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NCT Number: NCT02892955
MOMENTUM 3 CAP
Multi-Center Study of MagLev Technology in Patients Undergoing MCS Therapy With HeartMate 3™ Continued Access Protocol: Post-Approval Continued Follow-up
Study Document No: ABT-CIP-10440
Version A
Date: 14-JAN-2019

Sponsor

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United States

Thoratec® LLC

MOMENTUM 3
Multi-Center Study **o**f **M**agLev T**e**chnology i**n** Pa**t**ients **U**ndergoing **M**CS Therapy with HeartMate **3** ™

Continued Access Protocol: Post-Approval Continued Follow-up

PMA P160054

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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)
CAP ..... Continued Access Protocol
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
FEV1..... Forced Expiratory Volume in One
Second FVC..... Forced Vital Capacity
FWA..... Federal Wide Assurance

LIST OF ABBREVIATIONS

GI..... Gastrointestinal
GLP ..... Good Laboratory Practices
H0..... Null Hypothesis
HA..... 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
PAS..... Post-Approval Study
PI ..... Principal Investigator
PMA..... Premarket Approval
PRBC..... Packed Red Blood Cells
PT ..... Prothrombin Time
PTT..... Partial Thromboplastin Time

LIST OF ABBREVIATIONS

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, LLC
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

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[1-3,9]. 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 MOMENTUM 3 Investigational Device Exemption (IDE) clinical trial is a prospective, multicenter, randomized pivotal study with an innovative trial design comparing the HeartMate 3 (HM3) Left Ventricular Assist System (LVAS) with the HM II LVAS in advanced-stage heart failure patients. It was conducted at 69 US investigative centers and enrolled 1028 patients in a 1:1 randomized fashion stratified by site.

The HM3 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). This study included multiple pre-specified cohorts: 1. A Safety Cohort (N=30) in lieu of a pilot study, 2. A Short Term (ST) Cohort of first 294 patients (including the 30 patients in the Safety Cohort) powered to demonstrate non-inferiority of HM3 to HM II at 6 months for survival free of debilitating stroke and device replacement, 3. A Long Term (LT) Cohort of first 366 patients (including patients in the ST Cohort) powered to demonstrate non-inferiority at 2 years, 4. A Full Cohort of all 1028 patients powered to demonstrate superiority of HM3 to HM II for pump replacement at 2 years. Adults with an ejection fraction ≤ 25%, in New York Heart Association (NYHA) Class III with dyspnea on mild physical activity or NYHA Class IV, inotrope dependent or with Cardiac Index (CI) ≤ 2.2 l/min/m2 while not on inotropes and who were either on optimal medical management for 45 of 60 days or listed for transplant were enrolled in this study after obtaining signed informed consent.

The first patient was enrolled in MOMENTUM 3 on September 2, 2014. Enrollment in the ST cohort was completed on October 14, 2015 with 6-month follow-up completed on April 13, 2016. A Premarket Approval (PMA) application in support of a short-term indication for use was submitted to FDA and approval was received in August 2017. The LT Cohort completed enrollment on November 7, 2015 and the full trial cohort (n=1028) completed enrollment on August 23, 2016; 24-month follow-up for the LT cohort was completed in November 2017 and in September 2018 for the full trial cohort.

In August 2016, following completion of enrollment in the full cohort of MOMENTUM 3, FDA approved a Continued Access Protocol (CAP). Enrollment in the CAP began on August 31, 2016. Approval for the long-term indication was received from the FDA on October 18, 2018. The last implant in CAP occurred on October 25, 2018 for a total enrollment of 1685 patients. As a condition of approval, all patients enrolled in the CAP

study will complete the 24 month follow-up specified in this protocol to fulfil a post-approval study (PAS) requirement.

2 INDICATIONS FOR USE

The HM3 LVAS is indicated for providing short- and long-term mechanical circulatory support (e.g., as bridge to transplant or myocardial recovery, or destination therapy) in patients with advanced refractory left ventricular heart failure.

