgb, Bleeding/Coagulation: INR, aPTT/PTT, PT
   b. Chemistry: Potassium, BUN, creatinine, uric acid, sodium, eGFR (calculated), serum BNP or NT-proBNP, total protein, albumin, pre-albumin, CRP (hs-CRP if available)
   c. Lipids: cholesterol
   d. Liver Enzymes: LDH, AST, ALT, total bilirubin
7. Echocardiogram: LVEF, LVEDD, LVESD, AV opening, AI, MR, TR including severity and/or grade.
8. NYHA Classification (determined by an independent assessor defined as an advanced practice practitioner other than the treating investigator)
9. Pump Parameters (HM II and HM III)
10. HM III Pump Log files (pump period log, pump event log, controller period log, and controller event log) will be submitted to Thoratec
11. Occurrence of AEs (date of adverse event, determination of seriousness and/or relation to the device, resolution of the adverse event)
12. Device Malfunctions
13. Reoperations/Operative procedures
14. Pump Replacements/Explants/Device Exchanges
15. Driveline Management Assessment
16. Collect UB-04 Form
17. Modified Rankin Score (only if a stroke has occurred and 60 days post-stroke)

18. HM II Pump Log files will be submitted to Thoratec (only if a pump-related AE or malfunction has occurred)

16.7 Subject Follow-up Assessments

16.7.1 Clinic Follow-up Post-implant: 30 Days (+/- 7 days) for 1 month assessment, 90 Days (+/- 30 days) for 3 month assessment, and 180 days (+/- 30 days) for 6 month assessment

The Subject must be seen for a clinic visit to assess the following:

1. Current Subject Status: whether or not the Subject is ongoing on VAD support
2. Subject Outcome: whether or not the Subject has been transplanted, or explanted
3. Current medications (total daily dose): anticoagulation/anti platelet, antibiotics, and cardiovascular medications including ACE inhibitors, ARBs, beta blockers, statins, nitrates, allopurinol, aldosterone blockers, and diuretics including metolazone, hydrochlorothiazide and furosemide
4. Vital Signs
5. Laboratory Assessments:
   a. Hematology: hemoglobin, hematocrit, percent lymphocytes, platelet count, WBC, PHgb, Bleeding/Coagulation: INR, aPTT/PTT, PT
   b. Chemistry: Potassium, BUN, creatinine, uric acid, sodium, eGFR (calculated), serum BNP or NT-proBNP, total protein, albumin, pre-albumin, CRP (hs-CRP if available)
   c. Lipids: cholesterol
   d. Liver Enzymes: LDH, AST, ALT, total bilirubin
6. Echocardiogram : LVEF, LVEDD, LVESD, AV opening, AI, MR, TR including severity and/or grade.
7. Chest x-ray: PA and Lateral (30 Days and 180 Days only)
8. NYHA Classification (determined by an independent assessor defined as an advanced practice practitioner other than the treating investigator)
9. 6 Minute Walk Test (6MWT) (if Subject is able; reason must be provided if not performed)
10. EQ-5D-5L
11. Kansas City Cardiomyopathy Questionnaire (KCCQ) (90 Days and 180 Days only)
12. Pump Parameters (HM II and HM III)
13. Rehospitalizations
    a. If rehospitalized, collect UB-04 form
14. HM III Pump Log files (pump period log, pump event log, controller period log, and controller event log) will be submitted to Thoratec.
15. Occurrence of AEs (date of adverse event, determination of the seriousness and/or relation to the device, resolution of the adverse event)
16. Device Malfunctions
17. Reoperations/Operative procedures
18. Pump Replacements/Explants/Device Exchanges
19. Driveline Management Assessment
20. Modified Rankin Score (only if a stroke has occurred and 60 days post-stroke)

21. HM II Pump Log files will be submitted to Thoratec (only if a pump-related AE or malfunction has occurred)

16.7.2 Clinic Follow-up Post-implant: 360 Days (+/- 30 days) for 12 month assessment, 540 Days (+/- 30 days) for 18 month assessment, and 720 Days (+/- 30 days) for 24 month assessment

The Subject must be seen for a clinic visit to assess the following:

1. Current Subject Status: whether the Subject is ongoing on VAD support
2. Subject Outcome: whether or not the Subject has been transplanted, or explanted
3. Current medications (total daily dose): anticoagulation/anti platelet, antibiotics, and cardiovascular medications including ACE inhibitors, ARBs, beta blockers, statins, nitrates, allopurinol, aldosterone blockers, and diuretics including metolazone, hydrochlorothiazide and furosemide
4. Vital Signs
5. Laboratory Assessments:
   a. Hematology: hemoglobin, hematocrit, percent lymphocytes, platelet count, WBC, PHgb, Bleeding/Coagulation: INR, aPTT/PTT, PT
   b. Chemistry: Potassium, BUN, creatinine, uric acid, sodium, eGFR (calculated), serum BNP or NT-proBNP, total protein, albumin, pre-albumin, CRP (hs-CRP if available)
   c. Lipids: cholesterol
   d. Liver Enzymes: LDH, AST, ALT, total bilirubin
6. Echocardiogram: LVEF, LVEDD, LVESD, AV opening, AI, MR, TR including severity and/or grade.
7. Chest x-ray: PA and Lateral (360 Days and 720 Days only)
8. NYHA Classification (determined by an independent assessor defined as an advanced practice practitioner other than the treating investigator)
9. 6 Minute Walk Test (6MWT) (if Subject is able; reason must be provided if not performed)
10. EQ-5D-5L
11. Kansas City Cardiomypathy Questionnaire (KCCQ)
12. Pump Parameters (HM II and HM III)
13. Rehospitalizations
    a. If rehospitalized, collect UB-04 form
14. HM III Pump Log files (pump period log, pump event log, controller period log, and controller event log) will be submitted to Thoratec.
15. Occurrence of AEs (date of the adverse event, determination of seriousness and/or relation to device, resolution of the adverse event)
16. Device Malfunctions
17. Reoperations/Operative procedures
18. Pump Replacements/Explants/Device Exchanges
19. Driveline Management Assessment
20. Modified Rankin Score (only if a stroke has occurred and 60 days post-stroke)
21. HM II Pump Log files will be submitted to Thoratec (only if a pump-related AE or malfunction has occurred)

For a detailed list of assessments and timelines, refer to the Study Visit Schedule in Section 34, Table 2.

16.8 Additional Data Collection:

16.8.1 Pump Log Files

Pump log files will be submitted to Thoratec at defined time points. In addition, Thoratec may periodically collect pump log files, outside of the pre-specified time points and/or may request additional supportive hemodynamic data, if performed as part of the standard of care, for characterization of pump operation and system diagnostic purposes. No specific pre-defined analysis will be performed on this data.

16.8.2 Chest X-Rays

Chest x-rays will be submitted to Thoratec at defined time points. No specific pre-defined analysis will be performed on this data.

16.8.3 Health Economics Data

Upon hospital discharge for the initial implant hospitalization and subsequent re-hospitalizations, UB-04 bills, or similar detailed hospital billing data will be sent to Thoratec.

17 ANTICOAGULATION

Subjects implanted with the HM III and HM II must be properly anticoagulated to decrease the possibility of thromboembolism and/or pump thrombosis. Anticoagulation guidelines are provided in the HM III and HM II Instructions for Use (IFU).

18 INFECTION CONTROL GUIDELINES

It is recommended that all investigational centers follow the Patient Care and Management Guidelines developed for the HM II and HM III LVAS. Guidelines for infection control and driveline management are provided in the HM II and HM III IFU.

19 BLOOD PRESSURE GUIDELINES

Post-Implantation hypertension may be treated at the discretion of the attending physician. Any therapy that consistently maintains mean arterial blood pressure less than 90 mm Hg should be considered adequate.

20 POST-MORTEM EXAMINATION

All attempts to obtain permission for a full body autopsy should be made for all Subjects that expire during the study. Performance of an autopsy is to be noted on the eCRF and a copy of the autopsy report is to be provided to Thoratec. The primary objective of the autopsy is to determine the cause of death, complications, and other relevant findings. In addition, special attention should be directed toward documentation of Subject-prosthesis interaction and any HM II or HM III LVAD associated complications.

21 DEVICE RETRIEVAL AND ANALYSIS

Upon Subject death, device explantation, or device malfunction all explanted HM II and HM III pumps must be retrieved and returned to Thoratec for evaluation and analysis within 48 hours of explant. Devices must be returned in accordance with Thoratec instructions.

Any system component other than the pump, (for example: controller, MPU, batteries) associated with any suspected device malfunction must also be returned to Thoratec for analysis.

22 SUBJECT WITHDRAWAL

The Subject retains the right to withdraw from the study at any time. Should the Subject elect to withdraw from the study, the reason for withdrawal must be documented in the CRF.

Reasons for withdrawal include:

- Subject chooses to withdraw
- Investigator decides to withdraw Subject
- Subject has pump exchanged to any device other than HM II or HM III
- Subject is not implanted with device after randomization

23 RISKS

The HM III LVAS is an investigational device and has not been approved by the U.S. FDA or any other regulatory authority. Extensive testing has been performed on the device in the laboratory and in animal studies providing assurance to proceed with human use of the HM III LVAS.

The potential risks including anticipated adverse events and possible interactions with concomitant medical treatments related to use of the HM III are expected to be similar to those seen with commercially available mechanical circulatory support.

The recent HM II BTT Post-approval study followed 169 patients from 53 sites in the United States for 6 months. The HM II DT Post-approval study followed 247 patients from 61 hospitals in the United States for 24 months. If it is assumed that adverse event rates experienced in the HM III study will be within the upper 99% confidence interval of that reported in the HM II Post-approval studies, then the expected rates for HM III adverse events[3] would be as reported in Table 1. In addition, the recent commercial data, as reported by Kirklin et al, shows that freedom from pump exchange or death due to pump thrombosis at 6 months is 94%[11].

Table 1 – Expected Incidence Rate of Adverse Events

Adverse Event	Incidence Rate at 6 Months[3] Less than or Equal to:	Incidence Rate at 24 Months[12] Less than or Equal to:
Death	11%	47%
Bleeding	56%	62%
Cardiac Arrhythmia	37%	45%
Hemolysis	7%	11%
Hepatic Dysfunction	12%	12%
Driveline Infection	26%	22%
Blood Infection	28%	26%
Other Localized Infection	39%	53%
Stroke	12%	19%
Other Neurological Dysfunction	9%	18%
Pericardial Drainage	17%	13%
Psychiatric Episode	15%	19%
Renal Dysfunction	17%	25%
Respiratory Failure	29%	34%
Right Heart Failure	23%	25%
Venous Thromboembolism	12%	9%
Device Thrombosis	3%[13]	7%
All Other Adverse Events	5%	3%

[3]Starling RC, Naka Y, Boyle AJ et al. Results of the Post U.S. Food and Drug Administration-Approval Study with a Continuous Flow Left Ventricular Assist Device as a Bridge to Heart Transplantation, J Am Coll Cardiol 2011; 57:1890-1898
[12] Thoratec Final Post Approval Report to the FDA on the HM II Destination Therapy – INTERMACS Post Approval Study
[13] Thoratec Data : HM II Bridge to transplant – INTERMACS Post Approval Study

Residual risks associated with the HeartMate III device are expected to be similar to those seen with market approved VADs. Additional information related to the Risk Management process, including residual risks can be found in the Investigator's Brochure.

A list of potential anticipated adverse events for this study can be found in Appendix 1 of this protocol.

24 MITIGATIONS

Mitigations and treatment for all adverse events should be per the current practice standards/standards of care as determined by the investigator.

Subject risk from study participation will be mitigated by ensuring that only experienced LVAD personnel will be involved in the care of research Subjects. In addition to providing product specific Instructions for Use (IFU), study staff will undergo product,

implant and study training prior to initiating study activities, and all Subjects will be closely monitored throughout the study duration, at pre-specified time points to assess their clinical status.

25 BENEFITS

Commercially available mechanical circulatory support devices have been previously shown to provide safe and effective hemodynamic support in advanced heart failure Subjects with clinical meaningful improvement in survival, quality of life and functional capacity when compared to optimal medical management. It is therefore expected that similar benefits may be observed with the HM III LVAS, and these benefits will outweigh the risks associated with the device and the required implant surgery[1,2].

Potential benefit of fewer HM III device replacements will be further evaluated in this study as a powered secondary endpoint. Additional potential benefits of the HM III, such as reduced adverse events, will also be evaluated in a descriptive manner.

26 ETHICAL REQUIREMENTS

26.1 Informed Consent

Informed consent must be obtained in accordance with 21 CFR Part 50. Written informed consent must be obtained by the Principal Investigator or designee, before any study related procedures or tests are performed that would otherwise not be performed according to the standard of care. If the Subject is unable to participate in the informed consent process, consent must be obtained from a legally authorized representative prior to administering any study related test or procedure. The use of a legally authorized representative is only permissible if allowed by the IRB.

If new information becomes available by the Sponsor that may affect a Subject's participation in the study, Investigators will be required to update/revise the informed consent as necessary, and all Subjects will be re-consented by the site.

Revisions to the informed consent will be approved by the Sponsor and the IRB prior to re-consenting Subjects.

Each clinical site is responsible for keeping the original signed informed consent forms, and any updated signed informed consent forms for each Subject on file, and available for inspection by Thoratec.

The process of obtaining Informed consent must be documented in each Subject's medical record.

26.2 IRB Review

Investigators will conduct the study in compliance with the Declaration of Helsinki and local and national regulatory requirements.

Thoratec will comply with all IRB and FDA regulatory requirements.

Before initiation of the study, IRB approval of the protocol and the ICF must be obtained. Modifications made to the ICF must be sent to Thoratec for approval, prior to submitting to the IRB. Copies of the IRB submission and approval, including the approved ICF, must be forwarded to Thoratec prior to the enrollment of Subjects into the study. Sites will submit Study progress reports as required by 21 CFR 812.150(a)(3) in writing to Sponsor and the IRB at least yearly. As required by 21 CFR 812.150(a)(6), sites will submit to Sponsor and the IRB a final report on the Study within 3 months of completion or earlier termination of the study. Copies of all submissions to and correspondence from the IRB (approvals and disapprovals) must be sent to Thoratec and maintained on file at the study site.

26.3 Confidentiality

No individually identifiable/confidential Subject data collected as part of this study will be released beyond Thoratec. Unique Subject study identification codes will be assigned to all Subjects and sites must use these unique identification codes with Subject initials on all study related materials. Personal identifiable information, such as name, social security number, and medical record number, should be redacted by the site prior to submission to Thoratec.

27 PROTOCOL DEVIATIONS

This study should be conducted as described in this protocol. All deviations from the protocol will be tracked and evaluated through the EDC system.

For sites who demonstrate repeated deviations that may affect the safety of Subjects, and/or the integrity of the data, corrective measures will be instituted such as re-training.

Sites must notify their IRB of protocol deviations in accordance with IRB requirements.

Refer to Section 31.6 for additional information on Sponsor management of Investigator compliance.

28 PROTOCOL AMENDMENTS

Significant changes to the protocol will be handled by a formal protocol amendment. Protocol amendments will be submitted to Investigators with instructions to submit to their IRB for approval. Any study changes requested by the FDA will be provided to all affected IRBs.

29 DATA COLLECTION, CASE REPORT FORMS AND RECORD KEEPING REQUIREMENTS

29.1 Database and Electronic Case Report Forms (eCRFs)

An EDC system that complies with United States regulations on electronic records and signatures[7] (21 CFR Part 11) will be utilized for this study. Users will have unique usernames and passwords, and the user list will be maintained by a Thoratec administrator for all study personnel. The Investigator must ensure that the observations

and study findings are recorded correctly and completely in the eCRFs. Each eCRF requiring a signature must be signed and dated by the authorized personnel.

Data being submitted through the course of the clinical study will be reviewed by the Sponsor for accuracy and completion. Database cleaning and the process for issuing and/or resolving queries will be documented in the Sponsors study specific data management plan.

29.2 Device Accountability Records

The Thoratec HeartMate III LVAS is an investigational device. All investigational devices must be stored in a location that is accessible only by authorized study personnel. The Sponsor and investigator must maintain accurate Device Accountability records indicating the date of shipment, receipt of product, date of use and assignment to study Subject, and final disposition (return) of the devices.

Traceability of investigational devices will be maintained by the Sponsor through the use of unique serial and/or lot numbers.

All unused investigational components must be returned to the Sponsor, as directed.

NOTE: Investigational devices should only be used on Subjects who are enrolled in the study and randomized to the HM III arm.

29.3 Source Documentation

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

During monitoring visits, source documents will be reviewed to ensure accuracy and validity of data recorded on the eCRFs. Source document verification will be performed by Thoratec, or its designee, with due regard to Subject confidentiality.

29.4 Maintenance of Study Documentation

The following documents should be maintained by the study site, and copies of site specific documents sent to Thoratec:

- Copy of the Study Protocol
- IRB Approval(s)
- Pertinent IRB Correspondence
- IRB approved Informed Consent Form(s)
- IRB Membership Roster(s) or Federal wide Assurance (FWA) number
- Financial Disclosure(s)
- Investigator's Agreement(s)
- Curriculum Vitae(s)
- Study Staff Signature and Delegation of Responsibilities Log

- Laboratory Certification(s) and Normals
- Source documentation (such as Subject clinic charts, medical records, laboratory records)
- Clinical Study Agreement (CSA)
- Confidentiality Agreement, if separate from CSA
- Thoratec Correspondence
- Annual/Semi- annual Regulatory Reports
- Documentation of Training
- Monitoring Visit Log
- Device Accountability
- Investigator Brochure
- Instructions for Use (IFU)
- Patient Manual

29.5 Regulatory Reporting Requirements

29.5.1 Site Reporting

Sites will submit Study progress reports as required by 21 CFR 812.150(a)(3) in writing to the Sponsor and the IRB at least yearly. As required by 21 CFR 812.150(a)(6), sites will submit to Sponsor and the IRB a final report on the study within 3 months of completion or earlier termination of the study.

29.5.2 Sponsor Reporting

Thoratec Corporation will submit Study progress reports as required by 21 CFR 812.150(b)(5) to all reviewing IRBs at least yearly. Thoratec will submit a final report to FDA and all reviewing IRBs and participating investigators within six months after completion or termination, as required by 21 CFR 812.150(b)(7). Thoratec will comply with all other reporting requirements as outlined in CFR 812.150(b).

29.6 Retention of Records

In accordance with 21 CRF Part 812.40 the site will retain the Study records in accordance with and for the period required by applicable laws, and at least two years after the date of the latter: (1) the date on which the Study is terminated or completed, or (2) the date that the records are no longer required for purposes of supporting a marketing application. This includes a copy of the protocol, the device labeling, case report forms, medical records, original test result reports, all study related correspondence, a record of written informed consent, and any other documents pertaining to the conduct of this study.

In addition, any and all records maintained in electronic form by Site, Investigator, or Subinvestigators shall be maintained at all times in compliance with applicable laws, including 21 CFR Part 11[7].

The investigator must not dispose of any records relevant to this study without either (1) written permission from Thoratec or (2) providing an opportunity for Thoratec to collect such records. The investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data

generated during this study. Such documentation is subject to inspection by Thoratec and regulatory authorities.

29.7 Laboratory Accreditation and Normal Values

Before initiation of the study, appropriate accreditation for all laboratories to be used in the study will be requested by Thoratec. Throughout the study, the Investigator shall provide Thoratec documentation of all renewals of accreditation. The range of values considered normal for the laboratory tests being performed for the study must be provided to Thoratec in order to allow the data to be pooled.

30 INSURANCE

Thoratec will obtain insurance to cover potential injury to Subjects in accordance with national requirements.

31 QUALITY CONTROL

31.1 Independent Monitoring Boards

31.1.1 Data Safety Monitoring Board (DSMB):

To meet the study's ethical responsibility to its Subjects and to protect the safety of the Subjects, an independent DSMB, comprised of experts in the field, will monitor the study. Pre-specified guidelines related to governance of the DSMB, data review, and recommendations by the committee to stop the study, or continue the study with or without modification (s), will be outlined in a DSMB charter.

31.1.2 Clinical Events Committee (CEC):

An independent CEC comprised of experienced experts in the field, will review and adjudicate adverse events to provide consistency in the categorization of adverse events. Event adjudication will be performed in accordance with the study's pre-specified adverse event definitions and in accordance with the CEC charter.

31.2 Investigator Selection

Prior to the initiation of the study, investigators will be selected based on their qualifications and experience (qualified by education and training) to ensure Subject safety and adherence to the protocol.

31.3 Site Selection

Prior to the initiation of the study, study sites will be selected based on experience with the care of LVAD Subjects, on adequate access to the intended population, adequate resources to conduct the study in accordance with the protocol, and adequate facilities/equipment to perform required tests and procedures as described in the protocol.

The Sponsor will maintain an updated list of principal investigators, investigational sites and/or institutions separately from the protocol. The list will be included in clinical investigation reports as required by 21 CFR part 812.150.

31.4 Site Staff Training

Only trained personnel can perform study related procedures. All clinical personnel (principal investigators, co-investigators, study coordinators) must be thoroughly familiar with the function, care and maintenance of the HM III LVAS. These individuals will undergo training by Thoratec or designee, and documentation of that training will be maintained. The Thoratec HM III LVAS Instructions for Use will be provided to assist the healthcare team on the proper care and operation of the device.

31.5 Monitoring

Thoratec Corporation is responsible for monitoring the study. Thoratec will monitor in accordance with FDA Guidance document OMB 0910-0733, Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring. After the study has been initiated, Thoratec or its designee will perform periodic monitoring visits to assess study progress, perform device accountability, assess the adequacy of records, and to ensure adherence to the study protocol.

A summary of the monitoring visit, including documentation of completed previous action items and/or new or outstanding action items, and/or significant findings will be provided to the Investigator.

In addition to periodic on-site monitoring visits, Thoratec will perform remote monitoring to ensure data is submitted in a timely manner. Ongoing communication with investigators and study staff will be performed through written correspondence and telephone conversations.

Details related to site monitoring will be documented in the Sponsor's study specific monitoring plan.

31.5.1 Pre-Investigational (Initiation) Visit:

Thoratec or its designee will be responsible for determining and documenting that each investigator clearly understands and accepts the responsibilities and obligations of conducting a clinical study. If the site attends a study-specific investigator meeting, the investigator meeting may take the place of an on-site initiation visit. Prior to enrollment, the Sponsor or its designee will ensure that the investigator:

- Understands the requirements for device accountability
- Understands the nature of the clinical protocol
- Understands reporting obligations
- Understands and accepts the obligations to obtain informed consent
- Understands and accepts the obligation to obtain IRB review and approval of the clinical investigation before it is initiated and to ensure continuing

review of the study by the IRB, and to keep the Sponsor informed of all IRB actions concerning the study
- Has adequate facilities and access to an adequate number of suitable Subjects to conduct the investigation

31.5.2 Periodic Monitoring Visits:

Monitoring visits will be conducted in accordance with applicable regulations, the study specific monitoring plan, and Thoratec's procedures. This study will be monitored to ensure the following:

- Facilities continue to be adequate and acceptable
- The protocol is being properly followed
- The IRB has approved or been notified of any protocol changes per IRB requirements
- Accurate, complete and current records are being maintained, and the information recorded and submitted to the Sponsor is representative of the Subject's record and other supporting documentation
- Accurate, complete and timely adverse event reports are being submitted to the Sponsor
- Informed consent has been obtained
- The reason for a Subject's withdrawal from the study has been documented
- Required reports are being submitted to the IRB and Sponsor
- The appropriate staff is carrying out study activities

The Investigator or designee must, upon request, provide to the sponsor the necessary study records for a thorough review of the study's progress. These records include, but are not limited to, access to investigational device storage and accountability records, case report forms and original source documents and records such as hospital and clinic charts, consent forms, and operative reports.

31.5.3 Study Closeout Activities:

The following study closeout activities will be performed prior to completion of the study in accordance with Thoratec's procedures:

- Ensure that all required eCRFs have been completed/submitted
- Ensure final disposition of investigational devices
- Remind the investigator of the obligation to retain the records in accordance with FDA and Sponsor requirements, and prepare a final report for the Sponsor and IRB

31.6 Investigator and/or Study Site Termination/Suspension

A pattern of non-compliance and continued deviations will result in Thoratec instituting a formal written request for corrective action. If there is an inadequate response from the Investigator, Thoratec may cease shipment of the investigational device and notify the IRB of this action.

Thoratec may consider terminating or suspending an investigator and/or study site in the following cases:

- Confirmed serious or repeated deviations and general non-compliance to the protocol
- Unacceptable critical changes in personnel, administrative, or scientific standards
- Unacceptable risk to Subject safety is confirmed

In such cases, Thoratec will notify the appropriate regulatory authority, and/or other participating centers as required by local and national regulations.

31.7 Early Study Termination

Thoratec reserves the right to discontinue the study prior to fulfillment of the intended number of Subjects. Thoratec intends to exercise this right only for valid scientific or administrative reasons. After such a decision, all unused investigational products must be returned to Thoratec and all collected data must be entered into EDC.

The study could be prematurely discontinued in the following cases:

- New findings about the investigational product(s) that changes the risk/benefit ratio where the risk to study Subjects is unacceptable.
- For any other valid scientific or administrative reason(s) as determined by Thoratec.

32 EMERGENCY CONTACTS

Thoratec Clinical Affairs personnel are available 24 hours a day via the protocol pager to provide assistance with all device related emergencies and/or for safety reporting. The number for the protocol pager is 1-877-479-0299.

33 PUBLICATION POLICY

The first publication or presentation of Clinical Study Results shall be made as a joint, multi-center publication/presentation of the Study results with the investigators and institutions from all appropriate sites contributing data, analyses and comments. All publications will be reviewed by the study investigators and the Sponsor, and in accordance with the site specific Clinical Study Agreement (CSA).