3 DEVICE DESCRIPTION AND THEORY OF OPERATION

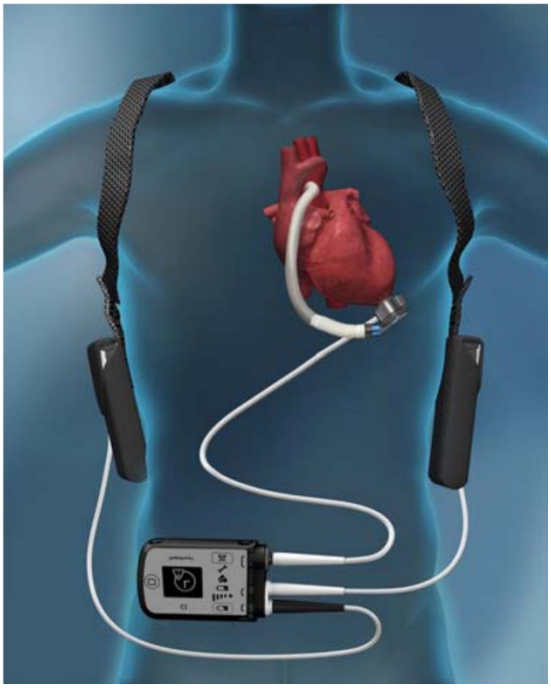
The HM3 LVAS is a set of equipment and materials that together comprise a medical device designed to provide therapeutic benefit to those afflicted with advanced heart failure. In service, the LVAS assumes some or all of the workload of the left ventricle, thereby restoring the patient's systemic perfusion 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. Subjects implanted with HM3 will be discharged from the hospital with the MPU, without the system monitor, as their primary source of power.

The HM3 LVAD is part of the HM3 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 HM3 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.

A complete list of HM3 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 HM3 IFU.

4 DEVICE TESTING

4.1 Device Testing: Bench

The HM3 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 HM3 IFU 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 HM3 LVAS. The in vivo tests verified:

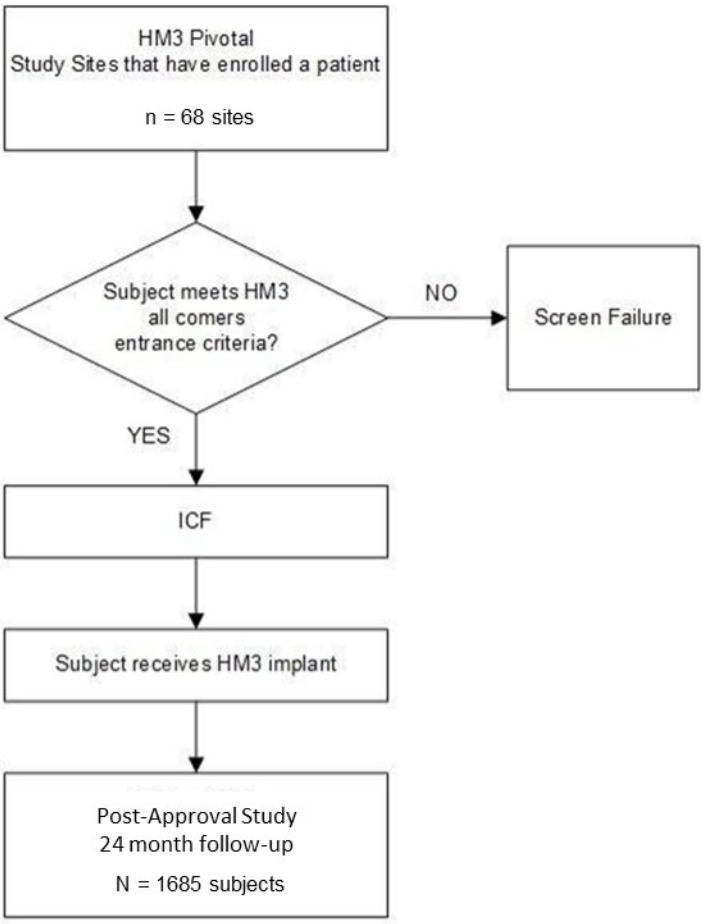
- Surgical human factors and usability data
- Device performance characterization
- Biological effects (thrombosis, hemolysis, bleeding)

Testing was conducted under Good Laboratory Practices (GLP) Guidelines[8].

5 STUDY DESIGN

The study will be a single arm, prospective, multi-center study for continued evaluation of safety and clinical performance of the HM3 LVAS. Subjects who receive a device exchange to any device other than HM3, at any time during the study, will be withdrawn from the study and will not be followed any further in the trial. This study fulfills a PAS requirement as part of the FDA condition of approval for the long-term indication.

Figure 2 – Study Flow



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 at 68 clinical sites. A total of 1685 subjects were enrolled in the MOMENTUM 3 CAP.