34 HM III IDE STUDY VISIT SCHEDULE

Table 2 – Schedule of Events for Randomized Subjects

	Screening[1]	Baseline[1]	Implant	Post-Op Day 1	1 Week Post Implant (+/- 1 day)	Discharge (-1 day)	30 Days Post Implant (+/- 7 days)	90 Days Post Implant (+/- 30 days)	180 Days Post Implant (+/- 30 days)	360 Days Post Implant (+/- 30 days)	540 Days Post Implant (+/- 30 days)	720 Days Post Implant (+/- 30 days)	As Occurs
Inclusion/ Exclusion	X												
Enrollment / Randomization	X[17]												
Demographics	X												
Intended Use[11]	X												
General and Cardiac Medical History		X											
Current Medications / Cardiovascular Medications[9]		X	X		X	X	X	X	X	X	X	X	
Physical Exam		X											
Vital Signs[2]		X			X	X	X	X	X	X	X	X	
Hemodynamic Measurements[3]		X											
Laboratory Assessments		X			X	X	X	X	X	X	X	X	
Echocardiogram		X		X[15]	X	X	X	X	X	X	X	X	
ECG		X											
Chest X-ray [13] (PA and Lateral)				X[16]			X		X	X		X	
Modified Rankin Score		X	X[6]		X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]
NYHA Classification [5]		X				X	X	X	X	X	X	X	
INTERMACS Profile		X											
6 Minute Walk Test		X					X	X	X	X	X	X	
EQ-5D-5L		X					X	X	X	X	X	X	
KCCQ		X						X	X	X	X	X	
VO_2 Max[10]		X											
Implant Data/CPB Time/Blood Products			X										X

	Screening[1]	Baseline[1]	Implant	Post-Op Day 1	1 Week Post Implant (+/- 1 day)	Discharge (-1 day)	30 Days Post Implant (+/- 7 days)	90 Days Post Implant (+/- 30 days)	180 Days Post Implant (+/- 30 days)	360 Days Post Implant (+/- 30 days)	540 Days Post Implant (+/- 30 days)	720 Days Post Implant (+/- 30 days)	As Occurs
HM II and HM III Pump Parameters[7]			X		X	X	X	X	X	X	X	X	X[14]
Concurrent Procedures at Pump Implant			X										X
Subject Status					X	X	X	X	X	X	X	X	X
Subject Outcome					X	X	X	X	X	X	X	X	X
ICU Time						X							
Rehospitalizations							X	X	X	X	X	X	X
HM III Pump Log Files[8]			X	X	X	X	X	X	X	X	X	X	X[14]
HM II Pump Log Files													X[14]
Adverse Events [4]			X		X	X	X	X	X	X	X	X	X
Device Malfunctions[4]			X		X	X	X	X	X	X	X	X	X
Operative Procedures[4]					X	X	X	X	X	X	X	X	X
Pump Replacements / Explants / Exchanges [4]					X	X	X	X	X	X	X	X	X
Driveline Management Assessment					X	X	X	X	X	X	X	X	X
Collection of UB-04 Form						X							X[12]
Autopsy													X

[1] *Screening and Baseline assessments can be conducted as one visit or separate visits.*
[2] *Vital Signs include: height (only at baseline), weight, temperature, respiratory rate, heart rate, blood pressure and mean arterial pressure.*
[3] *Hemodynamic Measurements include: Pulmonary Capillary Wedge Pressure, Pulmonary Arterial Systolic Pressure, Pulmonary Arterial Diastolic Pressure, Pulmonary Arterial Mean Pressure, Central Venous Pressure, Cardiac Index, Cardiac Output, Pulmonary Vascular Resistance, Right Arterial pressure and Left Arterial pressure.*
[4] *Post Implant or during implant procedure.*
[5] *Must be performed by an independent assessor.*
[6] *Required only if a stroke has occurred and 60 days post-stroke.*
[7] *HM II and HM III Pump Parameters include: Pump Flow, Pump Speed, Pulsatility Index and Pump Power.*
[8] *Pump Log Files include: Pump Period Log, Pump Event Log, Controller Period Log, and Controller Event Log.*
[9] *If Subject is on inotropes at the time of screening/baseline, list how long the Subject has been on inotropes.*
[10] *If Subject is able. If Subject is unable to perform, must provide reason this was not done.*
[11] *At the time of implant and as defined by INTERMACS; refer to Appendix 6.*
[12] *To be collected any time subject is rehospitalized.*
[13] *Images to be submitted to Thoratec.*
[14] *In addition to defined scheduled collection of pump parameters and pump logs, they must also be submitted when any pump-related AE or malfunction occurs.*

[15]*Post-operative TEE is also acceptable; can be performed POD 0 (post-implant) + 2 days*

[16]*AP view for HM III subjects; feeding tube view for HM II subjects*

[17]*Randomization should occur as close as possible to the implant date; if possible, within 72 hours.*

35 REFERENCES

1. Miller LW, Pagani FD, Russell SD, et al. Use of a continuous-flow device in patients awaiting heart transplantation. N Engl J Med 2007; 357: 885-896

2. Slaughter, MS, Rogers JG, Milano CA et al. Advanced Heart Failure Treated with Continuous-Flow Left Ventricular Assist Device N Engl J Med 2009; 361: 2241-2251

3. Starling RC, Naka Y, Boyle AJ et al. Results of the Post U.S. Food and Drug Administration-Approval Study with a Continuous Flow Left Ventricular Assist Device as a Bridge to Heart Transplantation, J Am Coll Cardiol 2011; 57:1890-1898.

4. Active Implantable Medical Device Directive (AIMDD) 90/385/EEC. (June 20, 1990)

5. EN ISO 14155: 2011 - Clinical investigation of medical devices for human subjects – Part 1: General requirements

6. FDA. United States Code of Federal Regulations, Electronic Records: Electronic Signatures; Final Rule. Source: 21 CFR Part 11 (April 1, 2013).

7. Guidelines on Clinical Investigation: a Guide for Manufacturers and Notified Bodies, MEDDEV 2.7/4

8. Organisation for Economic Co-operation and Development (OECD) Principles of Good Laboratory Practice (GLP) in 1997

9. Rogers JG, Aaronson KD, Boyle AJ et al. Continuous Flow Left Ventricular Assist Device Improves Functional Capacity and Quality of Life of Advanced Heart Failure Patients. J Am Coll Cardiol. 2010; 55:1826-34.

10. . Wang C, Keller DS, Lan KKG. Sample size re-estimation for binary data via conditional power. Joint Statistical Meetings – Biopharmaceutical Section. 2002

11. Kirklin JK, Naftel DC, Kormos RL et al. INTERMACS Analysis of Pump Thrombosis in the Heartmate II Left Ventricular Assist Device. J. Heart Lung Transplant. 2014; 33:12-22.

12. Thoratec Final Post Approval Report to the FDA on the HM II Destination Therapy – INTERMACS Post Approval Study

13. Thoratec Data: HM II Bridge to Transplant – INTERMACS Post Approval Study

14. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. 2013

APPENDIX 1: ANTICIPATED ADVERSE EVENT DEFINITIONS

Bleeding
An episode of SUSPECTED INTERNAL OR EXTERNAL BLEEDING that results in one or more of the following:
a. Death,
b. Reoperation,
c. Hospitalization,
d. Transfusion of red blood cells as follows:
   - If transfusion is selected, then apply the following rules:

     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 the first 7 days post-implant

     After 7 days Post-implant*
     - Any 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 event and not as a separate bleeding event.
*Any transfusion of ≥ 2U packed red blood cells (PRBC) after 7 days following implant will be considered a serious bleed

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

Pericardial Fluid Collection
Accumulation of fluid or clot in the pericardial space that requires surgical intervention or percutaneous catheter drainage. This event will be subdivided into those with clinical signs of tamponade (e.g. increased central venous pressure and decreased cardiac/VAD output) and those without signs of tamponade.

Device Malfunctions
A Device Malfunction occurs when any component of the MCSD system ceased to operate to its designated performance specifications or otherwise fails to perform as intended. Performance specifications include all claims made in the Instructions for Use.

Internal Component Malfunction: Malfunction of any device system component that is implanted within the patient. A malfunction to these components may require further surgery to repair or replace.

External Component Malfunction: Malfunction of a device system component that is used external to the patient and can be replaced or repaired without the need for further surgery.

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

a. Presence of hemolysis
b. Worsening heart failure or inability to decompress the left ventricle
c. Abnormal pump parameters

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

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

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

Hemolysis*
A plasma-free hemoglobin value that is greater than 40 mg/dl, concomitant with a rise in serum LDH above three times the upper limit of normal, in association with clinical signs associated with hemolysis (e.g., anemia, low hematocrit, hyperbilirubinemia) occurring after the first 72 hours post-implant.
*Hemolysis in the presence of worsening heart failure or inability to decompress the left ventricle or abnormal pump parameters should be reported as suspected device thrombosis, not as hemolysis

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

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

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

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

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

Internal Pump Component, Inflow or Outflow Tract Infection
Infection of blood-contacting surfaces of the LVAD documented by positive site culture.

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

Myocardial Infarction
Two categories of myocardial infarction will be identified:

Peri-Operative Myocardial Infarction
The clinical suspicion of myocardial infarction together with CK-MB or Troponin > 10 times the local hospital upper limits of normal, found within 7 days following VAD implant together with ECG findings consistent with acute myocardial infarction. (This definition uses the higher suggested limit for serum markers due to apical coring at the time of VAD placement, and does not use wall motion changes because the apical sewing ring inherently creates new wall motion abnormalities.)

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

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

Neurologic Dysfunction
Any new, temporary or permanent, focal or global neurological deficit, ascertained by a standard neurological history and examination administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests and consultation note; or an abnormality

identified by surveillance neuroimaging. The examining physician will classify the event as defined below:

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

*Modified Rankin Score will be used to classify the severity of all strokes
**Acute encephalopathy is a sign or symptom of some underlying cerebral disorder, and is manifest as depressed consciousness with or without any associated new global or multifocal neurologic deficits in cranial nerve, motor, sensory, reflexes and cerebellar function.

Psychiatric Episode
Disturbance in thinking, emotion or behavior that causes substantial impairment in functioning or marked subjective distress requiring intervention. Intervention is the addition of new psychiatric medication or hospitalization. Suicide is included in this definition.

Renal Dysfunction
Two categories of renal dysfunction will be identified:

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

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

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

Right Heart Failure
Symptoms and signs of persistent right ventricular dysfunction requiring RVAD implantation, or requiring inhaled nitric oxide or inotropic therapy for a duration of more than 1 week at any time after LVAD implantation.

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

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

This definition excludes neurological events.

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

Wound Dehiscence
Disruption of the exposed surfaces of a surgical incision, excluding infectious etiology, and requiring surgical repair.

Other
An event that causes clinically relevant changes in the Subject's health (e.g. cancer).

APPENDIX 2: INTERMACS PROFILE/CLASSIFICATION

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

*Stevenson, L.W. et al. INTERMACS Profiles of Advanced Heart Failure: The Current Picture, J Heart Lung Transplant. 2009 28(6): 535-541

APPENDIX 3: NYHA CLASSIFICATION

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

APPENDIX 4: 6MWT PROTOCOL

SIX-MINUTE HALLWAY WALK TEST INSTRUCTIONS

Purpose
The purpose of the 6-Minute Hallway Walk test (6MWT) is to walk as far as possible for 6-minutes, without running or jogging, as a way of measuring functional status.

Preparing for the test
1. Establish a 30-meter walking course in an enclosed corridor, preferably free of distractions and close to a wall so that if needed, the Subject may rest against it during the test (note: a treadmill is not an acceptable alternate method for this study).
2. Mark the course at 3-meter intervals using a method unnoticeable to the Subject.
3. Place noticeable markers at either end of the 30-meter course to indicate the turnaround points.
4. The distance covered during the preceding walk test will not be revealed to the Subject during the study.
5. A warm up prior to the test should not be performed.

Explaining the test procedure to the Subject
1. Clearly explain to the Subject what is required of him/her using the following instructions verbatim:

   THE PURPOSE OF THIS TEST IS TO WALK AS FAR AS POSSIBLE FOR SIX-MINUTES. YOU WILL START FROM THIS POINT AND FOLLOW THE HALLWAY TO THE MARKER AT THE END, THEN TURN AROUND AND WALK BACK. WHEN YOU ARRIVE BACK AT THE STARTING POINT, YOU WILL GO BACK AND FORTH AGAIN. YOU WILL GO BACK AND FORTH AS MANY TIMES AS YOU CAN IN THE SIX-MINUTE PERIOD. IF YOU NEED TO, YOU ARE PERMITTED TO SLOW DOWN, TO STOP, AND TO REST AS NECESSARY. YOU MAY LEAN AGAINST THE WALL WHILE RESTING, BUT RESUME WALKING AS SOON AS YOU ARE ABLE. HOWEVER, THE MOST IMPORTANT THING ABOUT THE TEST IS THAT YOU COVER AS MUCH GROUND AS YOU POSSIBLY CAN DURING THE SIX MINUTES. I WILL KEEP TRACK OF THE NUMBER OF LAPS YOU COMPLETE AND I WILL LET YOU KNOW WHEN THE SIX MINUTES ARE UP. WHEN I SAY STOP, PLEASE STAND RIGHT WHERE YOU ARE.

   DO YOU HAVE ANY QUESTIONS ABOUT THE TEST?

   PLEASE EXPLAIN TO ME WHAT YOU ARE GOING TO DO.

2. The Subject will re-state the instructions. If the Subject does not seem to understand, repeat the entire instructions.

   Conducting the test
   1. Position the Subject at the starting line.
   2. Repeat the sentence:

      THE MOST IMPORTANT THING ABOUT THE TEST IS THAT YOU COVER AS MUCH GROUND AS YOU POSSIBLY CAN DURING THE SIX MINUTES.

      ARE YOU READY?

      START NOW, OR WHENEVER YOU ARE READY.

3. Start the timer as soon as the Subject takes the first step.
4. During the test, the walking pace of the Subject should not be influenced. The test supervisor must walk behind the Subject – do not walk with, rush up behind, or rush past the Subject.
5. Each time the Subject returns to the starting line, record the lap.
6. While walking, encourage the Subject at one minute intervals with the following phrases:

1 minute:	YOU ARE DOING WELL. YOU HAVE 5 MINUTES TO GO.
2 minutes:	KEEP UP THE GOOD WORK. YOU HAVE 4 MINUTES TO GO.
3 minutes:	YOU ARE DOING WELL. YOU ARE HALFWAY DONE.
4 minutes:	KEEP UP THE GOOD WORK. YOU HAVE ONLY 2 MINUTES LEFT.
5 minutes:	YOU ARE DOING WELL. YOU HAVE ONLY ONE MINUTE TO GO.

7. The Subject should be spoken to only during the 1-minute encouragements; no response should be made to the Subject's questions about the time and distance elapsed.
   a. If the Subject is not concentrating on the walking, the Subject can be reminded at a 1-minute mark:

      THIS IS A WALKING TEST, TALKING WILL UTILIZE YOUR ENERGY RESERVE AND INTERFERE WITH YOUR PERFORMANCE.

7. When only 15 seconds remain, state:

   IN A MOMENT I AM GOING TO TELL YOU TO STOP. WHEN I DO, STOP RIGHT WHERE YOU ARE AND I WILL COME TO YOU.

9. When the timer reads 6-minutes, instruct the Subject to STOP and walk over to him/her. Consider bringing a chair if the Subject appears exhausted. Mark the spot where the Subject stopped.

   If the Subject wishes to stop walking during the test
   If the Subject is slowing down and expresses that he/she wants to pause, keep the timer running and state:

   REMEMBER, IF YOU NEED TO, YOU MAY LEAN AGAINST THE WALL UNTIL YOU CAN CONTINUE WALKING AGAIN.

   If the Subject wishes to stop before the 6-minutes are complete and refuses to continue (or you decide that he/she should not continue), provide a chair for the Subject to sit on and discontinue the test. Record the distance completed, the time the test was stopped and the reason for pre-maturely stopping.

   Immediately after the test
   1. Total the number of completed laps and add the additional distance covered in the final partial lap. Record the distance walked to the nearest meter.
   2. Observe the Subject sitting in a chair for at least 10 minutes after the test is completed.

APPENDIX 5: MODIFIED RANKIN SCORE

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

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

APPENDIX 6: INTERMACS DEFINITIONS FOR INTENDED USE OF DEVICE

Bridge to recovery - Use of a durable device to allow recovery from chronic cardiac failure (at least 3 months in duration)

Rescue therapy - Use of a durable device to support resolution from an acute event without major previous cardiac dysfunction

Bridge to transplant– This is for a patient ALREADY listed for transplant or listed within 24 hours before device implantation

Possible bridge to transplant - *Likely to be eligible*: defines a patient in whom the transplant evaluation has not been completed, but no contra-indications are anticipated, or in whom a current contra-indication is anticipated to resolve rapidly, such as recent infection.

Possible bridge to transplant - *Moderate likelihood of becoming eligible*: similar to above, but with some potential concerns that might prevent eligibility.

Possible bridge to transplant - *Unlikely to become eligible:* should be used for a patient in whom major concerns have already been identified. These may not have been quantified yet, such as in a patient with known chronic lung disease without recent pulmonary function test measurement, or might be reversible, such as severe renal insufficiency or pulmonary hypertension that might improve after chronic mechanical support. It may be the expectation at the time of implant that the patient will most likely have the assist device as “permanent” or “destination” therapy.

Destination therapy - patient definitely not eligible for transplant.

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REVISION HISTORY

Version	Date	Revision Summary	Originator	Release Date
1	3/6/2014	Original Protocol	Kelly Maslin	3/6/2014
2	4/22/2014	Update to Inclusion Criteria #6, update to functional status and independent assessor, clarification of pump log collection, modification to Modified Rankin Score timing, updated enrollment numbers, clarification of AE definitions; updated pager number; updated references	Kelly Maslin	4/24/2014
3	6/17/2014	Update to Exclusion Criteria #5, clarification to timeframe for randomization, clarification of x-ray collection, allow for collection of TEE post-implant, update number of study sites	Kelly Maslin	6/17/2014
4	8/1/2014	Update to study design to reflect 10 additional subjects allowable during FDA review; update to figure 2 to reflect 60 study sites; addition of independent assessor requirement for Modified Rankin Score; revised screening visit so that informed consent is signed after inclusion/exclusion assessment; subjects now considered enrolled at time of study consent; revised schedule of events such that INTERMACS profile is assessed immediately prior to implantation; updated reporting requirement to DSMB and FDA; updated treatment-by-site interaction effect to be tested at 0.15 level of significance	Kelly Maslin	8/4/14

Version	Date	Revision Summary	Originator	Release Date
5	4/1/2015	Updated Sponsor contact information; clarification of exclusion criteria 12c , 12e, and 14; clarification of time of enrollment in section 13.4; clarified all laboratory assessments to reflect only albumin or pre-albumin, and CRP or hs-CRP are required; clarification of pump log collection schedule in section 16.8.1; addition of HeartMate 3 TM symbol.	Kelly Maslin	4/2/2015
6	8/4/2015	Changed study name from HeartMate III IDE to MOMENTUM 3 IDE; changed HeartMate III to HeartMate 3; removed breakdown of number of subjects per arm; clarified use of MPU in section 3; clarified 50 patient enrollment cap in section 13.4; added 90 day window to assess eligibility in section 16.1 added visit window to post-op day 1 in section 16.4; clarification of pump log submissionin all follow-up visits; added subject withdrawal and lost to follow-up language in section 22; updated Figure 2 flow chart; added HeartLine emergency contact to section 32; updated Left atrial pressure to be collected if available inTable 2, corrected typographical errors in Table 2.	Kelly Maslin	8/5/2015
7	3/3/2016	Increased number of study sites from 60 to 70; clarification to power source while in hospital in section 3; clarification to assessment timepoints in section 13.15 and 13.16.	Kelly Maslin	3/21/2016

Version	Date	Revision Summary	Originator	Release Date
8	5/8/2017	Section 14.2: Changed required SAE reporting time from 24 hours to 3 days to align with Abbott clinical trial standard. Section 15: Changed required UADE reporting time from 24 hours to 3 days to align with Abbott clinical trial standard. Footer: added Sponsor document number and version (for internal use only).	Kelly Maslin	5/12/2017

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List of Abbreviations

6MWT .....Six-Minute Walk Test
AAA.....Abdominal Aortic Aneurysm
ACE.....Angiotensin Converting Enzyme
ADL .....Activities of Daily Living
AE .....Adverse Event
AHA.....American Heart Association
AI.....Aortic Insufficiency
AICD .....Automatic Internal Cardiac Defibrillator
AIMDD .....Active Implantable Medical Device Directive
ALT .....Alanine Aminotransferase
aPTT .....Activated Partial Thromboplastin Time
ARB.....Angiotensin Receptor Blocker
AST .....Aspartate Aminotransferase
AT .....As Treated
AV .....Aortic Valve
BNP.....B-type Natriuretic Peptide
BSA.....Body Surface Area
BTT .....Bridge to Cardiac Transplantation
BUN .....Blood Urea Nitrogen (Urea, blood)
CEC .....Clinical Events Committee
CFR.....Code of Federal Regulations
CI .....Cardiac Index
CIP .....Clinical Investigation Plan
CK.....Creatine Kinase
CNS .....Central Nervous System
COPD.....Chronic Obstructive Pulmonary Disease
CPB.....Cardiopulmonary Bypass
CRF.....Case Report Form
CRP .....C-reactive Protein
CRT.....Cardiac Resynchronization Therapy
CSA.....Clinical Study Agreement
CT .....Computed Tomography
CV.....Cardiovascular
CVP.....Central Venous Pressure
DT .....Destination Therapy
DSMB .....Data Safety Monitoring Board
ECG .....Electrocardiogram
eCRF.....Electronic Case Report Form
EDC .....Electronic Data Capture
EEG .....Electroencephalogram
eGFR .....Glomerular Filtration Rate
EQ-5D-5L.....EuroQol Health Utility Index
FDA.....U.S. Food and Drug Administration
FEV_1 .....Forced Expiratory Volume in One Second
FVC.....Forced Vital Capacity

List of Abbreviations

FWA .....Federal Wide Assurance
GI .....Gastrointestinal
GLP.....Good Laboratory Practices
H_0 .....Null Hypothesis
H_A.....Alternative Hypothesis
HF .....Heart Failure
HIE .....Hypoxic-Ischemic Injury
HM II .....HeartMate II
HM3 .....HeartMate 3
HR.....Heart Rate
Hs-CRP .....High Sensitivity C-reactive Protein
IABP.....Intra Aortic Balloon Pump
IB.....Investigator's Brochure
ICD.....Internal Cardiac Defibrillator
ICH.....Intracranial Hemorrhage
ICF .....Informed Consent Form
ICU.....Intensive Care Unit
IDE .....Investigational Device Exemption
IFU .....Instructions For Use
INTERMACS.....Interagency Registry for Mechanically Assisted Circulatory Support
INR.....International Normalized Ratio
IRB .....Institutional Review Board
ITT.....Intent-to-treat
KCCQ.....Kansas City Cardiomyopathy Questionnaire
LDH.....Lactic Acid Dehydrogenase
LOS.....Length of Stay
LV.....Left Ventricle
LVAD.....Left Ventricular Assist Device
LVAS.....Left Ventricular Assist System
LVEDD .....Left Ventricular End Diastolic Diameter
LVEF .....Left Ventricular Ejection Fraction
LVESD .....Left Ventricular End Systolic Diameter
MB.....Myocardial Band
MCS .....Mechanical Circulatory Support
MCS .....Mechanical Circulatory Support Device
MPU .....Mobile Power Unit
MR .....Mitral Regurgitation
NT-ProBNP .....N terminal B-type natriuretic peptide
NYHA .....New York Heart Association
OMM .....Optimal Medical Management
PHgb .....Plasma Free Hemoglobin
PA .....Posterior-anterior
PI.....Principal Investigator
PMA .....Premarket Approval
PRBC .....Packed Red Blood Cells

List of Abbreviations

PT .....Prothrombin Time
PTT .....Partial Thromboplastin Time
PVD.....Peripheral Vascular Disease
PVR.....Pulmonary Vascular Resistance
RCT.....Randomized Controlled Trial
RV .....Right Ventricle
RVAD .....Right Ventricular Assist Device
SAE.....Serious Adverse Event
SBP.....Systolic Blood Pressure
SHFM.....Seattle Heart Failure Model
Thoratec.....Thoratec Corporation
tPA……..Tissue Plasminogen Activator
TR .....Tricuspid Regurgitation
UADE .....Unanticipated Adverse Device Effect
UNOS……United Network for Organ Sharing
VAD.....Ventricular Assist Device
VAS.....Visual Analogue Scale
WBC.....White Blood Cells
WMA .....World Medical Association

STUDY SYNOPSIS	
Device	HeartMate 3 (HM3) Left Ventricular Assist System (LVAS)
Indications for Use	The HM3 LVAS is intended to provide hemodynamic support in patients with advanced, refractory left ventricular heart failure; either for short term support, such as a bridge to cardiac transplantation (BTT) or myocardial recovery, or as long term support, such as destination therapy (DT). The HM3 is intended for use inside or outside the hospital.
Study Objective	The objective of the study is to evaluate the safety and effectiveness of the HM3 LVAS by demonstrating non-inferiority to the HM II LVAS (HM II) when used for the treatment of advanced, refractory, left ventricular heart failure.
Study Population	Advanced Heart Failure New York Heart Association (NYHA) Class III patients with dyspnea upon mild physical activity, or NYHA Class IV who are refractory to advanced heart failure management.
Study Design	The study will be a prospective, multi-center, unblinded, randomized, controlled, non-inferiority study comparing the HM3 LVAS to the HM II LVAS. The study will be conducted as a staged pivotal study that includes a pre-specified early assessment for safety. Other key elements include: – Up to 5 centers in the United States (U.S.) will be initiated to enroll up to 10 randomized HM3 Subjects. A pre-specified analysis for safety will be performed after the first 10 randomized HM3 Subjects have completed 30 days of follow-up. The results of this early safety analysis will be reviewed by the Data Safety Monitoring Board (DSMB), after which the DSMB report, along with supporting safety data from the HM3 CE Mark study will be sent to FDA as an IDE supplement, with a request to gain full IDE approval to expand the study to up to a total of 60 centers in the U.S. The first 5 U.S. centers will continue to enroll up to a total of 30 subjects (including those in the early safety analysis) during FDAs review of this IDE Supplement. – An adaptive design will be used, if required to adjust the sample size at a pre-specified time during the study. – **Primary Endpoint Analysis** – Perform an analysis and submit the Premarket Approval (PMA) when the specified number of Subjects complete 6 months of support for a short term indication – Perform an analysis and submit a PMA supplement when the specified number of Subjects complete 24 months of support for a long term indication – **Powered Secondary Endpoint Analysis** – Once the Subjects have been enrolled for the primary endpoint analysis, randomization will continue until sufficient Subjects have been enrolled to evaluate a pre-specified powered secondary endpoint. – Analysis of the pre-specified secondary endpoint will be used to update HM3 labeling.
Control Group	The HM II will serve as the control group. Subjects will be randomized 1 HM3 to 1 HM II.

STUDY SYNOPSIS	
Primary Study Endpoints	1. Short Term Indication: a. Composite of Survival to transplant, recovery or 6 months of LVAD support free of debilitating stroke (Modified Rankin Score > 3) or reoperation to replace the pump. 2. Long Term Indication: a. Composite of Survival to transplant, recovery or 24 months of LVAD support free of debilitating stroke (Modified Rankin Score > 3) or reoperation to replace the pump.
Secondary Study Endpoints	The following secondary objectives will be evaluated: 1. Quality of Life as measured by EuroQoL 5D-5L (EQ-5D-5L) and Kansas City Cardiomyopathy Questionnaire (KCCQ) 2. Functional status as measured by the 6-minute walk test (6MWT) and NYHA classification 3. Frequency and incidence of all re-operations 4. Frequency and incidence of all rehospitalizations 5. Frequency, incidence and rates of pre-defined anticipated adverse events. 6. Frequency and incidence of device malfunctions
Pre- Specified Powered Secondary Endpoint	In addition to powering the study on the primary endpoints for PMA approval, the study will pre-specify a powered secondary endpoint to evaluate incidence of pump replacements at 24 months.
Sample Size	Total sample size = 1028 (Randomized 1:1).
Study Hypothesis and Sample Size	Short Term Indication Hypothesis: − HM3 non-inferior to HM II at 6 months − Assumes 87% composite success rate for HM3 and 85% for HM II at 6 months. − 294 Subjects provides 80% power to show non-inferiority when the margin of non-inferiority is 10% and alpha = 0.025. Sample size accounts for early transplants. Long Term Indication Hypothesis: − HM3 non-inferior to HM II at 24 months − Assumes 55% composite success at 24 months for the HM3 arm and 50% for the HM II arm − 366 Subjects provides 80% power to show non-inferiority when the margin of non-inferiority is 10% and alpha = 0.025. Sample size accounts for early transplants. Pre-Specified Secondary Analysis of Pump Replacements − When enrollment to evaluate the primary objective is complete, randomization will continue to enroll Subjects to determine if the pump replacement rate for HM3 is superior to HM II at 24 months − The pump replacement rate for the HM II is about 7% at 24 months in the United States. − In order to determine if the rate of HM3 pump replacements have been reduced to 3% at 24 months, 1028 Subjects will be required (power=0.8; alpha = 0.05, two-sided). This will require the randomization of 662 additional Subjects.
Study Duration	All randomized Subjects will be followed for 24 months or to outcome (transplant, explant, or death), whichever occurs first.

STUDY SYNOPSIS	
Inclusion Criteria	1) Subject or legal representative has signed Informed Consent Form (ICF) 2) Age ≥ 18 years 3) BSA ≥ 1.2 m^2 4) NYHA Class III with dyspnea upon mild physical activity, or NYHA Class IV 5) LVEF ≤ 25% 6) a) Inotrope dependent OR b) CI < 2.2 L/min/m^2, while not on inotropes and subjects must also meet one of the following: • On Optimal Medical Management (OMM), based on current heart failure practice guidelines for at least 45 out of the last 60 days and are failing to respond • Advanced Heart Failure for at least 14 days AND dependent on intra-aortic balloon pump (IABP) for at least 7 days 7) Females of child bearing age must agree to use adequate contraception

STUDY SYNOPSIS	
Exclusion Criteria	1) Etiology of heart failure (HF) due to or associated with uncorrected thyroid disease, obstructive cardiomyopathy, pericardial disease, amyloidosis or restrictive cardiomyopathy 2) Technical obstacles which pose an inordinately high surgical risk, in the judgment of the investigator 3) Existence of ongoing mechanical circulatory support (MCS) other than IABP 4) Positive pregnancy test if of childbearing potential 5) Presence of mechanical aortic valve that will not be either converted to a bioprosthesis or oversewn at the time of LVAD implant 6) History of any organ transplant 7) Platelet count < 100,000 x 10^3/L (< 100,000/ml) 8) Psychiatric disease/disorder, irreversible cognitive dysfunction or psychosocial issues that are likely to impair compliance with the study protocol and LVAS management 9) History of confirmed, untreated AAA > 5 cm in diameter within 6 months of enrollment 10) Presence of an active, uncontrolled infection 11) Intolerance to anticoagulant or antiplatelet therapies or any other peri/post-operative therapy the investigator will require based upon the patients' health status 12) Presence of any one of the following risk factors for indications of severe end organ dysfunction or failure: a) An INR ≥ 2.0 not due to anticoagulation therapy b) Total bilirubin > 43 umol/L (2.5 mg/dl), shock liver, or biopsy proven liver cirrhosis c) History of severe chronic obstructive pulmonary disease (COPD) defined by $FEV_1/FVC < 0.7$, and FEV_1 <50% predicted d) Fixed pulmonary hypertension with a most recent PVR ≥ 8 Wood units that is unresponsive to pharmacologic intervention e) History of stroke within 90 days prior to enrollment, or a history of cerebrovascular disease with significant (> 80%) uncorrected carotid stenosis f) Serum creatinine ≥ 221 umol/L (2.5 mg/dl) or the need for chronic renal replacement therapy g) Significant peripheral vascular disease (PVD) accompanied by rest pain or extremity ulceration 13) Patient has moderate to severe aortic insufficiency without plans for correction during pump implant 14) Pre albumin < 150 mg/L (15mg/dL) or Albumin < 30g/L (3 g/dL) (if only one available) ; pre albumin < 150 mg/L (15mg/dL) and Albumin < 30g/L (3 g/dL) (if both available) 15) Planned Bi-VAD support prior to enrollment 16) Patient has known hypo or hyper coagulable states such as disseminated intravascular coagulation and heparin induced thrombocytopenia 17) Participation in any other clinical investigation that is likely to confound study results or affect the study 18) Any condition other than HF that could limit survival to less than 24 months

STUDY SYNOPSIS	
Study Follow-up Intervals	Screening, Baseline, Implant, Post-op Day 1, 1 week, Discharge, Month(s) 1, 3, 6, 12, 18 and 24.
Data Collection	A 21 CFR part 11 compliant Electronic Data Capture (EDC) system will be used to collect data.
Statistical Analysis	Baseline data will be analyzed using Fisher's exact test and unpaired t-tests as appropriate. The HM3 will be considered non-inferior to the HM II for short term and long term indications if the lower 95% confidence limit of the difference between the success for the HM3 and HM II is greater than the non-inferiority margin of -10%. Once non-inferiority is inferred, the data will be analyzed for superiority using closed testing methods. Differences in survival between treatment groups will be analyzed using the Kaplan-Meier product-limit method. Safety, including device malfunctions, will be reported as incidence and event rate per patient year of support. A time to event analysis will also be performed. Comparison of adjudicated adverse events between HM3 and the HM II control group will be performed using Fisher's exact test or Poisson regression, as appropriate. Quality of Life and six minute walk data will be analyzed using mixed models. Subanalyses of the primary endpoints, survival, adverse events, and quality of life will also be performed and will include gender, ethnicity, age, VO2 Max, and intended use of the device at the time of implant as defined by INTERMACS. In addition to the primary outcome, the study will be powered to test if HM3 pump reliability is superior to HM II by analyzing the incidence of pump replacement. The percentage of HM3 pump replacements will be compared to HM II using Fisher's exact test.
Adverse Events	Anticipated adverse events will be captured using definitions described in this FDA approved protocol.
Adaptive Design	In case the assumptions of the study are incorrect, a pre-specified early look at the data will be performed by an independent statistician to determine if the study requires adjustment to the sample size. The adaptive design analysis will be performed to evaluate the conditional power.
Number of Investigational Sites	Up to 70 U.S. sites

1 INTRODUCTION

Over the last decade, mechanical circulatory support with left ventricular assist devices (LVADs) have become an important therapy for patients in advanced stage heart failure. The HeartMate® II (HM II) LVAD is a rotary axial-flow pump that has been approved by the U.S. Food and Drug Administration (FDA) for New York Heart Association Class (NYHA) IIIB/IV patients as a bridge to cardiac transplantation, and as permanent destination therapy. Numerous publications have documented the success of the HM II in extending and improving the quality of patient's lives[1, 2, 3, 9]. Adverse events associated with the HM II have included GI bleeding, pump thrombosis, and driveline issues which, in some cases, have resulted in pump replacement.

HeartMate 3 (HM3) Left Ventricular Assist System (LVAS) is the next generation of mechanical support device. The purpose of this study is to evaluate the safety and effectiveness of the HM3 LVAS. This multicenter study is designed to determine if the HM3 provides similar survival and quality of life benefits as the HM II by using a prospective, randomized, controlled, non-inferiority study design. Additional potential benefits of the HM3, such as reduced adverse events, will also be evaluated in a descriptive manner.

2 INDICATIONS FOR USE

The HM3 LVAS is intended to provide hemodynamic support in patients with advanced refractory left ventricular heart failure; either for short term support, such as a bridge to cardiac transplantation (BTT) or myocardial recovery, or as long term support, such as destination therapy (DT). The HM3 LVAS is intended for use inside or outside the hospital.

3 DEVICE DESCRIPTION AND THEORY OF OPERATION

The HeartMate 3 LVAS is a set of equipment and materials that together comprise a medical device designed to provide therapeutic benefit to those afflicted with advanced heart failure. In service, the LVAS assumes some or all of the workload of the left ventricle, thereby restoring the patient's systemic perfusion while palliating the underlying pathology. The LVAS features a Left Ventricular Assist Device (LVAD), a centrifugal magnetically levitated pump intended for long term implantation in such patients, an extracorporeal Controller, plus all of the features, controls, attachments, interfaces, power sources, supporting equipment, labeling, and tools required to achieve the desired therapeutic benefit.

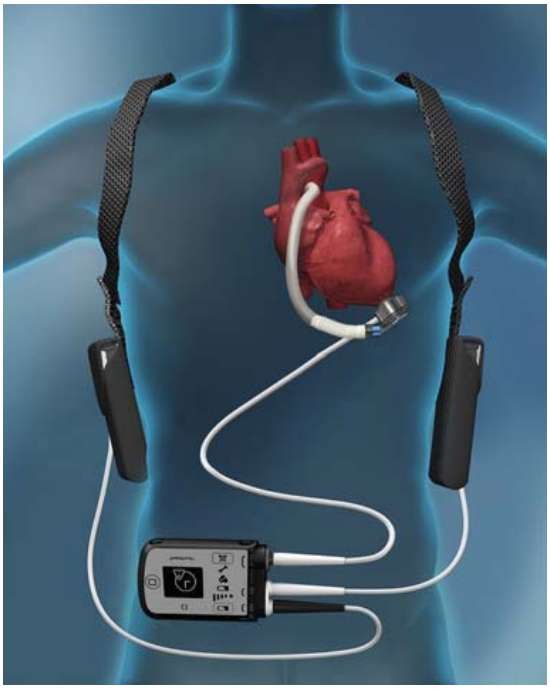
The LVAS may be used in either of two configurations. First, line power may be utilized through the Power Module or Mobile Power Unit (MPU) to run the LVAD indefinitely, convenient for sedentary or sleeping periods. Second, portable Battery power may be utilized for limited periods, convenient for active periods. Due to the bifurcation of the Patient Cable, switching among these configurations or from one set of Batteries to another (as when one set has been depleted and a fully charged set is available) may be accomplished without interrupting LVAS function. Whenever the Power Module is used

a System Monitor may also be used as a means of viewing operating conditions, changing operating parameters, and manipulating stored data.

While Subjects are in the hospital, either the Power Module or MPU can be used. However, Subjects implanted with HM3 will be discharged from the hospital with the MPU, without the system monitor, as their primary source of power. Subjects implanted with HMII can be discharged with either the MPU or Power Module.

The HeartMate 3 LVAD is part of the HeartMate 3 LVAS. See Figure 1. The LVAD is a blood pump intended for long term implantation in the thorax of patients with advanced heart failure. The LVAD is surgically connected to the patient's circulatory system via an Inflow Cannula placed into the left ventricular apex, and an Outflow Graft anastomosed to the ascending aorta. Detailed surgical, patient management and storage and handling instructions can be found in the HM3 Instructions For Use (IFU).

Figure 1 – HeartMate 3 System during Battery-powered Operation



The HM3 LVAD contains an Inflow Cannula, a Pump Cover, a Lower Housing, a Screw Ring to attach the Pump Cover to the Lower Housing, a Motor, the Outflow Graft, and a Pump Cable.

The HeartMate 3 Controller is also part of the HM3 LVAS. The Controller is an extracorporeal interface device that receives power from the Power Module, Mobile

Power Unit, or portable Batteries, and appropriately delivers that power to the HM3 LVAD. It is the primary user interface and has several important functions:

- Operating condition display,
- Source of audible and visible alarms,
- Communication link for transferring event/period log and alarm information, and
- Battery backup in the case of full power disconnection.

The HM3 LVAD is assembled in Thoratec Corporation's manufacturing facility in Zurich, Switzerland. All other HM3 components and accessories are manufactured at Thoratec Corporation's manufacturing facility in Pleasanton, California, U.S.A.

A complete list of HM33 LVAS components and accessories, including model and/or serial/lot numbers is included in the HM3 IFU.

For additional information about this product, including information about the biologically active materials used, please see the HM3Investigator's Brochure (IB).

4 DEVICE TESTING

4.1 Device Testing: Bench

The HeartMate 3 LVAD/LVAS is an implantable long term support device/system. As such, it has been designed in compliance with all applicable FDA and international standards[4,5,6,7]. The device/system has been subjected to a comprehensive verification and validation effort to ensure its safety including evaluation of biocompatibility, sterility and long term reliability. Please refer to the HeartMate 3 Investigator's Brochure for a more detailed description.

4.2 Device Testing: *In Vivo*

Extensive testing in animals has been done providing assurance to proceed with the use of the HM3 LVAS in humans.

In vivo studies were conducted to evaluate the safety of the HeartMate 3 LVAS. The *in vivo* tests verified:

- Surgical human factors and usability data
- Device performance characterization
- Biological effects (thrombosis, hemolysis, bleeding)

Testing was conducted under Good Laboratory Practices (GLP) Guidelines[8]. Please reference the Investigator's Brochure for additional information.

5 STUDY DESIGN

The study will be prospective, multi-center, unblinded, randomized, controlled, non-inferiority study, comparing the HM3 LVAS to the HM II LVAS. Short term use of the device will be evaluated when Subjects have been supported for 6 months. Long term use of the device will be evaluated when Subjects have been followed for 24 months.

Subjects who receive a device exchange to any device other than HM II or HM3, at any time during the study, will be withdrawn from the study and will not be followed.

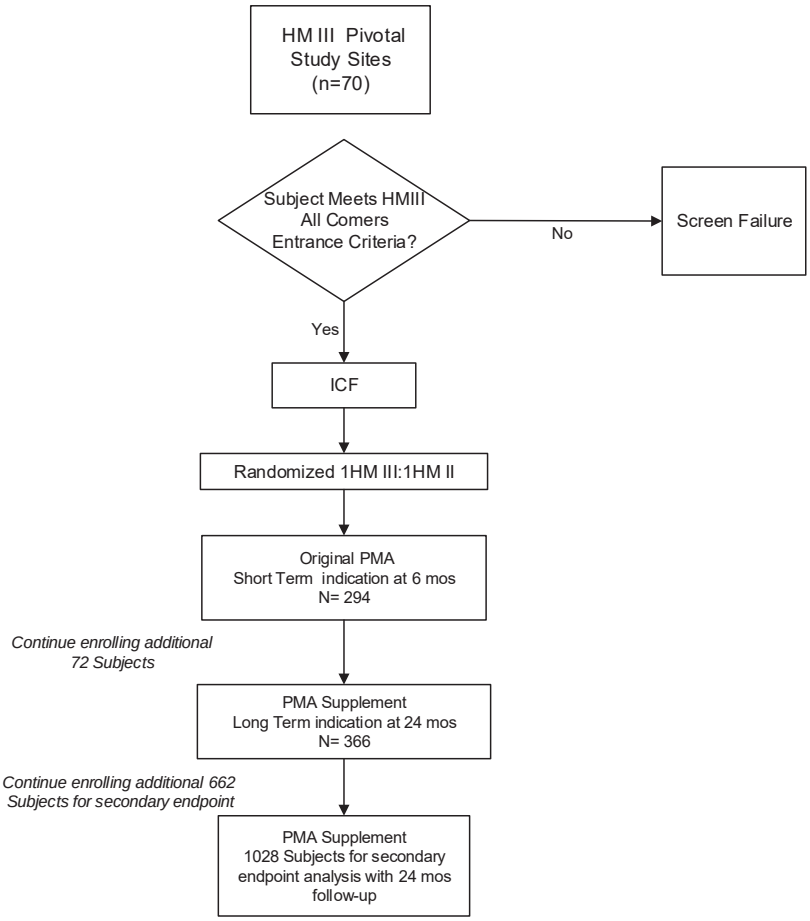
This study will be conducted as a staged pivotal study that includes a pre-specified early assessment for safety that is consistent with FDA's new Guidance for staged approval process, and in accordance with applicable local and federal regulations as specified in 21 CFR part 812.

During the early safety phase of the pivotal study, up to 5 centers in the United States (U.S.) will be initiated to enroll up to 10 randomized HM3 Subjects. A pre-specified analysis for safety will be performed after the first 10 randomized HM3 Subjects have completed 30 day follow-up. The results of this early safety analysis will be reviewed by the Data Safety Monitoring Board (DSMB), after which the DSMB report, along with supporting safety data from the HM3 CE Mark study will be sent to FDA as an IDE supplement, with a request to gain full IDE approval to expand the study to up to a total of 60 centers in the U.S. The first 5 U.S. centers will continue to enroll up to a total of 30 subjects (including those in the early safety analysis) during FDA's review of this IDE Supplement.

The study will include an adaptive design which will be used, if required to adjust the sample size at a pre-specified time during the study.

In addition to the primary study endpoint, the study will include a powered secondary endpoint to provide supplemental data for HM3 labeling.

Figure 2 – MOMENTUM 3 IDE Study Flow



Total sample size = 1028 (randomized 1:1).

6 STUDY POPULATION

Advanced heart failure NYHA Class III patients with dyspnea upon mild physical activity, or NYHA Class IV patients who are refractory to advanced heart failure management.

7 NUMBER OF CLINICAL SITES AND SUBJECTS

The study will be conducted in up to 70 clinical sites. The total sample size for this study is 1028 Subjects. Three hundred and sixty-six (366) Subjects will be enrolled and randomized to evaluate the primary endpoint. The data from the Subjects randomized for the primary endpoint will be used for PMA submission for the Short Term and Long Term indications. An additional 662 Subjects will be randomized to achieve 1028 Subjects needed for the powered secondary endpoint analysis. The data from the powered secondary endpoint will be used to update labeling under a Supplemental PMA. Refer to Figure 2.

8 STUDY DURATION

It is anticipated that it will take approximately 6 months to complete the early safety assessment phase of the study. After that, the first 5 U.S. centers will continue to enroll up to a total of 30 subjects (including those in the early safety analysis) while the IDE Supplement is under review with the FDA for full IDE approval to expand the study to 60 centers.

It is anticipated that it will take approximately 42 months to complete enrollment and follow up for the primary endpoint analysis of the study for the short and long term evaluation of the device. All randomized Subjects needed for the primary endpoint analysis will be followed for 24 months or to outcome (transplant, explant, or death), whichever occurs first.

It is anticipated that it will take approximately 13 additional months to enroll the randomized Subjects for the powered secondary endpoint. All randomized Subjects that are not required for the primary endpoint analysis will be followed for 24 months or to outcome, whichever occurs first.

9 STUDY OBJECTIVES

9.1 Primary Study Objective

The primary objective of the study is to evaluate the safety and effectiveness of the HM3 LVAS by demonstrating non-inferiority to the HM II LVAS when used for the treatment of advanced, refractory, left ventricular heart failure.

9.2 Secondary Study Objectives

Secondary objectives include:

- Assessment of adverse events
- Assessment of rehospitalizations and re-operations
- Assessment of quality of life and functional status
- Assessment of clinical reliability, device malfunctions, and device failures

10 CLINICAL STUDY ENDPOINTS

10.1 Primary Study Endpoints

- Composite of survival to transplant, recovery or 6 months of LVAD support free of debilitating stroke (Modified Rankin Score > 3) or reoperation to replace the pump
- Composite of survival to transplant, recovery or 24 months of LVAD support free of debilitating stroke (Modified Rankin Score > 3) or reoperation to replace the pump

The 6 month composite data will be submitted for the short term indication and the 24 month composite data will be submitted for the long term indication.

10.2 Secondary Study Endpoints

- Quality of Life: Quality of Life as measured by the EuroQoL-5D-5L (EQ-5D-5L) and the Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Functional Status: Functional status as measured by the Six Minute Walk Test (6MWT) and by NYHA Classification.
- Adverse Events: Frequency, incidence and rates of pre-defined anticipated adverse events
- Device Malfunctions: Frequency and incidence of device malfunctions
- Reoperations: Frequency and incidence of all reoperations
- Rehospitalizations: Frequency and incidence of all rehospitalizations

10.3 Powered Secondary Endpoint

- Incidence of pump replacements at 24 months

11 INCLUSION CRITERIA

1) Subject or legal representative has signed Informed Consent Form (ICF)
2) Age ≥ 18 years
3) BSA ≥ 1.2 m^2
4) NYHA Class III with dyspnea upon mild physical activity or NYHA Class IV
5) LVEF ≤ 25%
6) a) Inotrope dependent

   OR

   b) CI < 2.2 L/min/m^2, while not on inotropes and subjects must also meet one of the following:

   - On optimal medical management (OMM), based on current heart failure practice guidelines for at least 45 out of the last 60 days and are failing to respond
   - Advanced heart failure for at least 14 days AND dependent on intra-aortic balloon pump (IABP) for at least 7 days,

7) Females of child bearing age must agree to use adequate contraception

12 EXCLUSION CRITERIA

1) Etiology of HF due to or associated with uncorrected thyroid disease, obstructive cardiomyopathy, pericardial disease, amyloidosis, or restrictive cardiomyopathy
2) Technical obstacles which pose an inordinately high surgical risk, in the judgment of the investigator
3) Existence of ongoing mechanical circulatory support (MCS) other than IABP
4) Positive pregnancy test if of childbearing potential
5) Presence of mechanical aortic cardiac valve that will not be either converted to a bioprosthesis or oversewn at the time of LVAD implant
6) History of any organ transplant
7) Platelet count < 100,000 x 10^3/L (< 100,000/ml)
8) Psychiatric disease/disorder, irreversible cognitive dysfunction or psychosocial issues that are likely to impair compliance with the study protocol and LVAS management
9) History of confirmed, untreated Abdominal Aortic Aneurysm (AAA) > 5 cm in diameter within 6 months of enrollment
10) Presence of an active, uncontrolled infection
11) Intolerance to anticoagulant or antiplatelet therapies or any other peri/post-operative therapy that the investigator will require based upon the patients' health status
12) Presence of any one of the following risk factors for indications of severe end organ dysfunction or failure:
    a) An INR ≥ 2.0 not due to anticoagulation therapy
    b) Total bilirubin > 43 umol/L (2.5 mg/dl), shock liver, or biopsy proven liver cirrhosis
    c) History of severe chronic obstructive pulmonary disease (COPD) defined by FEV_1/FVC < 0.7, and FEV_1 <50% predicted
    d) Fixed pulmonary hypertension with a most recent PVR ≥ 8 Wood units that is unresponsive to pharmacologic intervention
    e) History of stroke within 90 days prior to enrollment, or a history of cerebrovascular disease with significant (> 80%) uncorrected carotid artery stenosis
    f) Serum Creatinine ≥ 221umol/L (2.5 mg/dl) or the need for chronic renal replacement therapy
    g) Significant peripheral vascular disease (PVD) accompanied by rest pain or extremity ulceration
13) Patient has moderate to severe aortic insufficiency without plans for correction during pump implant
14) Pre albumin < 150 mg/L (15mg/dL) or Albumin < 30g/L (3 g/dL) (if only one available); pre albumin < 150 mg/L (15mg/dL) and Albumin < 30g/L (3 g/dL) (if both available)
15) Planned Bi-VAD support prior to enrollment
16) Patient has known hypo or hyper coagulable states such as disseminated intravascular coagulation and heparin induced thrombocytopenia

17) Participation in any other clinical investigation that is likely to confound study results or affect the study
18) Any condition other than HF that could limit survival to less than 24 months

13 DATA ANALYSIS AND STATISTICAL ISSUES/JUSTIFICATION FOR STUDY DESIGN

13.1 General Statistical Analysis Plan:

The HM3 IDE study will investigate the safety and effectiveness of the HM3 LVAS for short term hemodynamic support, such as a bridge to cardiac transplantation (BTT) or myocardial recovery, or as long term support, such as destination therapy (DT). The HM3 IDE study is a prospective, multicenter, unblinded, randomized, controlled, non-inferiority study comparing the HM3 LVAS to the HM II LVAS.

In general, continuous data will be presented as the number of Subjects, mean with standard deviation, median, and minimum and maximum values. Categorical data will be reported as frequencies and percentages. Adverse events will also be reported as rates per patient year. Only adverse events that occur after the start of the implant procedure will be analyzed. Survival data will be presented using the Kaplan-Meier product limit method.

Data will be analyzed using the intent-to-treat method (ITT) defined as all randomized Subjects. Every effort will be made to avoid cross-over but in the event they occur, data will also be analyzed "as randomized" for efficacy analysis and "as treated" for safety analysis and all other secondary endpoints.

Every effort will be made to collect all required data. Missing primary endpoints will be imputed using multiple imputation techniques. Missing secondary endpoints will not be imputed, except as described below. 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.

Statistical analysis will be performed using SAS version 9.1 or higher.

13.2 Analysis Populations

13.2.1 Intent-to-treat: All Randomized Subjects

This is the primary analysis population for the primary endpoint. Subjects are analyzed under the treatment to which they were randomized.

13.2.2 As Treated: All Treated Subjects

This is the primary analysis population for the secondary endpoints. Subjects are analyzed under the treatment they received.

13.3 Study Hypothesis

13.3.1 Short Term Support:

The short term study endpoint is a composite of survival to transplant, myocardial recovery or 6 months of support (whichever occurs first) free of a debilitating stroke (modified Rankin Score > 3) or reoperation to replace the original pump. A Subject will be considered a success if they are:

- Electively transplanted or explanted for myocardial recovery prior to 6 months or
- Alive at 6 months, and
  - Have not experienced a stroke with a modified Rankin Score > 3, and
  - Have not received a device replacement or exchange, and
  - Have not received an urgent transplant due to a LVAS malfunction.

A Subject will be considered a failure if they:

- Expire prior to 6 months, or
- Experience a stroke with a modified Rankin Score > 3 prior to 6 months, or
- Have a device replaced or exchanged or deactivated for reasons other than myocardial recovery prior to 6 months, or
- Have received an urgent transplant due to a LVAS malfunction prior to 6 months, or
- Have withdrawn from the study for any reason prior to 6 months

HM3 short term success rate will be compared to that of the HM II control in a non-inferiority manner. The null and alternative hypotheses are:

H_o: $\pi_{HM3} \leq \pi_{HM\ II} - \Delta$
H_A: $\pi_{HM3} > \pi_{HM\ II} - \Delta$

where π_{HM3} and $\pi_{HM\ II}$ are the short term success rates of HM3 and HM II, respectively, and where Δ is the non-inferiority margin.

13.3.2 Long Term Support:

The long term study endpoint is a composite of survival to transplant, myocardial recovery or 24 months of support (whichever occurs first) free of a debilitating stroke (modified Rankin Score > 3) or reoperation to replace the original pump. A Subject will be considered a success if they are:

- Electively transplanted or explanted for myocardial recovery prior to 24 months or
- Alive at 24 months, and
  - Have not experienced a stroke with a modified Rankin Score > 3, and
  - Have not received a device replacement or exchange, and
  - Have not received an urgent transplant due to a device malfunction.