8 STUDY DURATION

Enrollment in the study was completed after 26 months. All Subjects will be followed for 24 months or to outcome (transplant, explant, or death), whichever occurs first.

9 STUDY OBJECTIVES

9.1 Primary Study Objective

The primary objective of the study is to continue to evaluate the safety and clinical performance of the HM3 LVAS for the treatment of advanced, refractory, left ventricular heart failure.

10 CLINICAL STUDY ENDPOINTS

All endpoints will be descriptively compared to the arms of the MOMENTUM 3 IDE trial.

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

11 INCLUSION CRITERIA

1) Subject or legal representative has signed Informed Consent Form (ICF)
2) Age ≥ 18 years
3) BSA ≥ 1.2 m2
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/m2, 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 FEV1/FVC < 0.7, and FEV1 <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 ≥ 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
19) Patients actively listed for heart transplant (this exclusion applies only after commercial approval of the HM3 for short-term use)

13 DATA ANALYSIS AND STATISTICAL ISSUES/JUSTIFICATION FOR STUDY DESIGN

13.1 General Statistical Analysis Plan

The HM3 continued access study will investigate the continued safety and clinical performance of the HM3 LVAS for short term hemodynamic support, such as a bridge to cardiac transplantation (BTT) or myocardial recovery, or for long term support, such as destination therapy (DT). It is a single arm, prospective, multicenter, study.

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. Missing data will not be imputed except as described below.

Quality of Life and functional improvement will be compared to baseline scores using a mixed model or a Wilcoxon test, as appropriate.

All data will be considered adjunctive data to the MOMENTUM 3 IDE trial and will be presented descriptively as a separate cohort.

13.2 Sample Size

CAP enrollment completed in October 2018 for a total of 1685 subjects.

13.3 Analysis of Descriptive Endpoints

All endpoints will be descriptively compared to the arms of the MOMENTUM 3 IDE trial.

Descriptive endpoints include:

- Composite of Survival to transplant, recovery or LVAD support free of debilitating stroke (Modified Rankin Score >3) or reoperation to replace the pump at 6 and 24 months
- Quality of Life as measured by EuroQoL 5D-5L (EQ-5D-5L) and Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Functional status as measured by the 6-minute walk test (6MWT) and NYHA classification
- Frequency and incidence of all re-operations
- Frequency and incidence of all rehospitalizations
- Frequency, incidence and rates of pre-defined anticipated adverse events
- Frequency and incidence of device malfunctions
- Frequency and incidence of pump replacement

- Overall Survival

13.4 Analysis of Adverse Events

All pre-defined adverse events will be captured. Tables will be created that show the incidences of all adverse events and the event rate per patient year of support. Serious adverse events (SAEs) will be analyzed in a similar manner as AEs.

13.5 Analysis of Device Malfunctions

All suspected HM3 device malfunctions will be reported. The Sponsor 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 Sponsor 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

13.6 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.

13.7 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.

13.8 Analysis of Functional Status

13.8.1 NYHA

The Subjects NYHA Functional Status will be assessed by an independent assessor at baseline and then at 1, 6, 12, 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.

13.8.2 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, 6, 12, and 24 post implant. Data will be analyzed using mixed modeling by comparing the distances walked over time to the baseline distance.

13.9 Analysis of Quality of Life

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

Cardiomyopathy Questionnaire (KCCQ).

13.9.1 EQ-5D-5L

The EQ-5D-5L VAS and total score will be assessed at baseline and then at 1, 6, 12, 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. In addition, the percentage of each component of the EQ-5D-5L will be graphically presented over time.

13.9.2 KCCQ

The KCCQ score will be assessed at baseline and then at 6, 12, and 24 months. Data will be analyzed using mixed modeling by comparing the KCCQ score at each assessment interval to the baseline score.

13.10 Analysis of Blood Pressure

The accuracy of various blood pressure (BP) techniques will be evaluated including arterial line, automated BP cuff and Doppler. To evaluate the accuracy of the automated cuff, systolic blood pressure (SBP) and diastolic blood pressure (DBP) will be correlated to the same measurements obtained from the arterial line. Similarly, the Doppler measurement will be correlated individually to SBP, DBP, as well as the mean arterial pressure (MAP) derived from the arterial line. Doppler BP will also be correlated with the automated cuff measurements. The correlation of MAP and pulse pressure with death, stroke, bleeding, and symptomatic dizziness will also be evaluated.