A Subject will be considered a failure if they:

- Expire prior to 24 months, or
- Experience a stroke with a modified Rankin Score > 3 prior to 24 months, or
- Have a device replaced or exchanged or deactivated for any reason other than myocardial recovery prior to 24 months, or
- Have received an urgent transplant due to a LVAS malfunction prior to 24 months, or
- Have withdrawn from the study for any reason prior to 24 months

The 24 month success rate of the HM3 Subjects will be compared to the HM II control. The null and alternative hypotheses are:

H_o: $\pi_{HM3} \leq \pi_{HM\ II} - \Delta$
H_A: $\pi_{HM3} > \pi_{HM\ II} - \Delta$

where π_{HM3} and $\pi_{HM\ II}$ are the long term success rates of HM3 and HM II, respectively, and where Δ is the non-inferiority margin.

13.4 Randomization

Subjects will be randomized in a 1:1 fashion (1 HM3: 1 HM II). The randomization will be stratified by study center and blocked to maintain the 1:1 ratio over time. Randomization will be implemented through the Electronic Data Capture (EDC) system. Study centers will be allowed a maximum of 50 randomized Subjects. Centers may have their maximum enrollment number increased with prior Sponsor approval. An analysis will be conducted to determine if there is site bias. Subjects will be considered enrolled in the study upon signing informed consent; all subjects will be randomized and will be included in the intent-to-treat analysis.

13.5 Sample Size

13.5.1 Assumptions

- Larger gap between the rotor and pump housing in the HM3 may result in less thrombus than HM II
- Larger gap between the rotor and pump housing in the HM3 may result in less pump replacement due to ingested thrombus than HM II
- HM3 modular driveline may reduce pump replacements due to driveline damage or fatigue.

13.5.2 Short Term Indication

Based on a review of recent INTERMACS and Thoratec data, it is assumed that the HM II will achieve a composite success rate of 85% at 6 months. It is also assumed that the HM3 will have a composite success rate of 87% due to less pump replacements at 6 months caused by thrombus or driveline issues. It will take 276 total Subjects to achieve 80% power to prove the HM3 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.

INTERMACS HM II data from 26 sites likely to participate in the HM3 IDE study was reviewed. Eight hundred and twenty (820) patients were implanted with the HM II in 2012 at these sites and 52 (6%) received a transplant or explant due to myocardial recovery prior to 6 months. In order to have sufficient data to evaluate the 6 month success rate, an additional 9 Subjects will be randomized per arm (6% of 138) to account for these early outcomes. This results in 294 total Subjects.

13.5.3 Long Term Indication

Based on the results from the HM II Destination Therapy IDE study, it is assumed that 50% of the HM II Subjects will successfully achieve the composite primary endpoint. It is also assumed that the HM3 will have a composite success rate of 55% due to less pump replacements at 24 months caused by thrombus or driveline issues. It will take HM3348 total Subjects to achieve 80% power to prove the HM3 is non-inferior to HM II when the margin of non-inferiority (=Δ in the above null and alternative hypotheses) is -10% using the Farrington-Manning risk difference approach to non-inferiority at a one-sided alpha = 0.025.

INTERMACS HM II data from 26 sites likely to participate in the HM3 IDE study was reviewed. Eight hundred and twenty (820) patients were implanted with the HM II in 2012 at these sites and 52 (6%) received a transplant or explant due to myocardial recovery prior to 6 months. In order to have sufficient data to evaluate the 24 month success rate, an additional 9 Subjects will be randomized per arm (6% of 138) to account for these early outcomes. This results in 366 total Subjects.

13.6 Early Safety Assessment

The HM3 IDE study will include an early safety assessment in lieu of a feasibility study. The first 10 HM3 Subjects enrolled in the study will be included and their data analyzed when they have achieved 30 days of support. A table describing the 30 days status of the Subjects will be prepared. Adverse events will be presented as the percentage of Subjects who experience the event, the number of events and the event rate per 30 days. The data will be presented to the DSMB and FDA for a recommendation to continue the study and to expand to remaining study centers. All Subjects included in the early safety assessment will continue to be followed per protocol and will be included in the final Short Term and Long Term analysis.

13.7 Analysis of Primary Endpoint

The HM3 will be considered non-inferior to the HM II for both short and long term indications if the lower two-sided 95% confidence limit of the risk difference in the composite success between treatment arms (HM3 minus HM II) is greater than -10% (“negative 10%”, where 10% is the non-inferiority Δ in the above null and alternative hypotheses). Once non-inferiority is inferred, the data will be analyzed for superiority at a one-sided 0.025 level of significance using closed testing methods via the z-test of proportions using the normal approximation to the binomial distribution. Since the short term and long term evaluations are two distinct endpoints, no adjustment for multiple comparisons is required.

13.7.1 Primary Endpoint Stratified by Components of the Composite Endpoint

Differences in success rates between HM3 and HM II will be performed for each component of the composite endpoint to evaluate if a single component is influencing the outcome. Specifically, for each component, two-sided 95% confidence intervals of the differences and a z-test of proportions will be generated using the normal approximation to the binomial distribution.

13.7.2 Effect of Site Bias on the Primary Endpoint

In order to determine if a few superior investigational sites are influencing the primary endpoint results, a comparison of results across sites will be performed. Specifically, for each of the short term and long term outcomes, the significance of the treatment-by-site interaction effect will be assessed using logistic regression with the main effects for treatment and site, and with a treatment-by-site interaction effect. The treatment-by-site interaction effect will be tested at the 0.15 level of significance. A non-significant interaction or an interaction that is significant but only quantitative and not qualitative in nature will support the pooling of Subjects across sites for the primary analyses. Given that a number of sites will contribute only small numbers of Subjects, we will pool sites with less than 5 Subjects for the analysis.

13.7.3 Unblinded Interim Efficacy Analysis (Adaptive Design)

After 50% of Subjects are treated and followed for 6 months, an interim unblinded analysis comparing treatments on the 6-month short term outcome will be carried out. There will be no provision to stop the study at interim stage for overwhelming effectiveness and hence no adjustment of the significance level for the final analysis. The first purpose of the interim analysis is to calculate the power for non-inferiority, conditioned on the interim short term outcome rates in each treatment and on the non-inferiority margin of 10%. If conditional power is <50% or >80%, the study will continue as is; if conditional power is between 50-80%, the sample size will be re-estimated to maintain conditional power of 80% for the 6-month short term endpoint, controlling Type I error following the method in Wang et al[10]. Any sample size increase will then be applied to the long term endpoint.

13.8 Subgroup Analysis

Once the analyses comparing the treatment arms are complete, a series of subgroup analyses will be performed, assessing treatment difference within each subgroup. Each subgroup will be evaluated for the primary composite endpoint, survival, adverse events, device malfunction, quality of life and functional status, as described above. Subgroups will include but may not be limited to:

- Gender: Males vs Females
- Race: Caucasian/White vs African-American/ Black vs Other
- Age: 18 – 59 vs 60 – 75 vs > 75 years
- Intended Use at implant as defined by Appendix 6
- VO2 max
- INTERMACS Profile

The purpose of the subgroup analyses is not to reach a statistically significant result within each subgroup, but rather to assess consistency of treatment difference across subgroups.

13.9 Analysis of Survival and Subject Outcome

Overall survival will be assessed for each of the two treatments using the Kaplan-Meier product-limit method. Differences between treatments in survival distributions will be analyzed using a logrank test. Subjects surviving will be censored at last known follow-up time point.

A competing outcome graph will be prepared at 6 months for short term results and 24 months for long term results.

13.10 Analysis of Adverse Events

All pre-defined adverse events will be captured. Tables will be created for HM3 and HM II AEs that show the by-treatment incidences of all adverse events and the by-treatment event rate per patient year of support. Serious adverse events (SAEs) will be analyzed in a similar manner as AEs. Differences in event rates between the treatment arms will be analyzed using Fisher's Exact test or Poisson regression, as appropriate.

13.11 Analysis of Device Malfunctions

All suspected HM3 device malfunctions will be reported. Thoratec will ask that all explanted devices be returned for analysis. Data on device malfunctions will be analyzed and tables will be created that report the following:

- Events that are confirmed by analysis of the device by Thoratec engineers
- The component of the device involved
- Days to the malfunction
- Action taken in response to the malfunction
- Reoperations due to malfunction
- Death due to malfunction

13.12 Analysis of Pre-Implant Data

Tables will be created to define the study population at baseline. Tables will include demographics, all laboratory assessments, all hemodynamic assessment, cardiac history, INTERMACS profile, and concurrent interventions (Cardiac Resynchronization Therapy (CRT), Automatic Internal Cardiac Defibrillator (AICD), IABP, Inotropes, etc). The intended use of the device at implant will also be collected, as defined by INTERMACS (Appendix 6). Baseline data will be compared between treatment groups using unpaired t-tests or Fisher's exact test as appropriate.

13.13 Analysis of Implant and Discharge Data

Time on cardiopulmonary bypass during implant surgery will be collected and reported as a median, quartiles and range. All concurrent procedures carried out during implant surgery will be reported. Length of Stay (LOS) will be defined as the time from implant to discharge. LOS will be reported as a mean with standard deviation, median, quartiles and range. The time on cardiopulmonary bypass and LOS will be compared between treatment groups using the Wilcoxon Rank Sum test.

13.14 Analysis of Secondary Endpoints

Secondary endpoints will each be tested at the two-sided 0.05 level of significance. There will be no adjustment for multiple comparisons across the secondary endpoints. There will be no imputation of missing data for the secondary endpoints.

13.14.1 Pump Hemodynamics

The mean flow and pump index (flow/BSA) with standard deviation for the HM3 and HM II Subjects will be plotted over time. At each time point, treatments will be compared using the unpaired t-test.

13.14.2 Laboratory values

Mean laboratory values with standard deviations for HM3 and HM II Subjects will be plotted over time. At each time point, treatments will be compared using the unpaired t-test.

13.14.3 Rehospitalization

Time to rehospitalization and the reason for rehospitalization will be reported. Time in and out of the hospital will be reported for the HM3 and HM II Subjects. Treatments will be compared on time to re-hospitalization using the log-rank test. Subjects not re-hospitalized will be censored at last known follow-up.

13.14.4 Reoperations

Time to reoperation, frequency of reoperation, and the reason for the surgery will be reported for HM3 and HM II Subjects. Treatments will be compared on time to re-operation using the log-rank test. Subjects not re-operated will be censored at last known follow-up.

13.15 Analysis of Functional Status

13.15.1 NYHA

The Subjects NYHA Functional Status will be assessed by an independent assessor at baseline and then at 1, 3, 6, 12, 18, and 24 months. At each visit, treatments will be compared on NYHA functional status and on the change from baseline functional status using the Wilcoxon Rank Sum test. The Short Term indication will be limited to the 1, 3, and 6 month assessments. The Long Term indication will include all assessments until 24 months or outcome, whichever occurs first.

13.15.2 Six Minute Walk Test

Subjects may not be able to walk due to heart failure, especially at baseline. Subjects unable to walk due to heart failure will receive a score of 0 meters. For all other reasons for missing data the score will remain missing and not be included in the analysis. The Six Minute Walk test will be conducted at baseline and then at months 1, 3, 6, 12, 18 and 24 post implant. Data will be analyzed using mixed modeling by comparing the distances walked over time to the baseline distance. The Short Term indication will be limited to the 1, 3, and 6 month assessments. The long term indication will include all assessments until 24 months or outcome, whichever occurs first.

13.16 Analysis of Quality of Life

Quality of Life will be measured using the EuroQol (EQ-5D-5L) and the Kansas City Cardiomyopathy Questionnaire (KCCQ).

13.16.1 EQ-5D-5L

The EQ-5D-5L VAS and total score will be assessed at baseline and then at 1, 3, 6, 12, 18, and 24 months. Data will be analyzed using mixed modeling by comparing the EQ-5D-5L score at each assessment interval to the baseline score. The Short Term indication will be limited to the 1, 3, and 6 month assessments. The Long Term indication will include all assessments until 24 months or outcome, whichever occurs first. In addition, the percentage of each component of the EQ-5D-5L will be graphically presented over time.

13.16.2 KCCQ

The KCCQ score will be assessed at baseline and then at 3, 6, 12, 18, and 24 months. Data will be analyzed using mixed modeling by comparing the KCCQ score at each assessment interval to the baseline score. The Short Term indication will be limited to the 3 and 6 month assessments. The Long Term indication will include all assessments until 24 months or outcome, whichever occurs first.

13.17 Powered secondary analysis:

In addition to the primary outcome, the study will be powered to test if HM3 pump reliability is superior to HM II by analyzing the incidence of pump replacements. Randomization described in Section 13.4 will continue beyond the Subjects needed to power the primary endpoint until a sufficient sample size has been enrolled to test the secondary endpoint. The null and alternative hypotheses are:

H_o: $\pi_{HM3} \geq \pi_{HM\ II}$
H_A: $\pi_{HM3} < \pi_{HM\ II}$

where π_{HM3} is the HM3 pump replacement rate and $\pi_{HM\ II}$ is the HM II pump replacement rate.

Based on data contained in Thoratec's device tracking database, 7% of the HM II Subjects receive a pump replacement by 24 months. If we assume that HM3 pump replacements will be reduced to 3% at 24 months, then 1028 Subjects will be needed to prove superiority with a power of 80% and alpha = 0.05 (2-sided).

Once the 366 Subjects needed for the long term indication are enrolled, Thoratec will continue to randomize 662 more Subjects for this secondary analysis. Data for this secondary analysis is not needed for the short or long term indications, but rather will be used to provide additional labeling information.

The Subjects will be followed for 24 months or to outcome, whichever occurs first, and analyzed using the Fisher's exact test. Treatments will also be compared on time-to-pump replacement using the log-rank test where Subjects without a replacement are censored at last known follow-up. Otherwise, there will be no imputation of missing data for this analysis.

14 ADVERSE EVENTS (AE)

14.1 Adverse Events

Adverse Events are any unfavorable and unintended sign (including abnormal labs), or symptom or disease temporally associated with the investigational product and whether or not related to the use of the investigational product. Investigators are responsible for reporting required pre-defined AEs to the Study Sponsor in a timely manner by submitting AEs through the EDC, and for reporting AEs to their Institutional Review Board (IRB) as required.

All pre-defined, anticipated AEs, including those occurring after discharge, will be reported and will be categorized as related to the device or not.

All anticipated AE definitions can be found in Appendix 1.

14.2 Serious Adverse Event (SAE)

Serious adverse events are defined as those adverse events causing death, or congenital abnormality or birth defect, or a life-threatening illness or injury that results in permanent disability, requires hospitalization, or prolongs a hospitalization, and/or requires intervention to prevent permanent injury or damage.

SAEs must be reported to the Sponsor by submitting through the EDC as soon as possible but no later than three (3) calendar days from the day the study personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent. The date the site staff became aware that the event met the criteria of a serious adverse event must be recorded in the source document. The Investigator will further report the SAE to the local IRB according to the institution's IRB reporting requirements.

All SAEs will be reported and will be categorized as related to the device or not.

15 UNANTICIPATED ADVERSE DEVICE EFFECTS (UADE)

An unanticipated adverse device effect includes any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence. A UADE may also include any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of Subjects. Investigators are responsible for reporting any UADEs to Thoratec by telephone, email, or fax, and through the EDC as soon as the study site personnel are made aware of an event, but no later than three (3) calendar days of becoming aware that the event met the criteria for a UADE. Thoratec will review all malfunctions and determine if they are UADEs. Thoratec will report all such effects to the FDA, in accordance with regulatory requirements.

In addition to reporting UADEs to the Study Sponsor, Investigators must report UADEs to their IRB as required.

16 STUDY PROCEDURES AND ASSESSMENTS

Participating centers will utilize their own local laboratories for protocol required laboratory assessments, and will be instructed to follow their institution's requirements for maintenance and/or calibration of laboratory equipment.

16.1 Screening and Enrollment

1. Determine if the Subject is eligible: meets all inclusion and no exclusion criteria. Eligibility criteria can be assessed using data obtained within 90 days of screening, provided the data is representative of the patient's current clinical status.
2. Sign written informed consent. Subjects will be considered enrolled on the day they sign informed consent
3. Only Subjects who have met the eligibility criteria and signed informed consent and who have a scheduled implant date will be randomized through the EDC system. Consent and randomization should occur as close as possible to the implant date; if possible, within 72 hours.
4. Demographics: age, gender, ethnicity, race
5. Intended Use as defined by INTERMACS (Appendix 6)

16.2 Baseline Assessments

The following baseline assessments will be performed within 30 days prior to implant (refer to Section 34, Table 2 for the Study Visit Schedule):

1. Medical History, including cardiovascular history with etiology of HF and duration of HF
2. Physical Exam, including height, weight and vital signs
3. Current Medications (total daily dose): anticoagulation/anti platelet, antibiotics, and cardiovascular medications including ACE inhibitors, ARBs, beta blockers, statins, nitrates, allopurinol, aldosterone blockers, and diuretics including metolazone, hydrochlorothiazide and furosemide
4. Laboratory Assessments:
   a. Hematology: hemoglobin, hematocrit, percent lymphocytes, platelet count, WBC, PHgb, Bleeding/Coagulation: INR, aPTT/PTT, PT
   b. Chemistry: Potassium, Blood Urea Nitrogen (BUN), creatinine, uric acid, sodium, eGFR (calculated), serum BNP or NT-proBNP, total protein, albumin or pre-albumin, CRP or hs-CRP
   c. Lipids: cholesterol
   d. Liver Enzymes: LDH, AST, ALT, total bilirubin
5. Hemodynamic Measurements
6. Echocardiogram: LVEF, LVEDD, LVESD, AV opening, AI, MR, TR including severity and/or grade.
7. Electrocardiogram (ECG): Heart Rate, QRS duration, Arrhythmias
8. 6 Minute Walk Test (6MWT) (if Subject is able; reason must be provided if not performed)
9. EQ-5D-5L
10. Kansas City Cardiomyopathy Questionnaire (KCCQ)
11. VO2 Max (if Subject is able; reason must be provided if not performed)

12. Functional/clinical status using the following:
    a. Modified Rankin Score (as determined by an independent assessor; defined as an independent, trained, and certified clinician)
    b. NYHA Classification (as determined by an independent assessor; defined as an advanced practice practitioner other than the treating investigator)
    c. INTERMACS Patient Profile (to be assessed immediately prior to implantation; refer to Appendix 2 for definitions)

16.3 Implant

1. Current Medications (total daily dose): anticoagulation/anti platelet, antibiotics, and cardiovascular medications including ACE inhibitors, ARBs, beta blockers, statins, nitrates, allopurinol, aldosterone blockers, and diuretics including metolazone, hydrochlorothiazide and furosemide
2. Implant data/Total CPB time/Blood Product use
3. Pump Parameters (HM II and HM3)
4. HM3 Pump Log files (pump period log, pump event log, controller period log, and controller event log) will be submitted to Thoratec
5. Concurrent Procedures
6. Occurrence of AEs (date of adverse event, determination of seriousness and/or relation to the device, resolution of the adverse event)
7. Device Malfunctions
8. Modified Rankin Score (as determined by an independent assessor; defined as an independent, trained, and certified clinician, and only if a stroke has occurred and 60 days post-stroke)
9. HM II Pump Log files will be submitted to Thoratec (only if a pump-related or possibly related AE or malfunction has occurred)

16.4 Post Op Day 1 (+/- 1 Day)

1. HM3 Pump Log files (pump period log, pump event log, controller period log, and controller event log) will be submitted to Thoratec
2. HM II Pump Log files will be submitted to Thoratec (only if a pump-related or possibly related AE or malfunction has occurred)
3. AP chest x-ray for HM3 subjects; AP feeding tube view x-ray for HM II subjects
4. Echocardiogram or transesophageal echocardiogram (TEE): LVEF, LVEDD, LVESD, AV opening, AI, MR, TR including severity and/or grade (can be perfomed on post-operative day 0 (post-implant) +2 days)

16.5 1 Week Post-implant (+/- 1 Day)

1. Current Subject Status: whether or not the Subject is ongoing on VAD support
2. Subject Outcome: whether or not the Subject has been transplanted or explanted
3. Current Medications (total daily dose): anticoagulation/anti platelet, antibiotics, and cardiovascular medications including ACE inhibitors, ARBs, beta blockers, statins, nitrates, allopurinol, aldosterone blockers, and diuretics including metolazone hydrochlorothiazide and furosemide
4. Vital Signs
5. Laboratory Assessments:
    a. Hematology: hemoglobin, hematocrit, percent lymphocytes, platelet count, WBC, PHgb, Bleeding/Coagulation: INR, aPTT/PTT, PT

   b. Chemistry: Potassium, BUN, creatinine, uric acid, sodium, eGFR (calculated), serum BNP or NT-proBNP, total protein, albumin or pre-albumin, CRP or hs-CRP
   c. Lipids: cholesterol
   d. Liver Enzymes: LDH, AST, ALT, total bilirubin
6. Echocardiogram: LVEF, LVEDD, LVESD, AV opening, AI, MR, TR including severity and/or grade.
7. Pump Parameters (HM II and HM3)
8. HM3 Pump Log files (pump period log, pump event log, controller period log, and controller event log) will be submitted to Thoratec.
9. HM II Pump Log files will be submitted to Thoratec (only if a pump-related or possibly related AE or malfunction has occurred)
10. Occurrence of AEs (date of adverse event, determination of seriousness and/or relation to the device, resolution of the event)
11. Device Malfunctions
12. Reoperations/Operative procedures
13. Pump Replacements/Explants/Device Exchanges
14. Driveline Management Assessment
15. Modified Rankin Score (as determined by an independent assessor; defined as an independent, trained, and certified clinician, and only if a stroke has occurred and 60 days post-stroke)

16.6 Discharge (-1 day)

Subjects and his or her family member or caregiver (as applies) must be trained on the operation and care of their LVAS and its components, prior to discharge. Information related to required Subject and caregiver training can be found in the HM II or HM3 Instructions for Use and Patient Handbook. Training documentation will be required to show compliance to the required training.

1. Current Subject Status: whether or not the Subject is ongoing on VAD support
2. Subject Outcome: whether or not the Subject has been transplanted, or explanted
3. Current medications (total daily dose): anticoagulation/anti platelet, antibiotics, and cardiovascular medications including ACE inhibitors, ARBs, beta blockers, statins, nitrates, allopurinol, aldosterone blockers, and diuretics including metolazone, hydrochlorothiazide and furosemide
4. Number of days in ICU
5. Vital Signs
6. Laboratory Assessments:
   a. Hematology: hemoglobin, hematocrit, percent lymphocytes, platelet count, WBC, PHgb, Bleeding/Coagulation: INR, aPTT/PTT, PT
   b. Chemistry: Potassium, BUN, creatinine, uric acid, sodium, eGFR (calculated), serum BNP or NT-proBNP, total protein, albumin or pre-albumin, CRP or hs-CRP
   c. Lipids: cholesterol
   d. Liver Enzymes: LDH, AST, ALT, total bilirubin
7. Echocardiogram: LVEF, LVEDD, LVESD, AV opening, AI, MR, TR including severity and/or grade.
8. NYHA Classification (determined by an independent assessor defined as an advanced practice practitioner other than the treating investigator)
9. Pump Parameters (HM II and HM3)

10. HM3 Pump Log files (pump period log, pump event log, controller period log, and controller event log) will be submitted to Thoratec
11. HM II Pump Log files will be submitted to Thoratec (only if a pump-related or possibly related AE or malfunction has occurred)
12. Occurrence of AEs (date of adverse event, determination of seriousness and/or relation to the device, resolution of the adverse event)
13. Device Malfunctions
14. Reoperations/Operative procedures
15. Pump Replacements/Explants/Device Exchanges
16. Driveline Management Assessment
17. Collect UB-04 Form
18. Modified Rankin Score (as determined by an independent assessor; defined as an independent, trained, and certified clinician, and only if a stroke has occurred and 60 days post-stroke)

16.7 Subject Follow-up Assessments

16.7.1 Clinic Follow-up Post-implant: 30 Days (+/- 7 days) for 1 month assessment, 90 Days (+/- 30 days) for 3 month assessment, and 180 days (+/- 30 days) for 6 month assessment

The Subject must be seen for a clinic visit to assess the following:

1. Current Subject Status: whether or not the Subject is ongoing on VAD support
2. Subject Outcome: whether or not the Subject has been transplanted, or explanted
3. Current medications (total daily dose): anticoagulation/anti platelet, antibiotics, and cardiovascular medications including ACE inhibitors, ARBs, beta blockers, statins, nitrates, allopurinol, aldosterone blockers, and diuretics including metolazone, hydrochlorothiazide and furosemide
4. Vital Signs
5. Laboratory Assessments:
   a. Hematology: hemoglobin, hematocrit, percent lymphocytes, platelet count, WBC, PHgb, Bleeding/Coagulation: INR, aPTT/PTT, PT
   b. Chemistry: Potassium, BUN, creatinine, uric acid, sodium, eGFR (calculated), serum BNP or NT-proBNP, total protein, albumin or pre-albumin, CRP or hs-CRP
   c. Lipids: cholesterol
   d. Liver Enzymes: LDH, AST, ALT, total bilirubin
6. Echocardiogram : LVEF, LVEDD, LVESD, AV opening, AI, MR, TR including severity and/or grade.
7. Chest x-ray: PA and Lateral (30 Days and 180 Days only)
8. NYHA Classification (determined by an independent assessor defined as an advanced practice practitioner other than the treating investigator)
9. 6 Minute Walk Test (6MWT) (if Subject is able; reason must be provided if not performed)
10. EQ-5D-5L
11. Kansas City Cardiomyopathy Questionnaire (KCCQ) (90 Days and 180 Days only)
12. Pump Parameters (HM II and HM3)

13. Rehospitalizations
    a. If rehospitalized, collect UB-04 form
14. HM3 Pump Log files (pump period log, pump event log, controller period log, and controller event log) will be submitted to Thoratec.
15. HM II Pump Log files will be submitted to Thoratec (only if a pump-related or possibly related AE or malfunction has occurred)
16. Occurrence of AEs (date of adverse event, determination of the seriousness and/or relation to the device, resolution of the adverse event)
17. Device Malfunctions
18. Reoperations/Operative procedures
19. Pump Replacements/Explants/Device Exchanges
20. Driveline Management Assessment
21. Modified Rankin Score (as determined by an independent assessor; defined as an independent, trained, and certified clinician, and only if a stroke has occurred and 60 days post-stroke)

16.7.2 Clinic Follow-up Post-implant: 360 Days (+/- 30 days) for 12 month assessment, 540 Days (+/- 30 days) for 18 month assessment, and 720 Days (+/- 30 days) for 24 month assessment

The Subject must be seen for a clinic visit to assess the following:

1. Current Subject Status: whether the Subject is ongoing on VAD support
2. Subject Outcome: whether or not the Subject has been transplanted, or explanted
3. Current medications (total daily dose): anticoagulation/anti platelet, antibiotics, and cardiovascular medications including ACE inhibitors, ARBs, beta blockers, statins, nitrates, allopurinol, aldosterone blockers, and diuretics including metolazone, hydrochlorothiazide and furosemide
4. Vital Signs
5. Laboratory Assessments:
    a. Hematology: hemoglobin, hematocrit, percent lymphocytes, platelet count, WBC, PHgb, Bleeding/Coagulation: INR, aPTT/PTT, PT
    b. Chemistry: Potassium, BUN, creatinine, uric acid, sodium, eGFR (calculated), serum BNP or NT-proBNP, total protein, albumin or pre-albumin, CRP or hs-CRP
    c. Lipids: cholesterol
    d. Liver Enzymes: LDH, AST, ALT, total bilirubin
6. Echocardiogram: LVEF, LVEDD, LVESD, AV opening, AI, MR, TR including severity and/or grade.
7. Chest x-ray: PA and Lateral (360 Days and 720 Days only)
8. NYHA Classification (determined by an independent assessor defined as an advanced practice practitioner other than the treating investigator)
9. 6 Minute Walk Test (6MWT) (if Subject is able; reason must be provided if not performed)
10. EQ-5D-5L
11. Kansas City Cardiomypathy Questionnaire (KCCQ)
12. Pump Parameters (HM II and HM3)
13. Rehospitalizations

a. If rehospitalized, collect UB-04 form

14. HM3 Pump Log files (pump period log, pump event log, controller period log, and controller event log) will be submitted to Thoratec.
15. HM II Pump Log files will be submitted to Thoratec (only if a pump-related or possibly related AE or malfunction has occurred)
16. Occurrence of AEs (date of the adverse event, determination of seriousness and/or relation to device, resolution of the adverse event)
17. Device Malfunctions
18. Reoperations/Operative procedures
19. Pump Replacements/Explants/Device Exchanges
20. Driveline Management Assessment
21. Modified Rankin Score (as determined by an independent assessor; defined as an independent, trained, and certified clinician, and only if a stroke has occurred and 60 days post-stroke)

For a detailed list of assessments and timelines, refer to the Study Visit Schedule in Section 34, Table 2.

16.8 Additional Data Collection:

16.8.1 Pump Log Files

Pump log files will be submitted to Thoratec at defined time points. Pump parameters and pump logs must also be submitted when any pump-related or possibly related AE or malfunction occurs. In addition, Thoratec may periodically collect pump log files, outside of the pre-specified time points and/or may request additional supportive hemodynamic data, if performed as part of the standard of care, for characterization of pump operation and system diagnostic purposes. No specific pre-defined analysis will be performed on this data.

16.8.2 Chest X-Rays

Chest x-rays will be submitted to Thoratec at defined time points. No specific pre-defined analysis will be performed on this data.

16.8.3 Health Economics Data

Upon hospital discharge for the initial implant hospitalization and subsequent re-hospitalizations, UB-04 bills, or similar detailed hospital billing data will be sent to Thoratec.

17 ANTICOAGULATION

Subjects implanted with the HM3 and HM II must be properly anticoagulated to decrease the possibility of thromboembolism and/or pump thrombosis. Anticoagulation guidelines are provided in the HM3 and HM II Instructions for Use (IFU).

18 INFECTION CONTROL GUIDELINES

It is recommended that all investigational centers follow the Patient Care and Management Guidelines developed for the HM II and HM3 LVAS. Guidelines for infection control and driveline management are provided in the HM II and HM3 IFU.

19 BLOOD PRESSURE GUIDELINES

Post-Implantation hypertension may be treated at the discretion of the attending physician. Any therapy that consistently maintains mean arterial blood pressure less than 90 mm Hg should be considered adequate.

20 POST-MORTEM EXAMINATION

All attempts to obtain permission for a full body autopsy should be made for all Subjects that expire during the study. Performance of an autopsy is to be noted on the eCRF and a copy of the autopsy report is to be provided to Thoratec. The primary objective of the autopsy is to determine the cause of death, complications, and other relevant findings. In addition, special attention should be directed toward documentation of Subject-prosthesis interaction and any HM II or HM3 LVAD associated complications.

21 DEVICE RETRIEVAL AND ANALYSIS

Upon Subject death, device explantation, or device malfunction all explanted HM II and HM3 pumps must be retrieved and returned to Thoratec for evaluation and analysis within 48 hours of explant. Devices must be returned in accordance with Thoratec instructions.

Any system component other than the pump, (for example: controller, MPU, batteries) associated with any suspected device malfunction must also be returned to Thoratec for analysis.

22 SUBJECT WITHDRAWAL

The Subject retains the right to withdraw from the study at any time. Should the Subject elect to withdraw from the study, the reason for withdrawal must be documented in the CRF.

Reasons for withdrawal include:

- Subject chooses to withdraw
- Investigator decides to withdraw Subject
- Subject has pump exchanged to any device other than HM II or HM3
- Subject is not implanted with device after randomization.
    - Any subject that is not immediately implanted after randomization, due to deterioration or improvement of their health status, will be followed to implant or outcome or until the cohort is fully enrolled at which time they will be withdrawn as follows:
        - For the short term and long term cohorts, any subject not implanted or who has not achieved an outcome 30 days after the 366th subject is enrolled will be withdrawn.
        - For the powered secondary endpoint, any subject not implanted or who has not achieved an outcome 30 days after the 1028th subject is enrolled will be withdrawn.

- Subject is lost to follow-up
    - Subjects who can no longer be tracked for follow-up data collection at a participating MOMENTUM 3 center will be formally withdrawn from the study.

23 RISKS

The HM3 LVAS is an investigational device and has not been approved by the U.S. FDA or any other regulatory authority. Extensive testing has been performed on the device in the laboratory and in animal studies providing assurance to proceed with human use of the HM3 LVAS.

The potential risks including anticipated adverse events and possible interactions with concomitant medical treatments related to use of the HM3 are expected to be similar to those seen with commercially available mechanical circulatory support.

The recent HM II BTT Post-approval study followed 169 patients from 53 sites in the United States for 6 months. The HM II DT Post-approval study followed 247 patients from 61 hospitals in the United States for 24 months. If it is assumed that adverse event rates experienced in the HM3 study will be within the upper 99% confidence interval of that reported in the HM II Post-approval studies, then the expected rates for HM3 adverse events[3] would be as reported in Table 1. In addition, the recent commercial data, as reported by Kirklin et al, shows that freedom from pump exchange or death due to pump thrombosis at 6 months is 94%[11].

Table 1 – Expected Incidence Rate of Adverse Events

Adverse Event	**Incidence Rate at 6 Months[3] Less than or Equal to:**	**Incidence Rate at 24 Months[12] Less than or Equal to:**
Death	11%	47%
Bleeding	56%	62%
Cardiac Arrhythmia	37%	45%
Hemolysis	7%	11%
Hepatic Dysfunction	12%	12%
Driveline Infection	26%	22%
Blood Infection	28%	26%
Other Localized Infection	39%	53%
Stroke	12%	19%
Other Neurological Dysfunction	9%	18%
Pericardial Drainage	17%	13%
Psychiatric Episode	15%	19%
Renal Dysfunction	17%	25%
Respiratory Failure	29%	34%
Right Heart Failure	23%	25%

Adverse Event	Incidence Rate at 6 Months[3] Less than or Equal to:	Incidence Rate at 24 Months[12] Less than or Equal to:
Venous Thromboembolism	12%	9%
Device Thrombosis	3%[13]	7%
All Other Adverse Events	5%	3%

[3]Starling RC, Naka Y, Boyle AJ et al. Results of the Post U.S. Food and Drug Administration-Approval Study with a Continuous Flow Left Ventricular Assist Device as a Bridge to Heart Transplantation, J Am Coll Cardiol 2011; 57:1890-1898
[12] Thoratec Final Post Approval Report to the FDA on the HM II Destination Therapy – INTERMACS Post Approval Study
[13] Thoratec Data : HM II Bridge to transplant – INTERMACS Post Approval Study

Residual risks associated with the HeartMate 3 device are expected to be similar to those seen with market approved VADs. Additional information related to the Risk Management process, including residual risks can be found in the Investigator's Brochure.

A list of potential anticipated adverse events for this study can be found in Appendix 1 of this protocol.

24 MITIGATIONS

Mitigations and treatment for all adverse events should be per the current practice standards/standards of care as determined by the investigator.

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

25 BENEFITS

Commercially available mechanical circulatory support devices have been previously shown to provide safe and effective hemodynamic support in advanced heart failure Subjects with clinical meaningful improvement in survival, quality of life and functional capacity when compared to optimal medical management. It is therefore expected that similar benefits may be observed with the HM3 LVAS, and these benefits will outweigh the risks associated with the device and the required implant surgery[1,2].

Potential benefit of fewer HM3 device replacements will be further evaluated in this study as a powered secondary endpoint. Additional potential benefits of the HM3, such as reduced adverse events, will also be evaluated in a descriptive manner.

26 ETHICAL REQUIREMENTS

26.1 Informed Consent

Informed consent must be obtained in accordance with 21 CFR Part 50. Written informed consent must be obtained by the Principal Investigator or designee, before any study related procedures or tests are performed that would otherwise not be performed according to the standard of care. If the Subject is unable to participate in the informed consent process, consent must be obtained from a legally authorized representative prior to administering any study related test or procedure. The use of a legally authorized representative is only permissible if allowed by the IRB.

If new information becomes available by the Sponsor that may affect a Subject's participation in the study, Investigators will be required to update/revise the informed consent as necessary, and all Subjects will be re-consented by the site.

Revisions to the informed consent will be approved by the Sponsor and the IRB prior to re-consenting Subjects.

Each clinical site is responsible for keeping the original signed informed consent forms, and any updated signed informed consent forms for each Subject on file, and available for inspection by Thoratec.

The process of obtaining Informed consent must be documented in each Subject's medical record.

26.2 IRB Review

Investigators will conduct the study in compliance with the Declaration of Helsinki and local and national regulatory requirements.

Thoratec will comply with all IRB and FDA regulatory requirements.

Before initiation of the study, IRB approval of the protocol and the ICF must be obtained. Modifications made to the ICF must be sent to Thoratec for approval, prior to submitting to the IRB. Copies of the IRB submission and approval, including the approved ICF, must be forwarded to Thoratec prior to the enrollment of Subjects into the study. Sites will submit Study progress reports as required by 21 CFR 812.150(a)(3) in writing to Sponsor and the IRB at least yearly. As required by 21 CFR 812.150(a)(6), sites will submit to Sponsor and the IRB a final report on the Study within 3 months of completion or earlier termination of the study. Copies of all submissions to and correspondence from the IRB (approvals and disapprovals) must be sent to Thoratec and maintained on file at the study site.

26.3 Confidentiality

No individually identifiable/confidential Subject data collected as part of this study will be released beyond Thoratec. Unique Subject study identification codes will be assigned to all Subjects and sites must use these unique identification codes with Subject initials on all study related materials. Personal identifiable information, such as name, social

security number, and medical record number, should be redacted by the site prior to submission to Thoratec.

27 PROTOCOL DEVIATIONS

This study should be conducted as described in this protocol. All deviations from the protocol will be tracked and evaluated through the EDC system.

For sites who demonstrate repeated deviations that may affect the safety of Subjects, and/or the integrity of the data, corrective measures will be instituted such as re-training.

Sites must notify their IRB of protocol deviations in accordance with IRB requirements.

Refer to Section 31.6 for additional information on Sponsor management of Investigator compliance.

28 PROTOCOL AMENDMENTS

Significant changes to the protocol will be handled by a formal protocol amendment. Protocol amendments will be submitted to Investigators with instructions to submit to their IRB for approval. Any study changes requested by the FDA will be provided to all affected IRBs.

29 DATA COLLECTION, CASE REPORT FORMS AND RECORD KEEPING REQUIREMENTS

29.1 Database and Electronic Case Report Forms (eCRFs)

An EDC system that complies with United States regulations on electronic records and signatures[7] (21 CFR Part 11) will be utilized for this study. Users will have unique usernames and passwords, and the user list will be maintained by a Thoratec administrator for all study personnel. The Investigator must ensure that the observations and study findings are recorded correctly and completely in the eCRFs. Each eCRF requiring a signature must be signed and dated by the authorized personnel.

Data being submitted through the course of the clinical study will be reviewed by the Sponsor for accuracy and completion. Database cleaning and the process for issuing and/or resolving queries will be documented in the Sponsors study specific data management plan.

29.2 Device Accountability Records

The Thoratec HeartMate 3 LVAS is an investigational device. All investigational devices must be stored in a location that is accessible only by authorized study personnel. The Sponsor and investigator must maintain accurate Device Accountability records indicating the date of shipment, receipt of product, date of use and assignment to study Subject, and final disposition (return) of the devices.

Traceability of investigational devices will be maintained by the Sponsor through the use of unique serial and/or lot numbers.

All unused investigational components must be returned to the Sponsor, as directed.

NOTE: Investigational devices should only be used on Subjects who are enrolled in the study and randomized to the HM3 arm.

29.3 Source Documentation

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

During monitoring visits, source documents will be reviewed to ensure accuracy and validity of data recorded on the eCRFs. Source document verification will be performed by Thoratec, or its designee, with due regard to Subject confidentiality.

29.4 Maintenance of Study Documentation

The following documents should be maintained by the study site, and copies of site specific documents sent to Thoratec:

- Copy of the Study Protocol
- IRB Approval(s)
- Pertinent IRB Correspondence
- IRB approved Informed Consent Form(s)
- IRB Membership Roster(s) or Federal wide Assurance (FWA) number
- Financial Disclosure(s)
- Investigator's Agreement(s)
- Curriculum Vitae(s)
- Study Staff Signature and Delegation of Responsibilities Log
- Laboratory Certification(s) and Normals
- Source documentation (such as Subject clinic charts, medical records, laboratory records)
- Clinical Study Agreement (CSA)
- Confidentiality Agreement, if separate from CSA
- Thoratec Correspondence
- Annual/Semi- annual Regulatory Reports
- Documentation of Training
- Monitoring Visit Log
- Device Accountability
- Investigator Brochure
- Instructions for Use (IFU)
- Patient Manual

29.5 Regulatory Reporting Requirements

29.5.1 Site Reporting

Sites will submit Study progress reports as required by 21 CFR 812.150(a)(3) in writing to the Sponsor and the IRB at least yearly. As required by 21 CFR 812.150(a)(6), sites will submit to Sponsor and the IRB a final report on the study within 3 months of completion or earlier termination of the study.

29.5.2 Sponsor Reporting

Thoratec Corporation will submit Study progress reports as required by 21 CFR 812.150(b)(5) to all reviewing IRBs at least yearly. Thoratec will submit a final report to FDA and all reviewing IRBs and participating investigators within six months after completion or termination, as required by 21 CFR 812.150(b)(7). Thoratec will comply with all other reporting requirements as outlined in CFR 812.150(b).

29.6 Retention of Records

In accordance with 21 CFR Part 812.40 the site will retain the Study records in accordance with and for the period required by applicable laws, and at least two years after the date of the latter: (1) the date on which the Study is terminated or completed, or (2) the date that the records are no longer required for purposes of supporting a marketing application. This includes a copy of the protocol, the device labeling, case report forms, medical records, original test result reports, all study related correspondence, a record of written informed consent, and any other documents pertaining to the conduct of this study.

In addition, any and all records maintained in electronic form by Site, Investigator, or Subinvestigators shall be maintained at all times in compliance with applicable laws, including 21 CFR Part 11[7].

The investigator must not dispose of any records relevant to this study without either (1) written permission from Thoratec or (2) providing an opportunity for Thoratec to collect such records. The investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by Thoratec and regulatory authorities.

29.7 Laboratory Accreditation and Normal Values

Before initiation of the study, appropriate accreditation for all laboratories to be used in the study will be requested by Thoratec. Throughout the study, the Investigator shall provide Thoratec documentation of all renewals of accreditation. The range of values considered normal for the laboratory tests being performed for the study must be provided to Thoratec in order to allow the data to be pooled.

30 INSURANCE

Thoratec will obtain insurance to cover potential injury to Subjects in accordance with national requirements.

31 QUALITY CONTROL

31.1 Independent Monitoring Boards

31.1.1 Data Safety Monitoring Board (DSMB):

To meet the study's ethical responsibility to its Subjects and to protect the safety of the Subjects, an independent DSMB, comprised of experts in the field, will monitor the study. Pre-specified guidelines related to governance of the DSMB, data review, early stopping rules for key adverse events, and recommendations by the committee to stop the study, or continue the study with or without modification (s), will be outlined in a DSMB charter. After the 10th HM3 subject reaches 30-day follow-up, all safety data will be provided to the DSMB and a report provided to the FDA. A second formal safety report will be provided to the DSMB and FDA after the 10th HM3 subject reaches 6 months.

31.1.2 Clinical Events Committee (CEC):

An independent CEC comprised of experienced experts in the field, will review and adjudicate adverse events to provide consistency in the categorization of adverse events. Event adjudication will be performed in accordance with the study's pre-specified adverse event definitions and in accordance with the CEC charter.

31.2 Investigator Selection

Prior to the initiation of the study, investigators will be selected based on their qualifications and experience (qualified by education and training) to ensure Subject safety and adherence to the protocol.

31.3 Site Selection

Prior to the initiation of the study, study sites will be selected based on experience with the care of LVAD Subjects, on adequate access to the intended population, adequate resources to conduct the study in accordance with the protocol, and adequate facilities/equipment to perform required tests and procedures as described in the protocol.

The Sponsor will maintain an updated list of principal investigators, investigational sites and/or institutions separately from the protocol. The list will be included in clinical investigation reports as required by 21 CFR part 812.150.

31.4 Site Staff Training

Only trained personnel can perform study related procedures. All clinical personnel (principal investigators, co-investigators, study coordinators) must be thoroughly familiar with the function, care and maintenance of the HM3 LVAS. These individuals will undergo training by Thoratec or designee, and documentation of that training will be maintained. The Thoratec HM3 LVAS Instructions for Use will be provided to assist the healthcare team on the proper care and operation of the device.

31.5 Monitoring

Thoratec Corporation is responsible for monitoring the study. Thoratec will monitor in accordance with FDA Guidance document OMB 0910-0733, Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring. After the study has been initiated, Thoratec or its designee will perform periodic monitoring visits to assess study progress, perform device accountability, assess the adequacy of records, and to ensure adherence to the study protocol.

A summary of the monitoring visit, including documentation of completed previous action items and/or new or outstanding action items, and/or significant findings will be provided to the Investigator.

In addition to periodic on-site monitoring visits, Thoratec will perform remote monitoring to ensure data is submitted in a timely manner. Ongoing communication with investigators and study staff will be performed through written correspondence and telephone conversations.

Details related to site monitoring will be documented in the Sponsor's study specific monitoring plan.

31.5.1 Pre-Investigational (Initiation) Visit:

Thoratec or its designee will be responsible for determining and documenting that each investigator clearly understands and accepts the responsibilities and obligations of conducting a clinical study. If the site attends a study-specific investigator meeting, the investigator meeting may take the place of an on-site initiation visit. Prior to enrollment, the Sponsor or its designee will ensure that the investigator:

- Understands the requirements for device accountability
- Understands the nature of the clinical protocol
- Understands reporting obligations
- Understands and accepts the obligations to obtain informed consent
- Understands and accepts the obligation to obtain IRB review and approval of the clinical investigation before it is initiated and to ensure continuing review of the study by the IRB, and to keep the Sponsor informed of all IRB actions concerning the study
- Has adequate facilities and access to an adequate number of suitable Subjects to conduct the investigation

31.5.2 Periodic Monitoring Visits:

Monitoring visits will be conducted in accordance with applicable regulations, the study specific monitoring plan, and Thoratec's procedures. This study will be monitored to ensure the following:

- Facilities continue to be adequate and acceptable
- The protocol is being properly followed
- The IRB has approved or been notified of any protocol changes per IRB requirements

- Accurate, complete and current records are being maintained, and the information recorded and submitted to the Sponsor is representative of the Subject's record and other supporting documentation
- Accurate, complete and timely adverse event reports are being submitted to the Sponsor
- Informed consent has been obtained
- The reason for a Subject's withdrawal from the study has been documented
- Required reports are being submitted to the IRB and Sponsor
- The appropriate staff is carrying out study activities

The Investigator or designee must, upon request, provide to the sponsor the necessary study records for a thorough review of the study's progress. These records include, but are not limited to, access to investigational device storage and accountability records, case report forms and original source documents and records such as hospital and clinic charts, consent forms, and operative reports.

31.5.3 Study Closeout Activities:

The following study closeout activities will be performed prior to completion of the study in accordance with Thoratec's procedures:

- Ensure that all required eCRFs have been completed/submitted
- Ensure final disposition of investigational devices
- Remind the investigator of the obligation to retain the records in accordance with FDA and Sponsor requirements, and prepare a final report for the Sponsor and IRB

31.6 Investigator and/or Study Site Termination/Suspension

A pattern of non-compliance and continued deviations will result in Thoratec instituting a formal written request for corrective action. If there is an inadequate response from the Investigator, Thoratec may cease shipment of the investigational device and notify the IRB of this action.

Thoratec may consider terminating or suspending an investigator and/or study site in the following cases:

- Confirmed serious or repeated deviations and general non-compliance to the protocol
- Unacceptable critical changes in personnel, administrative, or scientific standards
- Unacceptable risk to Subject safety is confirmed

In such cases, Thoratec will notify the appropriate regulatory authority, and/or other participating centers as required by local and national regulations.

31.7 Early Study Termination

Thoratec reserves the right to discontinue the study prior to fulfillment of the intended number of Subjects. Thoratec intends to exercise this right only for valid scientific or administrative reasons. After such a decision, all unused investigational products must be returned to Thoratec and all collected data must be entered into EDC.

The study could be prematurely discontinued in the following cases:

- New findings about the investigational product(s) that changes the risk/benefit ratio where the risk to study Subjects is unacceptable.
- For any other valid scientific or administrative reason(s) as determined by Thoratec.

32 EMERGENCY CONTACTS

Thoratec Clinical Affairs personnel are available 24 hours a day via the protocol pager to provide assistance with all protocol-related questions and/or for safety reporting. The number for the protocol pager is 1-877-479-0299.

The Thoratec HeartLine is available 24 hours a day for all device-related emergencies. The number for the HeartLine is 1-800-456-1477.

33 PUBLICATION POLICY

The first publication or presentation of Clinical Study Results shall be made as a joint, multi-center publication/presentation of the Study results with the investigators and institutions from all appropriate sites contributing data, analyses and comments. All publications will be reviewed by the study investigators and the Sponsor, and in accordance with the site specific Clinical Study Agreement (CSA).

34 MOMENTUM 3 IDE STUDY VISIT SCHEDULE

Table 2 – Schedule of Events for Randomized Subjects

	Screening[1]	Baseline[1]	Implant	Post-Op Day 1 (+/- 1 day)	1 Week Post Implant (+/- 1 day)	Discharge (-1 day)	30 Days Post Implant (+/- 7 days)	90 Days Post Implant (+/- 30 days)	180 Days Post Implant (+/- 30 days)	360 Days Post Implant (+/- 30 days)	540 Days Post Implant (+/- 30 days)	720 Days Post Implant (+/- 30 days)	As Occurs
Inclusion/ Exclusion	X												
Enrollment / Randomization	X[17]												
Demographics	X												
Intended Use[11]	X												
General and Cardiac Medical History		X											
Current Medications / Cardiovascular Medications[9]		X	X		X	X	X	X	X	X	X	X	
Physical Exam		X											
Vital Signs[2]		X			X	X	X	X	X	X	X	X	
Hemodynamic Measurements[3]		X											
Laboratory Assessments		X			X	X	X	X	X	X	X	X	
Echocardiogram		X		X[15]	X	X	X	X	X	X	X	X	
ECG		X											
Chest X-ray [13] (PA and Lateral)				X[16]			X		X	X		X	
Modified Rankin Score[19]		X	X[6]		X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]
NYHA Classification [5]		X				X	X	X	X	X	X	X	
INTERMACS Profile[18]		X											
6 Minute Walk Test		X					X	X	X	X	X	X	
EQ-5D-5L		X					X	X	X	X	X	X	
KCCQ		X						X	X	X	X	X	

	Screening[1]	Baseline[1]	Implant	Post-Op Day 1 (+/- 1 day)	1 Week Post Implant (+/- 1 day)	Discharge (-1 day)	30 Days Post Implant (+/- 7 days)	90 Days Post Implant (+/- 30 days)	180 Days Post Implant (+/- 30 days)	360 Days Post Implant (+/- 30 days)	540 Days Post Implant (+/- 30 days)	720 Days Post Implant (+/- 30 days)	As Occurs
VO_2 Max[10]		X											
Implant Data/CPB Time/Blood Products			X										X
HM II and HM3 Pump Parameters[7]			X		X	X	X	X	X	X	X	X	X[14]
Concurrent Procedures at Pump Implant			X										X
Subject Status					X	X	X	X	X	X	X	X	X
Subject Outcome					X	X	X	X	X	X	X	X	X
ICU Time						X							
Rehospitalizations							X	X	X	X	X	X	X
HM3 Pump Log Files[8]			X	X	X	X	X	X	X	X	X	X	X[14]
HM II Pump Log Files													X[14]
Adverse Events [4]			X		X	X	X	X	X	X	X	X	X
Device Malfunctions[4]			X		X	X	X	X	X	X	X	X	X
Operative Procedures[4]					X	X	X	X	X	X	X	X	X
Pump Replacements / Explants / Exchanges [4]					X	X	X	X	X	X	X	X	X
Driveline Management Assessment					X	X	X	X	X	X	X	X	X
Collection of UB-04 Form						X							X[12]
Autopsy													X

[1] Screening and Baseline assessments can be conducted as one visit or separate visits.
[2] Vital Signs include: height (only at baseline), weight, temperature, respiratory rate, heart rate, blood pressure and mean arterial pressure.
[3] Hemodynamic Measurements include: Pulmonary Capillary Wedge Pressure, Pulmonary Arterial Systolic Pressure, Pulmonary Arterial Diastolic Pressure, Pulmonary Arterial Mean Pressure, Central Venous Pressure, Cardiac Index, Cardiac Output, Pulmonary Vascular Resistance, Right Atrial pressure, and Left Atrial pressure (LAP only if available).
[4] Post Implant or during implant procedure.
[5] Must be performed by an independent assessor.
[6] Required only if a stroke has occurred and 60 days post-stroke.