13.11 Analysis of Echocardiographic Data

Paired t-test testing or Wilcoxon signed rank testing (for correlated data) will be used to compare aortic valve (AV) opening duration and degree of opening with pulse pressure (obtained from BP measurement) and/or pulse perception (pulse yes or no) at each follow-up period. Events will be calculated as event rates and compared based on dichotomized AV function (to be determined based on data distribution).

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 OPTIONAL BIOBANK SUBSTUDY

The Biobank Substudy is an optional substudy of the MOMENTUM 3 CAP.

The proposed research will aim to address current gaps in knowledge in regards to molecular changes with LVAD placement by creating a biobank of blood and urine samples from a subset of subjects enrolled in the MOMENTUM 3 CAP. The long-term aim of this study is to assess longitudinally blood and urine biomarkers in subjects with stage D HF who are undergoing implantation of LVADs. This study design will allow for an exploration of the levels and variability of known biomarkers at different stages of mechanical circulatory support and allow for the discovery of novel markers in the future. This collection for future medical research is intended to expand translational R&D capability and will support future research aims that will advance our understanding of advanced HF and options for treatment.

See Appendix 7 for a complete description of the Biobank Substudy.

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

Subject who meets all inclusion and no exclusion criteria at the time written informed consent is obtained, and is implanted with the HM3 LVAS will be considered enrolled in this study
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.

16.2 Baseline Assessments

The following baseline assessments will be performed within 30 days prior to implant (refer to Table 2 – Schedule of Events 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)
13. Blood and Urine Sample Collection (only for optional Biobank Substudy)

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
4. HM3 Pump Log files (pump period log, pump event log, controller period log, and controller event log) will be submitted to the Sponsor (only if a pump-related or possibly related AE or malfunction has occurred)
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)

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 the Sponsor (only if a pump-related or possibly related AE or malfunction has occurred)
2. Echocardiogram or transesophageal echocardiogram (TEE): LVEF, LVEDD, LVESD, AV opening, AI, MR, TR including severity and/or grade (can be performed on post-operative day 0 (post-implant) +2 days). Protocol for echocardiographic assessments as well as additional data to be acquired are described in section 17.8.5
3. Blood Pressure (please refer to section 17.8.4 for details on data collection)

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 (including blood pressure – see section 17.8.4)
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. Protocol for echocardiographic assessments as well as additional data to be acquired are described in section 17.8.5
7. Pump Parameters
8. HM3 Pump Log files (pump period log, pump event log, controller period log, and controller event log) will be submitted to the Sponsor (only if a pump-related or possibly related AE or malfunction has occurred)
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 (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)
15. Blood and Urine Sample Collection (only for optional Biobank Substudy)

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 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 (including blood pressure – please see section 17.8.4)
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. Protocol for echocardiographic assessments as well as additional data to be acquired are described in section 17.8.5
8. NYHA Classification (determined by an independent assessor defined as an advanced practice practitioner other than the treating investigator)
9. Pump Parameters
10. HM3 Pump Log files (pump period log, pump event log, controller period log, and controller event log) will be submitted to the Sponsor (only if a pump-related or possibly related AE or malfunction has occurred)
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 (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, 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 (including blood pressure, please see section 17.8.4)
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. Protocol for echocardiographic assessments as well as additional data to be acquired are described in section 17.8.5
7. NYHA Classification (determined by an independent assessor defined as an advanced practice practitioner other than the treating investigator)
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) (180 Days only)
11. Pump Parameters
12. Rehospitalizations
    a. If rehospitalized, collect UB-04 form
13. HM3 Pump Log files (pump period log, pump event log, controller period log, and controller event log) will be submitted to the Sponsor (only if a pump-related or possibly related AE or malfunction has occurred)
14. Occurrence of AEs (date of adverse event, determination of the seriousness and/or relation to the device, resolution of the adverse event)
15. Device Malfunctions
16. Reoperations/Operative procedures
17. Pump Replacements/Explants/Device Exchanges
18. Driveline Management Assessment
19. 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)
20. Blood and Urine Sample Collection (only for optional Biobank Substudy)

16.7.2 Clinic Follow-up Post-implant: 360 Days (+/- 30 days) for 12 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 (including blood pressure – see section 17.8.4)
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. Protocol for echocardiographic assessments as well as additional data to be acquired are described in section 17.8.5
7. NYHA Classification (determined by an independent assessor defined as an advanced practice practitioner other than the treating investigator)
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. Pump Parameters
12. Rehospitalizations
    a. If rehospitalized, collect UB-04 form
13. HM3 Pump Log files (pump period log, pump event log, controller period log, and controller event log) will be submitted to the Sponsor (only if a pump-related or possibly related AE or malfunction has occurred)
14. Occurrence of AEs (date of the adverse event, determination of seriousness and/or relation to device, resolution of the adverse event)
15. Device Malfunctions
16. Reoperations/Operative procedures
17. Pump Replacements/Explants/Device Exchanges
18. Driveline Management Assessment
19. 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 Table 2 – Schedule of Events.