[7] *HM II and HM3 Pump Parameters include: Pump Flow, Pump Speed, Pulsatility Index and Pump Power.*
[8] *Pump Log Files include: Pump Period Log, Pump Event Log, Controller Period Log, and Controller Event Log.*
[9] *If Subject is on inotropes at the time of screening/baseline, list how long the Subject has been on inotropes.*
[10] *If Subject is able. If Subject is unable to perform, must provide reason this was not done.*
[11] *At the time of implant and as defined by INTERMACS; refer to Appendix 6.*
[12] *To be collected any time subject is rehospitalized.*
[13] *Images to be submitted to Thoratec.*
[14] *In addition to defined scheduled collection of pump parameters and pump logs, they must also be submitted when any pump-related or possibly related AE or malfunction occurs.*
[15] *Post-operative TEE is also acceptable; can be performed POD 0 (post-implant) + 2 days*
[16] *AP view for HM3 subjects; feeding tube view for HM II subjects*
[17] *Randomization should occur as close as possible to the implant date; if possible, within 72 hours.*
[18] *INTERMACS profile to be assessed immediately prior to implantation*
[19] *Must be performed by an independent assessor; defined as an independent, trained, and certified clinician*

35 REFERENCES

1. Miller LW, Pagani FD, Russell SD, et al. Use of a continuous-flow device in patients awaiting heart transplantation. N Engl J Med 2007; 357: 885-896

2. Slaughter, MS, Rogers JG, Milano CA et al. Advanced Heart Failure Treated with Continuous-Flow Left Ventricular Assist Device N Engl J Med 2009; 361: 2241-2251

3. Starling RC, Naka Y, Boyle AJ et al. Results of the Post U.S. Food and Drug Administration-Approval Study with a Continuous Flow Left Ventricular Assist Device as a Bridge to Heart Transplantation, J Am Coll Cardiol 2011; 57:1890-1898.

4. Active Implantable Medical Device Directive (AIMDD) 90/385/EEC. (June 20, 1990)

5. EN ISO 14155: 2011 - Clinical investigation of medical devices for human subjects – Part 1: General requirements

6. FDA. United States Code of Federal Regulations, Electronic Records: Electronic Signatures; Final Rule. Source: 21 CFR Part 11 (April 1, 2013).

7. Guidelines on Clinical Investigation: a Guide for Manufacturers and Notified Bodies, MEDDEV 2.7/4

8. Organisation for Economic Co-operation and Development (OECD) Principles of Good Laboratory Practice (GLP) in 1997

9. Rogers JG, Aaronson KD, Boyle AJ et al. Continuous Flow Left Ventricular Assist Device Improves Functional Capacity and Quality of Life of Advanced Heart Failure Patients. J Am Coll Cardiol. 2010; 55:1826-34.

10. Wang C, Keller DS, Lan KKG. Sample size re-estimation for binary data via conditional power. Joint Statistical Meetings – Biopharmaceutical Section. 2002

11. Kirklin JK, Naftel DC, Kormos RL et al. INTERMACS Analysis of Pump Thrombosis in the Heartmate II Left Ventricular Assist Device. J. Heart Lung Transplant. 2014; 33:12-22.

12. Thoratec Final Post Approval Report to the FDA on the HM II Destination Therapy – INTERMACS Post Approval Study

13. Thoratec Data: HM II Bridge to Transplant – INTERMACS Post Approval Study

14. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. 2013

APPENDIX 1: ANTICIPATED ADVERSE EVENT DEFINITIONS

Bleeding
An episode of SUSPECTED INTERNAL OR EXTERNAL BLEEDING that results in one or more of the following:
a. Death,
b. Reoperation,
c. Hospitalization,
d. Transfusion of red blood cells as follows:
   - If transfusion is selected, then apply the following rules:

     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 the first 7 days post-implant

     After 7 days Post-implant*
     - Any 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 event and not as a separate bleeding event.
*Any transfusion of ≥ 2U packed red blood cells (PRBC) after 7 days following implant will be considered a serious bleed

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

Pericardial Fluid Collection
Accumulation of fluid or clot in the pericardial space that requires surgical intervention or percutaneous catheter drainage. This event will be subdivided into those with clinical signs of tamponade (e.g. increased central venous pressure and decreased cardiac/VAD output) and those without signs of tamponade.

Device Malfunctions
A Device Malfunction occurs when any component of the MCSD system ceased to operate to its designated performance specifications or otherwise fails to perform as intended. Performance specifications include all claims made in the Instructions for Use.

Internal Component Malfunction: Malfunction of any device system component that is implanted within the patient. A malfunction to these components may require further surgery to repair or replace.

External Component Malfunction: Malfunction of a device system component that is used external to the patient and can be replaced or repaired without the need for further surgery.

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

a. Presence of hemolysis
b. Worsening heart failure or inability to decompress the left ventricle
c. Abnormal pump parameters

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

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

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

Hemolysis*
A plasma-free hemoglobin value that is greater than 40 mg/dl, concomitant with a rise in serum LDH above three times the upper limit of normal, in association with clinical signs associated with hemolysis (e.g., anemia, low hematocrit, hyperbilirubinemia) occurring after the first 72 hours post-implant.
*Hemolysis in the presence of worsening heart failure or inability to decompress the left ventricle or abnormal pump parameters should be reported as suspected device thrombosis, not as hemolysis

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

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

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

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

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

Internal Pump Component, Inflow or Outflow Tract Infection
Infection of blood-contacting surfaces of the LVAD documented by positive site culture.

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

Myocardial Infarction
Two categories of myocardial infarction will be identified:

Peri-Operative Myocardial Infarction
The clinical suspicion of myocardial infarction together with CK-MB or Troponin > 10 times the local hospital upper limits of normal, found within 7 days following VAD implant together with ECG findings consistent with acute myocardial infarction. (This definition uses the higher suggested limit for serum markers due to apical coring at the time of VAD placement, and does not use wall motion changes because the apical sewing ring inherently creates new wall motion abnormalities.)

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

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

Neurologic Dysfunction
Any new, temporary or permanent, focal or global neurological deficit, ascertained by a standard neurological history and examination administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests and consultation note; or an abnormality

identified by surveillance neuroimaging. The examining physician will classify the event as defined below:

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

*Modified Rankin Score will be used to classify the severity of all strokes
**Acute encephalopathy is a sign or symptom of some underlying cerebral disorder, and is manifest as depressed consciousness with or without any associated new global or multifocal neurologic deficits in cranial nerve, motor, sensory, reflexes and cerebellar function.

Psychiatric Episode
Disturbance in thinking, emotion or behavior that causes substantial impairment in functioning or marked subjective distress requiring intervention. Intervention is the addition of new psychiatric medication or hospitalization. Suicide is included in this definition.

Renal Dysfunction
Two categories of renal dysfunction will be identified:

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

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

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

Right Heart Failure
Symptoms and signs of persistent right ventricular dysfunction requiring RVAD implantation, or requiring inhaled nitric oxide or inotropic therapy for a duration of more than 1 week at any time after LVAD implantation.

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

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

This definition excludes neurological events.

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

Wound Dehiscence
Disruption of the exposed surfaces of a surgical incision, excluding infectious etiology, and requiring surgical repair.

Other
An event that causes clinically relevant changes in the Subject's health (e.g. cancer).

APPENDIX 2: INTERMACS PROFILE/CLASSIFICATION

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

*Stevenson, L.W. et al. INTERMACS Profiles of Advanced Heart Failure: The Current Picture, J Heart Lung Transplant. 2009 28(6): 535-541

APPENDIX 3: NYHA CLASSIFICATION

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

*For all post-enrollment NYHA assessments, any patient who is inotrope dependent will be considered NYHA Class IV.

APPENDIX 4: 6MWT PROTOCOL

SIX-MINUTE HALLWAY WALK TEST INSTRUCTIONS

Purpose
The purpose of the 6-Minute Hallway Walk test (6MWT) is to walk as far as possible for 6-minutes, without running or jogging, as a way of measuring functional status.

Preparing for the test
1. Establish a 30-meter walking course in an enclosed corridor, preferably free of distractions and close to a wall so that if needed, the Subject may rest against it during the test (note: a treadmill is not an acceptable alternate method for this study).
2. Mark the course at 3-meter intervals using a method unnoticeable to the Subject.
3. Place noticeable markers at either end of the 30-meter course to indicate the turnaround points.
4. The distance covered during the preceding walk test will not be revealed to the Subject during the study.
5. A warm up prior to the test should not be performed.

Explaining the test procedure to the Subject
1. Clearly explain to the Subject what is required of him/her using the following instructions verbatim:

   THE PURPOSE OF THIS TEST IS TO WALK AS FAR AS POSSIBLE FOR SIX-MINUTES. YOU WILL START FROM THIS POINT AND FOLLOW THE HALLWAY TO THE MARKER AT THE END, THEN TURN AROUND AND WALK BACK. WHEN YOU ARRIVE BACK AT THE STARTING POINT, YOU WILL GO BACK AND FORTH AGAIN. YOU WILL GO BACK AND FORTH AS MANY TIMES AS YOU CAN IN THE SIX-MINUTE PERIOD. IF YOU NEED TO, YOU ARE PERMITTED TO SLOW DOWN, TO STOP, AND TO REST AS NECESSARY. YOU MAY LEAN AGAINST THE WALL WHILE RESTING, BUT RESUME WALKING AS SOON AS YOU ARE ABLE. HOWEVER, THE MOST IMPORTANT THING ABOUT THE TEST IS THAT YOU COVER AS MUCH GROUND AS YOU POSSIBLY CAN DURING THE SIX MINUTES. I WILL KEEP TRACK OF THE NUMBER OF LAPS YOU COMPLETE AND I WILL LET YOU KNOW WHEN THE SIX MINUTES ARE UP. WHEN I SAY STOP, PLEASE STAND RIGHT WHERE YOU ARE.

   DO YOU HAVE ANY QUESTIONS ABOUT THE TEST?

   PLEASE EXPLAIN TO ME WHAT YOU ARE GOING TO DO.

2. The Subject will re-state the instructions. If the Subject does not seem to understand, repeat the entire instructions.

   Conducting the test
   1. Position the Subject at the starting line.
   2. Repeat the sentence:

      THE MOST IMPORTANT THING ABOUT THE TEST IS THAT YOU COVER AS MUCH GROUND AS YOU POSSIBLY CAN DURING THE SIX MINUTES.

      ARE YOU READY?

      START NOW, OR WHENEVER YOU ARE READY.

3. Start the timer as soon as the Subject takes the first step.
4. During the test, the walking pace of the Subject should not be influenced. The test supervisor must walk behind the Subject – do not walk with, rush up behind, or rush past the Subject.
5. Each time the Subject returns to the starting line, record the lap.
6. While walking, encourage the Subject at one minute intervals with the following phrases:

1 minute:	YOU ARE DOING WELL. YOU HAVE 5 MINUTES TO GO.
2 minutes:	KEEP UP THE GOOD WORK. YOU HAVE 4 MINUTES TO GO.
3 minutes:	YOU ARE DOING WELL. YOU ARE HALFWAY DONE.
4 minutes:	KEEP UP THE GOOD WORK. YOU HAVE ONLY 2 MINUTES LEFT.
5 minutes:	YOU ARE DOING WELL. YOU HAVE ONLY ONE MINUTE TO GO.

7. The Subject should be spoken to only during the 1-minute encouragements; no response should be made to the Subject's questions about the time and distance elapsed.
   a. If the Subject is not concentrating on the walking, the Subject can be reminded at a 1-minute mark:

      THIS IS A WALKING TEST, TALKING WILL UTILIZE YOUR ENERGY RESERVE AND INTERFERE WITH YOUR PERFORMANCE.

7. When only 15 seconds remain, state:

   IN A MOMENT I AM GOING TO TELL YOU TO STOP. WHEN I DO, STOP RIGHT WHERE YOU ARE AND I WILL COME TO YOU.

9. When the timer reads 6-minutes, instruct the Subject to STOP and walk over to him/her. Consider bringing a chair if the Subject appears exhausted. Mark the spot where the Subject stopped.

   If the Subject wishes to stop walking during the test
   If the Subject is slowing down and expresses that he/she wants to pause, keep the timer running and state:

   REMEMBER, IF YOU NEED TO, YOU MAY LEAN AGAINST THE WALL UNTIL YOU CAN CONTINUE WALKING AGAIN.

   If the Subject wishes to stop before the 6-minutes are complete and refuses to continue (or you decide that he/she should not continue), provide a chair for the Subject to sit on and discontinue the test. Record the distance completed, the time the test was stopped and the reason for pre-maturely stopping.

   Immediately after the test
   1. Total the number of completed laps and add the additional distance covered in the final partial lap. Record the distance walked to the nearest meter.
   2. Observe the Subject sitting in a chair for at least 10 minutes after the test is completed.

APPENDIX 5: MODIFIED RANKIN SCORE

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

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

APPENDIX 6: INTERMACS DEFINITIONS FOR INTENDED USE OF DEVICE

Bridge to recovery - Use of a durable device to allow recovery from chronic cardiac failure (at least 3 months in duration)

Rescue therapy - Use of a durable device to support resolution from an acute event without major previous cardiac dysfunction

Bridge to transplant– This is for a patient ALREADY listed for transplant or listed within 24 hours before device implantation

Possible bridge to transplant - *Likely to be eligible*: defines a patient in whom the transplant evaluation has not been completed, but no contra-indications are anticipated, or in whom a current contra-indication is anticipated to resolve rapidly, such as recent infection.

Possible bridge to transplant - *Moderate likelihood of becoming eligible*: similar to above, but with some potential concerns that might prevent eligibility.

Possible bridge to transplant - *Unlikely to become eligible:* should be used for a patient in whom major concerns have already been identified. These may not have been quantified yet, such as in a patient with known chronic lung disease without recent pulmonary function test measurement, or might be reversible, such as severe renal insufficiency or pulmonary hypertension that might improve after chronic mechanical support. It may be the expectation at the time of implant that the patient will most likely have the assist device as “permanent” or “destination” therapy.

Destination therapy - patient definitely not eligible for transplant.

Summary of Changes to the MOMENTUM 3 IDE Clinical Study Protocol		
Protocol Version	Date	Revision Summary
1.0	03/06/14	Original Protocol
2.0	04/22/14	Internal Version
3.0	06/17/14	Initial submission to FDA on June 19, 2014; granted conditional approval July 24, 2014
4.0	08/01/14	Submitted to FDA on September 5, 2014 with responses to conditional approval letter • Update to study design to reflect 10 additional subjects allowable during FDA review of safety data • Corrected typographical error in Figure 2 to reflect 60 study sites • Added INTERMACS profile to subgroup analysis • Revised screening visit so that informed consent is signed after inclusion/exclusion assessment; subjects now considered enrolled at time of study consent • Addition of independent assessor requirement for Modified Rankin Score • Revised schedule of events such that INTERMACS profile is assessed immediately prior to implantation • Updated reporting requirement to DSMB and FDA • Updated treatment-by-site interaction effect to be tested at 0.15 level of significance
5.0	04/01/15	Submitted to FDA as part of 2015 Annual Report • Updated Sponsor contact information • Clarification of exclusion criterion 12(c) to read: History of severe chronic obstructive pulmonary disease (COPD) defined by $FEV_1/FVC < 0.7$, and FEV_1 <50% predicted • Clarification of exclusion criterion 12(e) to read: History of stroke within 90 days prior to enrollment, or a history of cerebrovascular disease with significant (> 80%) uncorrected carotid artery stenosis • Clarification of exclusion criterion 14 to read: Pre albumin < 150 mg/L (15mg/dL) or Albumin < 30g/L (3 g/dL) (if only one available); pre albumin < 150 mg/L (15mg/dL) and Albumin < 30g/L (3 g/dL) (if both available) • Updated randomization section 13.4 to reflect previous change to time of enrollment • Clarified laboratory assessments to reflect that only albumin or pre-albumin is required (not both) and only CRP or hs-CRP is required (not both) • Clarification of pump log collection schedule in section 16.8.1
6.0	08/04/15	Changes submitted to FDA as part of 2016 Annual Report • Changed study name from HeartMate III IDE to MOMENTUM 3 IDE (FDA notified of name change in July 2015 Annual Report) • Changed HeartMate III to HeartMate 3 • Removed breakdown of number of subjects per arm, as the number randomized to each arm may not be equal • Clarified in Section 3.0 that HM3 subjects can only be discharged with the MPU • Clarified in Section 13.4 that centers may have their maximum enrollment increased beyond 50 with prior Sponsor approval • Added 90 day window to assess eligibility • Added +/- 1 day visit window to post-op day 1 visit • Clarification that HMII pump logs should be submitted whenever there is a pump-related or possibly related event • Added subject withdrawal and lost to follow-up language in Section 22 • Updated Figure 2 flow chart • Added Heartline emergency contact to Section 32 • Updated Left atrial pressure to be collected if available in Table 2 • Corrected typographical errors in Table 2
7.0	03/03/16	FDA approved increase in number of sites March 2016 • Increased number of study sites from 60 to 70 • Clarification that system monitor cannot be attached to MPU in Section 3 • Revised assessment time points of NYHA, 6 minute walk test, and EQ-5D-5L in section 13.15 and 13.16 to be consistent with rest of protocol
8.0	05/08/17	FDA approved changes to required Serious Adverse Event (SAE) and Unanticipated Adverse Device Effect (UADE) reporting times • Changed required SAE reporting time from 24 hours to 3 days to align with the clinical trial standard for Abbott • Changed required UADE reporting time from 24 hours to 3 days to align with the clinical trial standard for Abbott • Added Sponsor document number and version in the footer (for Sponsor use only)

Title: HeartMate III IDE Trial Statistical Analysis Plan

Device: HeartMate III Ventricular Assist Device

Sponsor: Thoratec Corporation

Date of Report: October 13, 2014

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2 ABBREVIATIONS AND DEFINITIONS

a. BSA = Body Surface Area
b. LVEF = Left Ventricular Ejection Fraction
c. CI = Cardiac Index
d. LVAS = Left Ventricular Assist System
e. LVAD = Left Ventricular Assist Device
f. IABP= Intra-aortic Balloon Pump
g. IRB
h. FDA= Food and Drug Administration

3 INTRODUCTION

The HeartMate III LVAS represents the next generation of a mechanical support device. The HeartMate III LVAD is a centrifugal mechanically levitated heart pump designed for both short and long term support in patients afflicted with advanced, refractory left-ventricular heart failure. The purpose of this clinical investigation is to evaluate the safety and effectiveness of the HeartMate III LVAS. This multicenter study is designed to determine if the HeartMate III LVAS provides survival and quality of life benefits that are non-inferior to the HeartMate II LVAS. The trial will enroll patients under one inclusion and exclusion criteria who will be evaluated for a short and long term indication. The trial design also features a pre-defined and powered secondary endpoint to to study pump reliability. The study will be conducted in compliance with the Declaration of Helsinki and all IRB and FDA regulatory requirements.

4 MODIFICATION TO THE PROTOCOL

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Study Objective

The primary objective of this study is to evaluate the safety and effectiveness of the HeartMate III LVAS by demonstrating non-inferiority to the HeartMate II when used for the treatment of advanced, refractory, left-ventricular heart failure.

5.2 Primary Study Endpoints

5.2.1 Short Term Indication

Composite of survival to transplant, recovery or 6 months of LVAD support free of debilitating stroke (Modified Rankin Score > 3) or reoperation to replace the pump.

5.2.2 Long Term Indication

Composite of survival to transplant, recovery or 24 months of LVAD support free of debilitating stroke (Modified Rankin Score> 3) or reoperation to replace the pump.

5.3 Secondary Endpoints

i. Quality of Life as measured by the EuroQoL-5D-5L (EQ-5D-5L) and Kansas City Cardiomyopathy Questionnaire (KCCQ)
ii. Functional status as measured by the Six Minute Walk Test (6MWT) and New York Heart Association (NYHA) classification
iii. Frequency and incidence of pre-defined anticipated adverse events

iv. Frequency and incidence of device malfunctions
v. Frequency and incidence of all reoperations
vi. Frequency and incidence of re-hospitalizations

6 STUDY POPULATION:

a. Subjects with advanced refractory left ventricular heart failure who meet the following inclusion and exclusion criteria.
b. Inclusion Criteria
   i. Subject or legal representative has signed Informed Consent Form (ICF)
   ii. Age ≥ 18 years
   iii. BSA ≥ 1.2 m^2
   iv. NYHA Class III with dyspnea upon mild physical activity, or NYHA Class IV
   v. LVEF ≦ 25%
   vi. Inotrope dependent OR
   CI < 2.2 L/min/m^2, while not on inotropes and subjects must also meet one of the following:
      - On Optimal Medical management (OMM), based on current heart failure practice guidelines for at least 45 out of the last 60 days and are failing to respond
      - Advanced heart failure for at least 14 days AND dependent on IABP for at least 7 days

   vii. Females of child bearing age must agree to use adequate contraception
c. Exclusion Criteria
   i. Etiology of HF due to or associated with uncorrected thyroid disease, obstructive cardiomyopathy, pericardial disease, amyloidosis or restrictive cardiomyopathy
   ii. Technical obstacles which pose an inordinately high surgical risk, in the judgment of the investigator
   iii. Existence of ongoing mechanical circulatory support (MCS) other than IABP
   iv. Positive pregnancy test if of childbearing potential
   v. Presence of mechanical aortic cardiac valve that will not be converted to a bioprosthesis or oversewn at the time of LVAD implant
   vi. History of any organ transplant
   vii. Platelet count < 100,000 x 10^3/L (< 100,000/ml)
   viii. Psychiatric disease/disorder, irreversible cognitive dysfunction or psychosocial issues that are likely to impair compliance with the study protocol and LVAS management
   ix. History of confirmed, untreated AAA > 5 cm in diameter within 6 months of enrollment
   x. Presence of an active, uncontrolled infection
   xi. Intolerance to anticoagulant or antiplatelet therapies or any other peri/post-operative therapy the investigator will require based upon the patients' health status

xii. Presence of any one of the following risk factors for indications of severe end organ dysfunction or failure:
   1. An INR ≥ 2.0 not due to anticoagulation therapy
   2. Total bilirubin > 43 umol/L (2.5 mg/dl), shock liver, or biopsy proven liver cirrhosis
   3. History of severe chronic obstructive pulmonary disease (COPD) defined by $FEV_1/FVC < 0.7$, or FEV_1 <50% predicted
   4. Fixed pulmonary hypertension with a most recent PVR ≥ 8 Wood units that is unresponsive to pharmacologic intervention
   5. History of stroke within 90 days prior to enrollment, or a history of cerebrovascular disease with significant (> 80%) carotid artery stenosis
   6. Serum creatinine ≥ 221 umol/L (2.5 mg/dl) or the need for chronic renal replacement therapy
   7. Significant peripheral vascular disease (PVD) accompanied by rest pain or extremity ulceration

xiii. Patient has moderate to severe aortic insufficiency without plans for correction during pump implant

xiv. Pre albumin < 150 mg/L, or Albumin < 30g/L (3 g/dL)

xv. Planned Bi-VAD support prior to enrollment

xvi. Patient has known hypo or hyper coagulable states such as disseminated intravascular coagulation and heparin induced thrombocytopenia

xvii. Participation in any other clinical investigation that is likely to confound study results or affect the study

xviii. Any condition other than HF that could limit survival to less than 24 months

7 STUDY PLAN

The study will be a prospective, multi-center, non-blinded, randomized, non-inferiority study comparing the HeartMate III LVAS to the HeartMate II LVAS. Short term use of the device will be evaluated when Subjects have been supported for 6 months, transplanted or explanted for recovery, whichever occurs first. Long term use of the device will be evaluated when Subjects have been followed for 24 months, transplanted or explanted for recovery, whichever occurs first.

a. **Missing Values and Data Conventions:** Every effort will be made to collect all required data. Missing primary endpoints will be imputed using multiple imputation techniques. Missing secondary endpoints wil not be imputed, except as described below.

b. **Multiplicity Adjustments:** No adjustments for multiplicity will be made in the analysis of secondary endpoints. No statistical claims will be made concerning secondary endpoints.

8 STATISTICAL PROCEDURES:

The HM III study is a prospective, multicenter, non-blinded, randomized study to test the success of the HM III LVAS for short term hemodynamic support, such as a bridge to cardiac transplant (BTT) or myocardial recovery, or as long term support, such as destination therapy (DT).

Since the device must be surgically implanted, the investigator cannot be blinded to the treatment. Similarly, since the Subject must be trained on driveline care and responses to warning alarms, the Subject cannot be blinded to treatment. The study design will allow for a scientifically rigorous examination of the performance and safety of the device.

In general, continuous data will be presented as the number of Subjects, mean with standard deviation, and median with minimum and maximum values. Categorical data will be reported as frequencies and percentages. Adverse events will also be reported as rates per patient year. Only adverse events that occur after the start of the implant procedure will be analyzed. Survival data will be presented using the Kaplan-Meier product limit method, as well as the percentage of Subjects who successfully reach the pre-defined study primary endpoint.

Data will be analyzed using the intent–to-treat method (ITT) defined as all randomized Subjects. Every effort will be made to avoid cross-over but in the event they occur, data will also be analyzed "as randomized" for efficacy analysis and "as treated" for safety analysis and all other secondary endpoints.

Statistical analysis will be performed using SAS version 9.1 or higher.

8.1 Analysis Population

8.1.1 Intent-to-treat: All Randomized Subjects

This is the primary analysis population for the primary endpoint. Subjects are analyzed under the treatment to which they were randomized.

8.1.2 As Treated: All Treated Subjects

This is the primary analysis population for the secondary endpoints. Subjects are analyzed under the treatment they actually receive.

8.1.3 As Randomized: All Treated Subjects

This population includes only the Subjects who receive the treatment they were randomized to.

8.2 Study Hypothesis

8.2.1 Short Term Support:

The short term study endpoint is a composite of survival to transplant, myocardial recovery or 6 months of support (whichever occurs first) free of a debilitating stroke (modified Rankin Score > 3) or reoperation to replace the original pump. A Subject will be considered a success if they are:

- Electively transplanted or explanted for myocardial recovery prior to 6 months or
- Alive at 6 months, and
  - Have not experienced a stroke with a modified Rankin Score > 3, and
  - Have not received a device replacement or exchange, and
  - Have not received an urgent transplant due to a LVAS malfunction.

A Subject will be considered a failure if they:

- Expire prior to 6 months, or
- Experience a stroke with a modified Rankin Score > 3 prior to 6 months, or

- Have a device replaced or exchanged or deactivated for reasons other than myocardial recovery prior to 6 months, or
- Have received an urgent transplant due to a LVAS malfunction prior to 6 months, or
- Have withdrawn from the study for any reason prior to 6 months

HM III short term success rate will be compared to that of the HM II control in a non-inferiority manner. The null and alternative hypotheses are:

$$H_o: \pi_{HM\ III} \leq \pi_{HM\ II} - \Delta$$
$$H_A: \pi_{HM\ III} > \pi_{HM\ II} - \Delta$$

where $\pi_{HM\ III}$ and $\pi_{HM\ II}$ are the short term success rates of HM III and HM II, respectively, and where Δ is the non-inferiority margin.

8.2.2 Long Term Support:

The long term study endpoint is a composite of survival to transplant, myocardial recovery or 24 months of support (whichever occurs first) free of a debilitating stroke (modified Rankin Score > 3) or reoperation to replace the original pump.

A Subject will be considered a success if they are:

- Electively transplanted or explanted for myocardial recovery prior to 24 months or
- Alive at 24 months, and
  - Have not experienced a stroke with a modified Rankin Score > 3, and
  - Have not received a device replacement or exchange, and
  - Have not received an urgent transplant due to a device malfunction.

A Subject will be considered a failure if they:

- Expire prior to 24 months, or
- Experience a stroke with a modified Rankin Score > 3 prior to 24 months, or
- Have a device replaced or exchanged or deactivated for any reason other than myocardial recovery prior to 24 months, or
- Have received an urgent transplant due to a LVAS malfunction prior to 24 months, or
- Have withdrawn from the study for any reason prior to 24 months

The 24 month success rate of the HM III Subjects will be compared to the HM II control. The null and alternative hypotheses are:

$$H_o: \pi_{HM\ III} \leq \pi_{HM\ II} - \Delta$$
$$H_A: \pi_{HM\ III} > \pi_{HM\ II} - \Delta$$

where $\pi_{HM\ III}$ and $\pi_{HM\ II}$ are the long term success rates of HM III and HM II, respectively, and where Δ is the non-inferiority margin.

8.3 Randomization

Subjects will be randomized in a 1:1 fashion (1 HM III: 1 HM II). The randomization will be stratified by study center and blocked to maintain the 1:1 ratio over time. Randomization will be implemented through the Electronic Data Capture (EDC) system. Study centers will be allowed a maximum of 50 randomized Subjects. Subjects will be

considered enrolled in the study upon randomization and will be included in the intent-to-treat analysis.

8.4 Sample Size

8.4.1 Assumptions

- Larger gap between the rotor and pump housing in the HM III may result in less thrombus than HM II
- Larger gap between the rotor and pump housing in the HM III may result in less pump replacement due to ingested thrombus than HM II
- HM III modular driveline may reduce pump replacements due to driveline damage or fatigue.

8.4.2 Short Term Indication

Based on a review of recent INTERMACS and Thoratec data, it is assumed that the HM II will achieve a composite success rate of 85% at 6 months. It is also assumed that the HM III will have a composite success rate of 87% due to less pump replacements at 6 months caused by thrombus or driveline issues. It will take 138 HM III and 138 HM II Subjects (276 total Subjects) to achieve 80% power to prove the HM III 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.

INTERMACS HM II data from 26 sites likely to participate in the HM III IDE study was reviewed. Eight hundred and twenty (820) patients were implanted with the HM II in 2012 at these sites and 52 (6%) received a transplant or explant due to myocardial recovery prior to 6 months. In order to have sufficient data to evaluate the 6 month success rate, an additional 9 Subjects will be randomized per arm (6% of 138) to account for these early outcomes. This results in a total of 147 Subjects randomized in each arm (294 total Subjects).

8.4.3 Long Term Indication

Based on the results from the HM II Destination Therapy IDE study, it is assumed that 50% of the HM II Subjects will successfully achieve the composite primary endpoint. It is also assumed that the HM III will have a composite success rate of 55% due to less pump replacements at 24 months caused by thrombus or driveline issues. It will take 174 HM III and 174 HM II Subjects (348 total Subjects) to achieve 80% power to prove the HM III is non-inferior to HM II when the margin of non-inferiority (=Δ in the above null and alternative hypotheses) is -10% using the Farrington-Manning risk difference approach to non-inferiority at a one-sided alpha = 0.025.

INTERMACS HM II data from 26 sites likely to participate in the HM III IDE study was reviewed. Eight hundred and twenty (820) patients were implanted with the HM II in 2012 at these sites and 52 (6%) received a transplant or explant due to myocardial recovery prior to 6 months. In order to have sufficient data to evaluate the 24 month success rate, an additional 9 Subjects will be randomized per arm (6% of 138) to account for these early outcomes. This results in a total of 183 Subjects randomized in each arm (366 total Subjects).

8.5 Early Safety Assessment

The HM III IDE study will include an early safety assessment in lieu of a feasibility study. The first 10 HM III Subjects enrolled in the study will be included and their data analyzed when they have achieved 30 days of support. A table describing the 30 days status of the Subjects will be prepared. Adverse events will be presented as the percentage of Subjects who experience the event, the number of events and the event rate per 30 days. The data will be presented to the DSMB and FDA for a recommendation to continue the study and to expand to remaining study centers. All Subjects included in the early safety assessment will continue to be followed per protocol and will be included in the final Short Term and Long Term analysis.

8.6 Analysis of Primary Endpoint

The HM III will be considered non-inferior to the HM II for both short and long term indications if the lower two-sided 95% confidence limit of the risk difference in the composite success between treatment arms (HM III minus HM II) is greater than -10% ("negative 10%", where 10% is the non-inferiority Δ in the above null and alternative hypotheses). Once non-inferiority is inferred, the data will be analyzed for superiority at a one-sided 0.025 level of significance using closed testing methods via the z-test of proportions using the normal approximation to the binomial distribution. Since the short term and long term evaluations are two distinct endpoints, no adjustment for multiple comparisons is required.

8.6.1 Primary Endpoint Stratified by Components of the Composite Endpoint

Differences in success rates between HM III and HM II will be performed for each component of the composite endpoint to evaluate if a single component is influencing the outcome. Specifically, for each component, two-sided 95% confidence intervals of the differences and a z-test of proportions will be generated using the normal approximation to the binomial distribution.

8.6.2 Effect of Site Bias on the Primary Endpoint

In order to determine if a few superior investigational sites are influencing the primary endpoint results, a comparison of results across sites will be performed. Specifically, for each of the short term and long term outcomes, the significance of the treatment-by-site interaction effect will be assessed using logistic regression with the main effects for treatment and site, and with a treatment-by-site interaction effect. The treatment-by-site interaction effect will be tested at the 0.15 level of significance. A non-significant interaction or an interaction that is significant but only quantitative and not qualitative in nature will support the pooling of Subjects across sites for the primary analyses. Given that a number of sites will contribute only small numbers of Subjects, we will pool sites with less than 5 Subjects for the analysis.

8.6.3 Unblinded Interim Efficacy Analysis (Adaptive Design)

After 74 of the planned 147 patients per treatment group required for the analysis on the short term primary outcome are treated and followed for 6 months, an interim unblinded analysis comparing treatments on the 6-month short term primary outcome will be carried out. The short term primary outcome is the binary composite endpoint of survival to elective transplant if transplant is prior to 6 months, survival to myocardial recovery prior if recovery is prior to 6 months, or survival for 6 months of LVAD support free of a debilitating stroke (modified Rankin Score > 3) and free of reoperation to replace the pump. There will be no

provision to stop the study at interim stage for overwhelming effectiveness and hence no adjustment of the significance level for the final analysis. The first purpose of the interim analysis is to calculate the power for non-inferiority, conditioned on the difference between treatments with respect to short term outcome rates and on the non-inferiority margin of 10% (or 0.10). Specifically, at the interim analysis, the conditional power for rejecting the following null hypothesis in favor of the alternative (i.e. for obtaining a non-inferiority conclusion at the final analysis for the short-term outcome) will be calculated:

H_0: $\pi_{HM\ III} \leq \pi_{HM\ II} - \Delta$
H_A: $\pi_{HM\ III} > \pi_{HM\ II} - \Delta$

where $\pi_{HM\ III}$ and $\pi_{HM\ II}$ are the short term success rates of HM III and HM II, respectively, and where Δ is the non-inferiority margin and is fixed at 10% (or 0.10). The conditional power will be calculated under the assumption that the interim observed estimate of the treatment difference is the true treatment difference. It will be calculated using the formula

$$1 - \Phi\left[\frac{Z_{1-\alpha} - B_\tau / \tau}{\sqrt{1-\tau}}\right]$$

where

a. $Z_{1-\alpha}$ is the (1-α)*100% percentile of the standard normal distribution (i.e., the critical value used to assess non-inferiority at the final analysis at overall one-sided significance level α); here, with one-sided α = 0.025, $Z_{1-\alpha}$ is set to 1.96.
b. τ is the information fraction (= proportion of patients in the first interim analysis = r/M where r is the number of patients per group in the interim analysis and M is the planned number of patients per group for the final analysis). Here, it is expected that r=74, M=147, and τ =0.503.
c. $B_\tau = Z_\tau \sqrt{\tau}$ where Z_τ = the Farrington-Manning non-inferiority test statistic calculated on the interim observed data; specifically

$$Z_t = \frac{\hat{p}_{HMIII} - \hat{p}_{HMII} - (-\Delta)}{\sqrt{\frac{\tilde{p}_{HMIII}(1-\tilde{p}_{HMIII})}{n_{HMIII}} + \frac{\tilde{p}_{HMII}(1-\tilde{p}_{HMII})}{n_{HMII}}}}$$

where

i. $\hat{p}_{HMIII}$ = the interim observed estimate of the true success rate ($\pi_{HM\ III}$) for HM III (=number of HM III subjects with success divided by number of HM III subjects in the interim analysis).
ii. $\hat{p}_{HMII}$ is the similarly defined interim observed estimate of the true success rate ($\pi_{HM\ II}$) for HM II.
iii. $\tilde{p}_{HMIII}$ and $\tilde{p}_{HMII}$ are the interim maximum likelihood estimates of $\pi_{HM\ III}$ and $\pi_{HM\ II}$ calculated under the above null hypothesis, as shown in Farrington and Manning (1990).
iv. n_{HMIII} and n_{HMII} are the sample sizes used for the interim analysis from HM III and HM II, respectively.
v. Δ is the non-inferiority margin of 0.10.

d. Φ is the cumulative distribution function of the standard normal distribution.

If the conditional power is <50% or >80% at the interim stage, the study will continue as is (there will be no stoppage of the study for futility nor will there be a sample size increase); if conditional power is between 50-80%, the sample size will be re-estimated to achieve conditional power of 80% for the 6-month short term endpoint as follows, assuming the interim observed effect size between treatments is the true effect size between treatments and controlling Type I error using the following method in Wang et al.: The total revised sample size per group, $M`$ required to achieve a conditional power of 80% to assess non-inferiority at the final analysis using a non-inferiority margin of 0.10 (or 10%) is found by solving the following equation for $M`$:

$$Z_{0.20}\sqrt{1-\frac{r}{M`}}+Z_{\tau}\sqrt{\frac{M`}{r}}-Z_{1-\alpha}=0$$

where $Z_{0.20}$ is the 20th percentile of the standard normal distribution (= -0.84) and where all other variables in this equation are defined above.

Note that the final sample size for the 6-month short-term outcome will NOT be decreased below the currently planned final sample size for the 6-month short-term outcome (and the sample size will not be increased to >1000 per group). Also, any sample size increase for the 6-month sort term outcome will also be applied to the final sample size used to assess the long-term outcome (there will be no interim unblinded analysis on the long-term outcome). The following table displays the sample size scenarios for each of the long-term and short-term outcome under various situations:

Endpoint	Sample Size Per Group at Interim	Sample Size Per Group at Final Analysis	
		In the Event of No Sample Size Increase at Interim	In the Event of a Sample Size Increase of *X* at Interim
6-month Short Term	After 78 patients per group are treated and followed for 6 months	After 147 patients per group are treated and followed for 6 months	After 147 + *X* patients per group are treated and followed for 6 months
24-month Long Term	This endpoint will not be analyzed in the interim.	After 183 patients per group are treated and followed for 24 months.	After 183 + *X* patients per group are treated and followed for 24 months.

The analyses on sample size re-estimation will be carried out by the independent statistician (non-voting) and presented only to the DSMB by the independent biostatistician. The DSMB will inspect the results and inform the sponsor of their final decision, without necessarily stating the reason for the decision. E.g., the DSMB will inform the sponsor “Continue the study as is” without informing the

sponsor as to whether the reason is because the conditional power is <50% or because the conditional power is >80%; if the DSMB recommends an increase in sample size, the DSMB will not give a reason for the increase or any details behind the recommendation until the study is complete.

8.7 Subgroup Analysis

Once the analyses comparing the treatment arms are complete, a series of subgroup analyses will be performed, assessing treatment difference within each subgroup. Each subgroup will be evaluated for the primary composite endpoint, survival, adverse events, device malfunction, quality of life and functional status, as described above. Subgroups will include but may not be limited to:

- Gender: Males vs Females
- Race: Caucasian/White vs African-American/ Black vs Other
- Age: 18 – 59 vs 60 – 75 vs > 75 years
- Intended Use at implant as defined by Appendix 6
- VO2 max
- INTERMACS Profile

The purpose of the subgroup analyses is not to reach a statistically significant result within each subgroup, but rather to assess consistency of treatment difference across subgroups.

8.8 Analysis of Survival and Subject Outcome

Overall survival will be assessed for each of the two treatments using the Kaplan-Meier product-limit method. Differences between treatments in survival distributions will be analyzed using a logrank test. Subjects surviving will be censored at last known follow-up time point.

A competing outcome graph will be prepared at 6 months for short term results and 24 months for long term results.

8.9 Analysis of Adverse Events

All pre-defined adverse events will be captured. Tables will be created for HM III and HM II AEs that show the by-treatment incidences of all adverse events and the by-treatment event rate per patient year of support. Serious adverse events (SAEs) will be analyzed in a similar manner as AEs. Differences in event rates between the treatment arms will be analyzed using Fisher's Exact test or Poisson regression, as appropriate.

8.10 Analysis of Device Malfunctions

All suspected HM III device malfunctions will be reported. Thoratec will ask that all explanted devices be returned for analysis. Data on device malfunctions will be analyzed and tables will be created that report the following:

- Events that are confirmed by analysis of the device by Thoratec engineers
- The component of the device involved
- Days to the malfunction
- Action taken in response to the malfunction
- Reoperations due to malfunction
- Death due to malfunction

8.11 Analysis of Pre-Implant Data

Tables will be created to define the study population at baseline. Tables will include demographics, all laboratory assessments, all hemodynamic assessment, cardiac history, INTERMACS profile, and concurrent interventions (Cardiac Resynchronization Therapy (CRT), Automatic Internal Cardiac Defibrillator (AICD), IABP, Inotropes, etc). The intended use of the device at implant will also be collected, as defined by INTERMACS (Appendix 6). Baseline data will be compared between treatment groups using unpaired t-tests or Fisher's exact test as appropriate.

8.12 Analysis of Implant and Discharge Data

Time on cardiopulmonary bypass during implant surgery will be collected and reported as a median, quartiles and range. All concurrent procedures carried out during implant surgery will be reported. Length of Stay (LOS) will be defined as the time from implant to discharge. LOS will be reported as a mean with standard deviation, median, quartiles and range. The time on cardiopulmonary bypass and LOS will be compared between treatment groups using the Wilcoxon Rank Sum test.

8.13 Analysis of Secondary Endpoints

Secondary endpoints will each be tested at the two-sided 0.05 level of significance. There will be no adjustment for multiple comparisons across the secondary endpoints. There will be no imputation of missing data for the secondary endpoints.

8.13.1 Pump Hemodynamics

The mean flow and pump index (flow/BSA) with standard deviation for the HM III and HM II Subjects will be plotted over time. At each time point, treatments will be compared using the unpaired t-test.

8.13.2 Laboratory values

Mean laboratory values with standard deviations for HM III and HM II Subjects will be plotted over time. At each time point, treatments will be compared using the unpaired t-test.

8.13.3 Rehospitalization

Time to rehospitalization and the reason for rehospitalization will be reported. Time in and out of the hospital will be reported for the HM III and HM II Subjects. Treatments will be compared on time to re-hospitalization using the log-rank test. Subjects not re-hospitalized will be censored at last known follow-up.

8.13.4 Reoperations

Time to reoperation, frequency of reoperation, and the reason for the surgery will be reported for HM III and HM II Subjects. Treatments will be compared on time to re-operation using the log-rank test. Subjects not re-operated will be censored at last known follow-up.

8.14 Analysis of Functional Status

8.14.1 NYHA

The Subjects NYHA Functional Status will be assessed by an independent assessor at baseline and then at 3, 6, 12, 18, and 24 months. At each visit, treatments will be compared on NYHA functional status and on the change from baseline functional status using the Wilcoxon Rank Sum test. The Short Term indication will be limited to the 3 and 6 month assessments. The Long Term

indication will include all assessments until 24 months or outcome, whichever occurs first.

8.14.2 Six Minute Walk Test

Subjects may not be able to walk due to heart failure, especially at baseline. Subjects unable to walk due to heart failure will receive a score of 0 meters. For all other reasons for missing data the score will remain missing and not be included in the analysis. The Six Minute Walk test will be conducted at baseline and then at months 3, 6, 12, 18 and 24 post implant. Data will be analyzed using mixed modeling by comparing the distances walked over time to the baseline distance. The Short Term indication will be limited to the 3 and 6 month assessment. The long term indication will include all assessments until 24 months or outcome, whichever occurs first.

8.15 Analysis of Quality of Life

Quality of Life will be measured using the EuroQol (EQ-5D-5L) and the Kansas City Cardiomyopathy Questionnaire (KCCQ).

8.15.1 EQ-5D-5L

The EQ-5D-5L VAS and total score will be assessed at baseline and then at 3, 6, 12, 18, and 24 months. Data will be analyzed using mixed modeling by comparing the EQ-5D-5L score at each assessment interval to the baseline score. The Short Term indication will be limited to the 3 and 6 month assessments. The Long Term indication will include all assessments until 24 months or outcome, whichever occurs first. In addition, the percentage of each component of the EQ-5D-5L will be graphically presented over time.

8.15.2 KCCQ

The KCCQ score will be assessed at baseline and then at 3, 6, 12, 18, and 24 months. Data will be analyzed using mixed modeling by comparing the KCCQ score at each assessment interval to the baseline score. The Short Term indication will be limited to the 3 and 6 month assessments. The Long Term indication will include all assessments until 24 months or outcome, whichever occurs first.

8.16 Powered secondary analysis:

In addition to the primary outcome, the study will be powered to test if HM III pump reliability is superior to HM II by analyzing the incidence of pump replacements. Randomization described in Section 13.4 will continue beyond the Subjects needed to power the primary endpoint until a sufficient sample size has been enrolled to test the secondary endpoint. The null and alternative hypotheses are:

$$H_o: \pi_{HM\ III} \geq \pi_{HM\ II}$$
$$H_A: \pi_{HM\ III} < \pi_{HM\ II}$$

where $\pi_{HM\ III}$ is the HM III pump replacement rate and $\pi_{HM\ II}$ is the HM II pump replacement rate.

Based on data contained in Thoratec's device tracking database, 7% of the HM II Subjects receive a pump replacement by 24 months. If we assume that HM III pump replacements will be reduced to 3% at 24 months, then 1028 Subjects (514 per arm) will be needed to prove superiority with a power of 80% and alpha = 0.05 (2-sided).

Once the 366 Subjects needed for the long term indication are enrolled, Thoratec will continue to randomize 662 more Subjects (331 HM III and 331 HM II) for this secondary analysis. Data for this secondary analysis is not needed for the short or long term indications, but rather will be used to provide additional labeling information.

The Subjects will be followed for 24 months or to outcome, whichever occurs first, and analyzed using the Fisher's exact test. Treatments will also be compared on time-to-pump replacement using the log-rank test where Subjects without a replacement are censored at last known follow-up. Otherwise, there will be no imputation of missing data for this analysis.

9 REFERENCES

1. Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. Stat Med 1990;9:1447-54.
2. White paper: Wang C, Keller DS, Lan KKG (2002). Sample size re-estimation for binary data via conditional power. Joint Statistical Meetings – Biopharmaceutical Section.

Title: HeartMate III IDE Trial Statistical Analysis Plan

Device: HeartMate III Ventricular Assist Device

Sponsor: Thoratec Corporation

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2 ABBREVIATIONS AND DEFINITIONS

a. BSA = Body Surface Area
b. LVEF = Left Ventricular Ejection Fraction
c. CI = Cardiac Index
d. LVAS = Left Ventricular Assist System
e. LVAD = Left Ventricular Assist Device
f. IABP= Intra-aortic Balloon Pump
g. IRB
h. FDA= Food and Drug Administration

3 INTRODUCTION

The HeartMate III LVAS represents the next generation of a mechanical support device. The HeartMate III LVAD is a centrifugal mechanically levitated heart pump designed for both short and long term support in patients afflicted with advanced, refractory left-ventricular heart failure. The purpose of this clinical investigation is to evaluate the safety and effectiveness of the HeartMate III LVAS. This multicenter study is designed to determine if the HeartMate III LVAS provides survival and quality of life benefits that are non-inferior to the HeartMate II LVAS. The trial will enroll patients under one inclusion and exclusion criteria who will be evaluated for a short and long term indication. The trial design also features a pre-defined and powered secondary endpoint to to study pump reliability. The study will be conducted in compliance with the Declaration of Helsinki and all IRB and FDA regulatory requirements.

4 MODIFICATION TO THE PROTOCOL

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Study Objective

The primary objective of this study is to evaluate the safety and effectiveness of the HeartMate III LVAS by demonstrating non-inferiority to the HeartMate II when used for the treatment of advanced, refractory, left-ventricular heart failure.

5.2 Primary Study Endpoints

5.2.1 Short Term Indication

Composite of survival to transplant, recovery or 6 months of LVAD support free of debilitating stroke (Modified Rankin Score > 3) or reoperation to replace the pump.

5.2.2 Long Term Indication

Composite of survival to transplant, recovery or 24 months of LVAD support free of debilitating stroke (Modified Rankin Score> 3) or reoperation to replace the pump.

5.3 Secondary Endpoints

i. Quality of Life as measured by the EuroQoL-5D-5L (EQ-5D-5L) and Kansas City Cardiomyopathy Questionnaire (KCCQ)
ii. Functional status as measured by the Six Minute Walk Test (6MWT) and New York Heart Association (NYHA) classification
iii. Frequency and incidence of pre-defined anticipated adverse events

iv. Frequency and incidence of device malfunctions
v. Frequency and incidence of all reoperations
vi. Frequency and incidence of re-hospitalizations

6 STUDY POPULATION:

a. Subjects with advanced refractory left ventricular heart failure who meet the following inclusion and exclusion criteria.
b. Inclusion Criteria
   i. Subject or legal representative has signed Informed Consent Form (ICF)
   ii. Age ≥ 18 years
   iii. BSA ≥ 1.2 m^2
   iv. NYHA Class III with dyspnea upon mild physical activity, or NYHA Class IV
   v. LVEF ≦ 25%
   vi. Inotrope dependent OR
   CI < 2.2 L/min/m^2, while not on inotropes and subjects must also meet one of the following:
      - On Optimal Medical management (OMM), based on current heart failure practice guidelines for at least 45 out of the last 60 days and are failing to respond
      - Advanced heart failure for at least 14 days AND dependent on IABP for at least 7 days

   vii. Females of child bearing age must agree to use adequate contraception
c. Exclusion Criteria
   i. Etiology of HF due to or associated with uncorrected thyroid disease, obstructive cardiomyopathy, pericardial disease, amyloidosis or restrictive cardiomyopathy
   ii. Technical obstacles which pose an inordinately high surgical risk, in the judgment of the investigator
   iii. Existence of ongoing mechanical circulatory support (MCS) other than IABP
   iv. Positive pregnancy test if of childbearing potential
   v. Presence of mechanical aortic cardiac valve that will not be converted to a bioprosthesis or oversewn at the time of LVAD implant
   vi. History of any organ transplant
   vii. Platelet count < 100,000 x 10^3/L (< 100,000/ml)
   viii. Psychiatric disease/disorder, irreversible cognitive dysfunction or psychosocial issues that are likely to impair compliance with the study protocol and LVAS management
   ix. History of confirmed, untreated AAA > 5 cm in diameter within 6 months of enrollment
   x. Presence of an active, uncontrolled infection
   xi. Intolerance to anticoagulant or antiplatelet therapies or any other peri/post-operative therapy the investigator will require based upon the patients' health status

xii. Presence of any one of the following risk factors for indications of severe end organ dysfunction or failure:
   1. An INR ≥ 2.0 not due to anticoagulation therapy
   2. Total bilirubin > 43 umol/L (2.5 mg/dl), shock liver, or biopsy proven liver cirrhosis
   3. History of severe chronic obstructive pulmonary disease (COPD) defined by $FEV_1/FVC < 0.7$, or FEV_1 <50% predicted
   4. Fixed pulmonary hypertension with a most recent PVR ≥ 8 Wood units that is unresponsive to pharmacologic intervention
   5. History of stroke within 90 days prior to enrollment, or a history of cerebrovascular disease with significant (> 80%) carotid artery stenosis
   6. Serum creatinine ≥ 221 umol/L (2.5 mg/dl) or the need for chronic renal replacement therapy
   7. Significant peripheral vascular disease (PVD) accompanied by rest pain or extremity ulceration

xiii. Patient has moderate to severe aortic insufficiency without plans for correction during pump implant

xiv. Pre albumin < 150 mg/L, or Albumin < 30g/L (3 g/dL)

xv. Planned Bi-VAD support prior to enrollment

xvi. Patient has known hypo or hyper coagulable states such as disseminated intravascular coagulation and heparin induced thrombocytopenia

xvii. Participation in any other clinical investigation that is likely to confound study results or affect the study

xviii. Any condition other than HF that could limit survival to less than 24 months

7 STUDY PLAN

The study will be a prospective, multi-center, non-blinded, randomized, non-inferiority study comparing the HeartMate III LVAS to the HeartMate II LVAS. Short term use of the device will be evaluated when Subjects have been supported for 6 months, transplanted or explanted for recovery, whichever occurs first. Long term use of the device will be evaluated when Subjects have been followed for 24 months, transplanted or explanted for recovery, whichever occurs first.

a. **Missing Values and Data Conventions:** Every effort will be made to collect all required data. Missing primary endpoints will be imputed using multiple imputation techniques. Missing secondary endpoints wil not be imputed, except as described below.

b. **Multiplicity Adjustments:** No adjustments for multiplicity will be made in the analysis of secondary endpoints. No statistical claims will be made concerning secondary endpoints.

8 STATISTICAL PROCEDURES:

The HM III study is a prospective, multicenter, non-blinded, randomized study to test the success of the HM III LVAS for short term hemodynamic support, such as a bridge to cardiac transplant (BTT) or myocardial recovery, or as long term support, such as destination therapy (DT).

Since the device must be surgically implanted, the investigator cannot be blinded to the treatment. Similarly, since the Subject must be trained on driveline care and responses to warning alarms, the Subject cannot be blinded to treatment. The study design will allow for a scientifically rigorous examination of the performance and safety of the device.

In general, continuous data will be presented as the number of Subjects, mean with standard deviation, and median with minimum and maximum values. Categorical data will be reported as frequencies and percentages. Adverse events will also be reported as rates per patient year. Only adverse events that occur after the start of the implant procedure will be analyzed. Survival data will be presented using the Kaplan-Meier product limit method, as well as the percentage of Subjects who successfully reach the pre-defined study primary endpoint.

Data will be analyzed using the intent–to-treat method (ITT) defined as all randomized Subjects. Every effort will be made to avoid cross-over but in the event they occur, data will also be analyzed “as randomized” and Per Protocol for efficacy analysis and “as treated” for safety analysis and all other secondary endpoints.

Statistical analysis will be performed using SAS version 9.1 or higher.

8.1 Analysis Population

8.1.1 Intent-to-treat: All Randomized Subjects

This is the primary analysis population for the primary endpoint. Subjects are analyzed under the treatment to which they were randomized.