16.8 Additional Data Collection

16.8.1 Pump Log Files

Pump parameters and pump logs must be submitted when any pump-related or possibly related AE or malfunction occurs. In addition, the Sponsor may periodically collect pump log files, 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 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 the Sponsor.

16.8.3 Blood Pressure Data

Accurate and precise noninvasive blood pressure (BP) measurement is a challenge for patients supported on continuous flow LVADs. Prior reports have demonstrated variability in BP accuracy in patients supported with a Heartmate

II LVAD when automated cuff and Doppler measures are employed[15]. Furthermore, there are several different automated cuff machines and a direct comparison of accuracy of different manufacturers has not been undertaken.

BP data is already being collected as part of the MOMENTUM 3 protocol, however as part of the CAP, additional data on BP is being collected in order to further the understanding of the accuracy of BP measurement techniques in HM3 subjects. The following data will be collected as part of this CAP:

- BP measurement utilizing the arterial line (gold standard): systolic BP (SBP)/diastolic BP (DBP), mean, and pulse pressure (PP=SBP-DBP). These measurements will be evaluated directly from the arterial line, and 3 measurements will be obtained for each subject within 3 minutes of each other. This data will be collected only if an arterial line is already in place.

- Automated cuff BP: BP Cuff type, SBP/DBP, and mean. These values will be obtained no more than 3 minutes apart for 3 measures. If the cuff is unable to read a pressure, an X will be documented as a failure.

- Doppler BP: These values will be obtained no more than 3 minutes apart for 3 measures. Equal Doppler BP measurements in both arms will be ensured at the time of Doppler BP measurement.

- Documentation of palpable radial pulse (≥1 in 5 seconds) for evidence of pulsatility.

- Documentation of any dizziness symptoms associated with hypotension or hypertension

If possible, BP measurement utilizing the 3 techniques will be done at the same time to allow for a direct comparison.

16.8.4 Echocardiographic Data

The degree and duration of AV opening is influenced by a number of parameters including the LVAD pump speed, native LV contractility, volume status (pre-load) and peripheral vascular resistance (afterload). Recent guidelines, albeit based on a paucity of data, recommend, that the pump speed be set low enough to permit at least intermittent AV opening. Potential and theoretical problems associated with persistent AV closure include the following: aortic fusion and development of de novo aortic insufficiency, aortic root status and clot formation and thromboembolic events, decreased AV pulsatility associated AVM formation and GI bleeding. Potential and theoretical problems associated with intermittent or AV opening with every cardiac cycle includes partial LV unloading and recurring and/or persistent clinical heart failure and relatively “low flow” with lower pump speeds and associated pump thrombosis. Although these mentioned clinical problems are multifactorial in underlying etiology a clearer understanding of AV function based on a prospective, multicenter protocol (MOMENTUM 3) is needed.

Echocardiographic data is already being collected as part of the MOMENTUM 3 at regular follow-up intervals. In order to further the understanding of the impact of AV function on clinical outcomes in HM3 subjects, additional data will be collected as part of the CAP. It is recommended that the Echocardiography data be acquired using M-Mode at a sweep speed of 25-50 mm/sec. When the AV opening duration is relatively constant, a faster sweep speed (eg, 75-100 mm/s) may be appropriate for the duration of 60 seconds. The following assessments should be made:

- Duration of AV opening (ms): Measured from the same M-Mode acquisitions using the average of 60 seconds to report an average value as well as a minimum and maximum AV opening duration
- AV opening status: Characterized into 3 types (opening every cardiac cycle, intermittent opening, and closed every beat)
- AV opening area: Degree of AV opening in mm as an average of 60 seconds as well as minimum and maximum values
- Additional Echocardiographic data: Left Ventricular Outflow Tract Time Velocity Integral (TVI) and AV velocities (if present), aortic insufficiency grade based on standard recommendation including the LVOT jet width/height ratio, LVEDP by AI jet, inflow and outflow cannula systolic and diastolic velocities, and RV systolic function (qualitative and quantitative) and RV size (qualitative and quantitative).