8.1.2 As Treated: All Treated Subjects

This is the primary analysis population for the secondary endpoints. Subjects are analyzed under the treatment they actually receive.

8.1.3 As Randomized: All Treated Subjects

This population includes only the Subjects who receive the treatment they were randomized to.

8.1.4 Per Protocol:

As Randomized patients who meet all protocol inclusion and exclusion criteria and are free of major protocol violations. Major protocol violations include:

1. Patients who sign consent after randomization or patients who sign an unapproved consent form
2. Implantation of the VAD using a technique other than sternotomy
3. Missing > 2 pre-specified visits after initial discharge
4. Missing data that may affect the primary outcome:
    i. Stroke reported but MRS never provided
    ii. Transplant or explant prior to a study endpoint but the reason for the procedure is not reported

8.2 Study Hypothesis

8.2.1 Short Term Support:

The short term study endpoint is a composite of survival to transplant, myocardial recovery or 6 months of support (whichever occurs first) free of a debilitating

stroke (modified Rankin Score > 3) or reoperation to replace the original pump. A Subject will be considered a success if they are:

- Electively transplanted or explanted for myocardial recovery prior to 6 months or
- Alive at 6 months, and
  - Have not experienced a stroke with a modified Rankin Score > 3, and
  - Have not received a device replacement or exchange, and
  - Have not received an urgent transplant due to a LVAS malfunction.

A Subject will be considered a failure if they:

- Expire prior to 6 months, or
- Experience a stroke with a modified Rankin Score > 3 prior to 6 months, or
- Have a device replaced or exchanged or deactivated for reasons other than myocardial recovery prior to 6 months, or
- Have received an urgent transplant due to a LVAS malfunction prior to 6 months, or
- Have withdrawn from the study for any reason prior to 6 months

HM III short term success rate will be compared to that of the HM II control in a non-inferiority manner. The null and alternative hypotheses are:

$$H_o: \ \pi_{HM\ III} \leq \pi_{HM\ II} - \Delta$$
$$H_A: \ \pi_{HM\ III} > \pi_{HM\ II} - \Delta$$

where $\pi_{HM\ III}$ and $\pi_{HM\ II}$ are the short term success rates of HM III and HM II, respectively, and where Δ is the non-inferiority margin.

8.2.2 Long Term Support:

The long term study endpoint is a composite of survival to transplant, myocardial recovery or 24 months of support (whichever occurs first) free of a debilitating stroke (modified Rankin Score > 3) or reoperation to replace the original pump.

A Subject will be considered a success if they are:

- Electively transplanted or explanted for myocardial recovery prior to 24 months or
- Alive at 24 months, and
  - Have not experienced a stroke with a modified Rankin Score > 3, and
  - Have not received a device replacement or exchange, and
  - Have not received an urgent transplant due to a device malfunction.

A Subject will be considered a failure if they:

- Expire prior to 24 months, or
- Experience a stroke with a modified Rankin Score > 3 prior to 24 months, or
- Have a device replaced or exchanged or deactivated for any reason other than myocardial recovery prior to 24 months, or
- Have received an urgent transplant due to a LVAS malfunction prior to 24 months, or
- Have withdrawn from the study for any reason prior to 24 months

The 24 month success rate of the HM III Subjects will be compared to the HM II control. The null and alternative hypotheses are:

$$H_o: \pi_{HM\ III} \leq \pi_{HM\ II} - \Delta$$
$$H_A: \pi_{HM\ III} > \pi_{HM\ II} - \Delta$$

where $\pi_{HM\ III}$ and $\pi_{HM\ II}$ are the long term success rates of HM III and HM II, respectively, and where Δ is the non-inferiority margin.

8.3 Randomization

Subjects will be randomized in a 1:1 fashion (1 HM III: 1 HM II). The randomization will be stratified by study center and blocked to maintain the 1:1 ratio over time. Randomization will be implemented through the Electronic Data Capture (EDC) system. Study centers will be allowed a maximum of 50 randomized Subjects. Subjects will be considered enrolled in the study upon randomization and will be included in the intent-to-treat analysis.

8.4 Sample Size

8.4.1 Assumptions

- Larger gap between the rotor and pump housing in the HM III may result in less thrombus than HM II
- Larger gap between the rotor and pump housing in the HM III may result in less pump replacement due to ingested thrombus than HM II
- HM III modular driveline may reduce pump replacements due to driveline damage or fatigue.

8.4.2 Short Term Indication

Based on a review of recent INTERMACS and Thoratec data, it is assumed that the HM II will achieve a composite success rate of 85% at 6 months. It is also assumed that the HM III will have a composite success rate of 87% due to less pump replacements at 6 months caused by thrombus or driveline issues. It will take 138 HM III and 138 HM II Subjects (276 total Subjects) to achieve 80% power to prove the HM III 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.

INTERMACS HM II data from 26 sites likely to participate in the HM III IDE study was reviewed. Eight hundred and twenty (820) patients were implanted with the HM II in 2012 at these sites and 52 (6%) received a transplant or explant due to myocardial recovery prior to 6 months. In order to have sufficient data to evaluate the 6 month success rate, an additional 9 Subjects will be randomized per arm (6% of 138) to account for these early outcomes. This results in a total of 147 Subjects randomized in each arm (294 total Subjects).

8.4.3 Long Term Indication

Based on the results from the HM II Destination Therapy IDE study, it is assumed that 50% of the HM II Subjects will successfully achieve the composite primary endpoint. It is also assumed that the HM III will have a composite success rate of 55% due to less pump replacements at 24 months caused by thrombus or

driveline issues. It will take 174 HM III and 174 HM II Subjects (348 total Subjects) to achieve 80% power to prove the HM III is non-inferior to HM II when the margin of non-inferiority (=Δ in the above null and alternative hypotheses) is -10% using the Farrington-Manning risk difference approach to non-inferiority at a one-sided alpha = 0.025.

INTERMACS HM II data from 26 sites likely to participate in the HM III IDE study was reviewed. Eight hundred and twenty (820) patients were implanted with the HM II in 2012 at these sites and 52 (6%) received a transplant or explant due to myocardial recovery prior to 6 months. In order to have sufficient data to evaluate the 24 month success rate, an additional 9 Subjects will be randomized per arm (6% of 138) to account for these early outcomes. This results in a total of 183 Subjects randomized in each arm (366 total Subjects). It is assumed that 75 HM 3 patients will achieve 730 days of support on their original pump by the time the long-term cohort has completed the long-term follow up. This will provide sufficient data to evaluate the clinical reliability of the pump. If the HM 3 is proven to be non-inferior to the HM II for the long-term indication but 75 HM 3 pumps have not achieved 730 days of support, the submission of data to the Agency will be delayed until 75 pumps with durations of at least 730 days have been evaluated and included in the dataset.

8.5 Early Safety Assessment

The HM III IDE study will include an early safety assessment in lieu of a feasibility study. The first 10 HM III Subjects enrolled in the study will be included and their data analyzed when they have achieved 30 days of support. A table describing the 30 days status of the Subjects will be prepared. Adverse events will be presented as the percentage of Subjects who experience the event, the number of events and the event rate per 30 days. The data will be presented to the DSMB and FDA for a recommendation to continue the study and to expand to remaining study centers. All Subjects included in the early safety assessment will continue to be followed per protocol and will be included in the final Short Term and Long Term analysis.

8.6 Analysis of Primary Endpoint

The HM III will be considered non-inferior to the HM II for both short and long term indications if the lower two-sided 95% confidence limit of the risk difference in the composite success between treatment arms (HM III minus HM II) is greater than -10% (“negative 10%”, where 10% is the non-inferiority Δ in the above null and alternative hypotheses). Once non-inferiority is inferred, the data will be analyzed for superiority at a one-sided 0.025 level of significance using closed testing methods via the z-test of proportions using the normal approximation to the binomial distribution. Since the short term and long term evaluations are two distinct endpoints, no adjustment for multiple comparisons is required. The long-term evaluation will only be made if the HM 3 is non-inferior to the HM II for the short-term indication, thus no adjustment to alpha will be made.

8.6.1 Primary Endpoint Stratified by Components of the Composite Endpoint

Differences in success rates between HM III and HM II will be performed for each component of the composite endpoint to evaluate if a single component is influencing the outcome. Specifically, for each component, two-sided 95%

confidence intervals of the differences and a z-test of proportions will be generated using the normal approximation to the binomial distribution.

8.6.2 Effect of Site Bias on the Primary Endpoint

In order to determine if a few superior investigational sites are influencing the primary endpoint results, a comparison of results across sites will be performed. Specifically, for each of the short term and long term outcomes, the significance of the treatment-by-site interaction effect will be assessed using logistic regression with the main effects for treatment and site, and with a treatment-by-site interaction effect. The treatment-by-site interaction effect will be tested at the 0.15 level of significance. A non-significant interaction or an interaction that is significant but only quantitative and not qualitative in nature will support the pooling of Subjects across sites for the primary analyses. Given that a number of sites will contribute only small numbers of Subjects, we will pool sites with less than 5 Subjects for the analysis.

8.6.3 Unblinded Interim Efficacy Analysis (Adaptive Design)

After 74 of the planned 147 patients per treatment group required for the analysis on the short term primary outcome are treated and followed for 6 months, an interim unblinded analysis comparing treatments on the 6-month short term primary outcome will be carried out. The short term primary outcome is the binary composite endpoint of survival to elective transplant if transplant is prior to 6 months, survival to myocardial recovery prior if recovery is prior to 6 months, or survival for 6 months of LVAD support free of a debilitating stroke (modified Rankin Score > 3) and free of reoperation to replace the pump. There will be no provision to stop the study at interim stage for overwhelming effectiveness and hence no adjustment of the significance level for the final analysis. The first purpose of the interim analysis is to calculate the power for non-inferiority, conditioned on the difference between treatments with respect to short term outcome rates and on the non-inferiority margin of 10% (or 0.10). Specifically, at the interim analysis, the conditional power for rejecting the following null hypothesis in favor of the alternative (i.e. for obtaining a non-inferiority conclusion at the final analysis for the short-term outcome) will be calculated:

$$H_0: \pi_{HM\ III} \leq \pi_{HM\ II} - \Delta$$
$$H_A: \pi_{HM\ III} > \pi_{HM\ II} - \Delta$$

where $\pi_{HM\ III}$ and $\pi_{HM\ II}$ are the short term success rates of HM III and HM II, respectively, and where Δ is the non-inferiority margin and is fixed at 10% (or 0.10). The conditional power will be calculated under the assumption that the interim observed estimate of the treatment difference is the true treatment difference. It will be calculated using the following formula as discussed in Lan and Wittes (1988):

$$1 - \Phi\left[\frac{Z_{1-\alpha} - B_{\tau} / \tau}{\sqrt{1-\tau}}\right]$$

where

a. $Z_{1-\alpha}$ is the (1-α)*100% percentile of the standard normal distribution (i.e., the critical value used to assess non-inferiority at the final analysis at overall one-sided significance level α); here, with one-sided α = 0.025, $Z_{1-\alpha}$ is set to 1.96.

b. τ is the information fraction (= proportion of patients in the first interim analysis = r/M where r is the number of patients per group in the interim analysis and M is the planned number of patients per group for the final analysis). Here, it is expected that r=74, M=147, and τ =0.503.

c. $B_\tau = Z_\tau \sqrt{\tau}$ where Z_τ = the Farrington-Manning non-inferiority test statistic calculated on the interim observed data; specifically

$$Z_t = \frac{\hat{p}_{HMIII} - \hat{p}_{HMII} - (-\Delta)}{\sqrt{\frac{\tilde{p}_{HMIII}(1-\tilde{p}_{HMIII})}{n_{HMIII}} + \frac{\tilde{p}_{HMII}(1-\tilde{p}_{HMII})}{n_{HMII}}}}$$

where

i. $\hat{p}_{HMIII}$ = the interim observed estimate of the true success rate ($\pi_{HM\ III}$) for HM III (=number of HM III subjects with success divided by number of HM III subjects in the interim analysis).

ii. $\hat{p}_{HMII}$ is the similarly defined interim observed estimate of the true success rate ($\pi_{HM\ II}$) for HM II.

iii. $\tilde{p}_{HMIII}$ and $\tilde{p}_{HMIII}$ are the interim maximum likelihood estimates of $\pi_{HM\ III}$ and $\pi_{HM\ II}$ calculated under the above null hypothesis, as shown in Farrington and Manning (1990).

iv. n_{HMIII} and n_{HMII} are the sample sizes used for the interim analysis from HM III and HM II, respectively.

v. Δ is the non-inferiority margin of 0.10.

d. Φ is the cumulative distribution function of the standard normal distribution.

Following the "promising zone" algorithm in Chen, Demets, Lan (2004), if the conditional power is <50% or >80% at the interim stage, the study will continue as is (there will be no stoppage of the study for futility nor will there be a sample size increase). If the conditional power is between 50-80% (the promising zone), the sample size will be re-estimated to achieve conditional power of 80% for the 6-month short term endpoint. . The total revised sample size per group, M` required to achieve a conditional power of 80% to assess non-inferiority at the final analysis using a non-inferiority margin of 0.10 (or 10%) is found by solving the following equation for $M$` (this formula is from Wang et al (2002), but it can also be derived algebraically from the above Lan and Wittes (1988) formula for conditional power by setting the above conditional power formula to 0.80 and solving for M'):

$$Z_{0.20}\sqrt{1-\frac{r}{M`}} + Z_\tau \sqrt{\frac{M`}{r}} - Z_{1-\alpha} = 0$$

where $Z_{0.20}$ is the 20th percentile of the standard normal distribution (= -0.84) and where all other variables in this equation are defined above. This formula assumes the interim observed effect size between treatments is the true effect size between treatments.

Note that the final sample size for the 6-month short-term outcome will NOT be decreased below the currently planned final sample size for the 6-month short-term outcome. According to Chen, Demets and Lan (2004), in order to maintain Type I error at the nominal level, the sample size will not be increased to beyond a percentage of the original sample size as determined by the bound *R*, where *R* satisfies:

$$\frac{\sqrt{1+R}\left(\sqrt{1+R}-1\right)}{\sqrt{(1+R)-t}}=\left(\left|Z_{0.20}\right| \Big/ Z_{1-\alpha}\right).$$

With $|Z_{0.20}| = 0.84$ and $Z_{1-\alpha} = 1.96$, it can be shown that $R = 1.513$, which means the sample size can increase up to 151.3% of the original planned sample size (up to 369 per group) without inflating Type I error.

Also, any sample size increase for the 6-month short term outcome will also be applied to the final sample size used to assess the long-term outcome (there will be no interim unblinded analysis on the long-term outcome). The following table displays the sample size scenarios for each of the long-term and short-term outcome under various situations:

Endpoint	Sample Size Per Group at Interim	Sample Size Per Group at Final Analysis	
		In the Event of No Sample Size Increase at Interim	In the Event of a Sample Size Increase of *X* at Interim
6-month Short Term	After 74 patients per group are treated and followed for 6 months	After 147 patients per group are treated and followed for 6 months	After 147 + *X* patients per group are treated and followed for 6 months
24-month Long Term	This endpoint will not be analyzed in the interim.	After 183 patients per group are treated and followed for 24 months.	After 183 + *X* patients per group are treated and followed for 24 months.

The analyses on sample size re-estimation will be carried out by the independent statistician (non-voting) and presented only to the DSMB by the independent biostatistician. The DSMB will inspect the results and inform the sponsor of their final decision, without necessarily stating the reason for the decision. E.g., the DSMB will inform the sponsor "Continue the study as is" without informing the sponsor as to whether the reason is because the conditional power is <50% or because the conditional power is >80%; if the DSMB recommends an increase in sample size, the DSMB will not give a reason for the increase or any details behind the recommendation until the study is complete.

8.7 Subgroup Analysis

Once the analyses comparing the treatment arms are complete, a series of subgroup analyses will be performed, assessing treatment difference within each subgroup. Each subgroup will be evaluated for the primary composite endpoint, survival, adverse events,

device malfunction, quality of life and functional status, as described above. Subgroups will include but may not be limited to:

- Gender: Males vs Females
- Race: Caucasian/White vs African-American/ Black vs Other
- Age: 18 – 59 vs 60 – 75 vs > 75 years
- Intended Use at implant as defined by Appendix 6
- VO2 max
- INTERMACS Profile
- A detailed evaluation of patients who survive to 730 days or more including the influence of the site, age, and INTERMACS profile
- Learning Curve Analysis: The first 2 patients implanted with the HeartMate 3 in centers with 4 or more HeartMate 3 patients will be compared to the later HeartMate 3 patients. Comparison will include survival and adverse events.
- Time Dependent Analysis: Patients implanted during the first 7 months of the trial will be compared to patients implanted after 7 months. Analysis will include survival and adverse events

The purpose of the subgroup analyses is not to reach a statistically significant result within each subgroup, but rather to assess consistency of treatment difference across subgroups.

8.8 Analysis of Survival and Subject Outcome

Overall survival will be assessed for each of the two treatments using the Kaplan-Meier product-limit method. Differences between treatments in survival distributions will be analyzed using a logrank test. Subjects surviving will be censored at last known follow-up time point.

A competing outcome graph will be prepared at 6 months for short term results and 24 months for long term results.

8.9 Analysis of Adverse Events

All pre-defined adverse events will be captured. Tables will be created for HM III and HM II AEs that show the by-treatment incidences of all adverse events and the by-treatment event rate per patient year of support. Serious adverse events (SAEs) will be analyzed in a similar manner as AEs. Differences in event rates between the treatment arms will be analyzed using Fisher's Exact test or Poisson regression, as appropriate.

8.10 Analysis of Device Malfunctions

All suspected HM III device malfunctions will be reported. Thoratec will ask that all explanted devices be returned for analysis. Data on device malfunctions will be analyzed and tables will be created that report the following:

- Events that are confirmed by analysis of the device by Thoratec engineers
- The component of the device involved
- Days to the malfunction
- Action taken in response to the malfunction
- Reoperations due to malfunction
- Death due to malfunction

8.11 Analysis of Pre-Implant Data

Tables will be created to define the study population at baseline. Tables will include demographics, all laboratory assessments, all hemodynamic assessment, cardiac history, INTERMACS profile, and concurrent interventions (Cardiac Resynchronization Therapy (CRT), Automatic Internal Cardiac Defibrillator (AICD), IABP, Inotropes, etc). The intended use of the device at implant will also be collected, as defined by INTERMACS (Appendix 6). Baseline data will be compared between treatment groups using unpaired t-tests or Fisher's exact test as appropriate.

8.12 Analysis of Implant and Discharge Data

Time on cardiopulmonary bypass during implant surgery will be collected and reported as a median, quartiles and range. All concurrent procedures carried out during implant surgery will be reported. Length of Stay (LOS) will be defined as the time from implant to discharge. LOS will be reported as a mean with standard deviation, median, quartiles and range. The time on cardiopulmonary bypass and LOS will be compared between treatment groups using the Wilcoxon Rank Sum test.

8.13 Analysis of Secondary Endpoints

Secondary endpoints will each be tested at the two-sided 0.05 level of significance. There will be no adjustment for multiple comparisons across the secondary endpoints. There will be no imputation of missing data for the secondary endpoints.

8.13.1 Pump Hemodynamics

The mean flow and pump index (flow/BSA) with standard deviation for the HM III and HM II Subjects will be plotted over time. At each time point, treatments will be compared using the unpaired t-test.

8.13.2 Laboratory values

Mean laboratory values with standard deviations for HM III and HM II Subjects will be plotted over time. At each time point, treatments will be compared using the unpaired t-test.

8.13.3 Rehospitalization

Time to rehospitalization and the reason for rehospitalization will be reported. Time in and out of the hospital will be reported for the HM III and HM II Subjects. Treatments will be compared on time to re-hospitalization using the log-rank test. Subjects not re-hospitalized will be censored at last known follow-up.

8.13.4 Reoperations

Time to reoperation, frequency of reoperation, and the reason for the surgery will be reported for HM III and HM II Subjects. Treatments will be compared on time to re-operation using the log-rank test. Subjects not re-operated will be censored at last known follow-up.

8.14 Analysis of Functional Status

8.14.1 NYHA

The Subjects NYHA Functional Status will be assessed by an independent assessor at baseline and then at 3, 6, 12, 18, and 24 months. At each visit, treatments will be compared on NYHA functional status and on the change from baseline functional status using the Wilcoxon Rank Sum test. The Short Term indication will be limited to the 3 and 6 month assessments. The Long Term

indication will include all assessments until 24 months or outcome, whichever occurs first.

8.14.2 Six Minute Walk Test

Subjects may not be able to walk due to heart failure, especially at baseline. Subjects unable to walk due to heart failure will receive a score of 0 meters. For all other reasons for missing data the score will remain missing and not be included in the analysis. The Six Minute Walk test will be conducted at baseline and then at months 3, 6, 12, 18 and 24 post implant. Data will be analyzed using mixed modeling by comparing the distances walked over time to the baseline distance. The Short Term indication will be limited to the 3 and 6 month assessment. The long term indication will include all assessments until 24 months or outcome, whichever occurs first.

8.15 Analysis of Quality of Life

Quality of Life will be measured using the EuroQol (EQ-5D-5L) and the Kansas City Cardiomyopathy Questionnaire (KCCQ).

8.15.1 EQ-5D-5L

The EQ-5D-5L VAS and total score will be assessed at baseline and then at 3, 6, 12, 18, and 24 months. Data will be analyzed using mixed modeling by comparing the EQ-5D-5L score at each assessment interval to the baseline score. The Short Term indication will be limited to the 3 and 6 month assessments. The Long Term indication will include all assessments until 24 months or outcome, whichever occurs first. In addition, the percentage of each component of the EQ-5D-5L will be graphically presented over time.

8.15.2 KCCQ

The KCCQ score will be assessed at baseline and then at 3, 6, 12, 18, and 24 months. Data will be analyzed using mixed modeling by comparing the KCCQ score at each assessment interval to the baseline score. The Short Term indication will be limited to the 3 and 6 month assessments. The Long Term indication will include all assessments until 24 months or outcome, whichever occurs first.

8.16 Powered secondary analysis:

In addition to the primary outcome, the study will be powered to test if HM III pump reliability is superior to HM II by analyzing the incidence of pump replacements. Randomization described in Section 13.4 will continue beyond the Subjects needed to power the primary endpoint until a sufficient sample size has been enrolled to test the secondary endpoint. The null and alternative hypotheses are:

$$H_o: \pi_{HM\ III} \geq \pi_{HM\ II}$$
$$H_A: \pi_{HM\ III} < \pi_{HM\ II}$$

where $\pi_{HM\ III}$ is the HM III pump replacement rate and $\pi_{HM\ II}$ is the HM II pump replacement rate.

Based on data contained in Thoratec's device tracking database, 7% of the HM II Subjects receive a pump replacement by 24 months. If we assume that HM III pump replacements will be reduced to 3% at 24 months, then 1028 Subjects (514 per arm) will be needed to prove superiority with a power of 80% and alpha = 0.05 (2-sided).

Once the 366 Subjects needed for the long term indication are enrolled, Thoratec will continue to randomize 662 more Subjects (331 HM III and 331 HM II) for this secondary analysis. Data for this secondary analysis is not needed for the short or long term indications, but rather will be used to provide additional labeling information.

The Subjects will be followed for 24 months or to outcome, whichever occurs first, and analyzed using the Fisher's exact test. Treatments will also be compared on time-to-pump replacement using the log-rank test where Subjects without a replacement are censored at last known follow-up. Otherwise, there will be no imputation of missing data for this analysis.

9 REFERENCES

5. Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. Stat Med 1990;9:1447-54.
6. White paper: Wang C, Keller DS, Lan KKG (2002). Sample size re-estimation for binary data via conditional power. Joint Statistical Meetings – Biopharmaceutical Section.
7. Lan KKG and Wittes J. The B-Value: A tool for monitoring data. Biometrics 1998:44:579-585.
8. Chen YH, DeMets DL, Lan KKG. Increasing the sample size when the unblinded interim result is promising. Stat Med 2004; 23:1023-1038.

Summary of Changes to the HeartMate III IDE Trial Statistical Analysis Plan		
Protocol Version	**Date**	**Revision Summary**
1.0	10/14/14	Original Protocol
2.0	01/22/16	• Updated *Analysis Population* Section (8.1) by adding definition of the *Per Protocol* population (sub-section 8.1.4), which are As Randomized patients who meet all protocol inclusion and exclusion criteria and are free of major protocol violations. • Updated *Sample Size - Long Term Indication* Section (8.4.3) by adding that 75 HM 3 patients that will achieve 730 days of support will be evaluated for the clinical reliability of the pump. If the HM 3 is proven to be non-inferior to the HM II for the long-term indication but 75 HM 3 pumps have not achieved 730 days of support, the submission of data to the Agency will be delayed until 75 pumps with durations of at least 730 days have been evaluated and included in the dataset. • Updated *Analysis of Primary Endpoint* Section (8.6) by adding the following statement "The long-term evaluation will only be made if the HM 3 is non-inferior to the HM II for the short-term indication, thus no adjustment to alpha will be made." • Added a reference to Lan and Wittes (1988) for the conditional power calculation formula in the *Unblinded Interim Efficacy Analysis (Adaptive Design)* Section (8.6.3). • Added a reference to Chen, Demets, Lan (2004) to the "promising zone" algorithm in the *Unblinded Interim Efficacy Analysis (Adaptive Design)* Section (8.6.3). • Added a reference to Wang et al (2002) to the revised sample size calculation formula in the *Unblinded Interim Efficacy Analysis (Adaptive Design)* Section (8.6.3). Also added the following statement in addition to the aforementioned reference: "it can also be derived algebraically from the above Lan and Wittes (1988) formula for conditional power by setting the above conditional power formula to 0.80 and solving for M'." • The statement that the sample size will not be increased to >1000 per group in the *Unblinded Interim Efficacy Analysis (Adaptive Design)* Section (8.6.3) was updated with the details on calculation and references below: According to Chen, Demets and Lan (2004), in order to maintain Type I error at the nominal level, the sample size will not be increased to beyond a percentage of the original sample size as determined by the bound R, where R satisfies: $$\frac{\sqrt{1+R}\,(\sqrt{1+R}-1}{\sqrt{(1+R)-t}} = (\frac{\lvert Z_{0.20}\rvert}{Z_{1-\alpha}})$$ With $\lvert Z_{0.20}\rvert$= 0.84 and $Z_{1-\alpha}$ = 1.96, it can be shown that R = 1.513, which means the sample size can increase up to 151.3% of the original planned sample size (up to 369 per group) without inflating Type I error. • Added Learning Curve Analysis (the first 2 patients implanted with the HM 3 in centers with 4 or more HM 3 patients compared to later HM 3 patients for survival and adverse events), Time Dependent Analysis (patients implanted during the first 7 months of the trial will be compared to patients implanted after 7 months for survival and adverse events), a detailed evaluation of patients surviving to 730 days or more to the *Subgroup Analysis* Section (8.7). • Two additional references to Lan and Wittes and to Chen, DeMets, and Lan were added to the *Reference* Section (9).