16.8.5 Blood and Urine Samples (Optional Biobank Substudy)

The biostorage plan calls for 5 aliquots of serum, 10 aliquots of plasma (5 EDTA, 5 citrate) and 5 aliquots of urine. Each aliquot will be at least 1 ml, and up to 1.5 ml.

DNA will not be collected as part of this study. Blood and urine will be drawn at the pre-specified times for the measurement of blood and urine markers of coagulation dysfunction, fibrosis, inflammation, and endothelial dysfunction.

See Appendix 7 for a complete description of the Biobank Substudy.

17 ANTICOAGULATION

Subjects implanted with the HM3 must be properly anticoagulated to decrease the possibility of thromboembolism and/or pump thrombosis. Anticoagulation guidelines are provided in the 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 HM3 LVAS. Guidelines for infection control and driveline management are provided in the 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 the Sponsor. 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 HM3 LVAD associated complications.

21 DEVICE RETRIEVAL AND ANALYSIS

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

Any system component other than the pump, (for example: controller, MPU, batteries) associated with any suspected device malfunction must also be returned to the Sponsor 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 HM3
- Subject is not implanted with device after consent
- Subject is lost to follow-up

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

23 RISKS

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.

Table 1 shows the incidence rates of adverse events in patients implanted with HM3 in the MOMENTUM 3 IDE clinical trial. These rates and additional results from the clinical trial are summarized in the IFU.

Table 1 – Incidence Rates of Adverse Events

Adverse Event	At 6 Months: HM3 Short Term Cohort	At 24 Months: HM3 Long Term Cohort
Death	11%	16%
Major infection	42%	55%
Localized	30%	37%
Sepsis	9%	14%
Driveline	12%	24%
Pump pocket or pseudo pocket	1%	1%
Pump or pump components	0%	0%
Bleeding	33%	43%
Bleeding requiring surgery	10%	12%
Gastrointestinal bleeding	16%	27%
Cardiac arrhythmia	31%	38%
Ventricular arrhythmia	18%	24%
Supraventricular arrhythmia	15%	18%
Both (ventricular and supraventricular arrhythmia)	1%	1%
Right heart failure	30%	32%
Right ventricular assist device (RVAD)	3%	3%
Respiratory failure	22%	24%
Renal dysfunction	11%	13%
Stroke	8%	10%
Hemorrhagic stroke	3%	4%
Ischemic stroke	5%	6%
Debilitating stroke	6%	7%
Other neurological event	6%	12%
Encephalopathy	2%	3%
Seizure	3%	3%
Transient ischemic attack (TIA)	1%	3%
Other[1]	1%	3%
Hepatic dysfunction	5%	4%
Psychiatric episode	5%	5%
Venous thromboembolism	5%	5%

Hypertension	3%	6%
Arterial non-CNS thromboembolism	2%	2%
Pericardial fluid collection	2%	2%
Myocardial infarction	1%	1%
Wound dehiscence	1%	1%
Hemolysis (not associated with suspected device thrombosis)	1%	1%
Suspected device thrombosis	0%	1%
Other adverse events	50%	70%

[1]*Other includes anoxic brain injury, traumatic brain injury, and intracranial bleed due to trauma.*

The HeartMate 3 LVAS has been approved by the FDA for a short- and long-term support.

Residual risks associated with the HM3 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 IFU.

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

25 BENEFITS

The HM3 LVAS has been shown to provide safe and effective hemodynamic support in advanced heart failure Subjects. Results from the LT cohort of the MOMENTUM 3 IDE trial show that the HM3 LVAS is superior to the HM II LVAS as assessed by the primary endpoint of survival free of debilitating stroke or reoperation to replace the pump at two years. Subjects in both arms of the trial demonstrated significant improvement in functional status and quality of life compared to pre-implant baseline[16].

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 the Sponsor.

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.

The Sponsor 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 the Sponsor for approval, prior to submitting to the IRB. Copies of the IRB submission and approval, including the approved ICF, must be forwarded to the Sponsor 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 the Sponsor 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 the Sponsor. 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 the Sponsor.

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 signatures7 (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 Sponsor administrator for all study personnel. The Investigator must ensure that the observations and study findings are recorded correctly and completely in the eCRFs. For each subject, a final signature page must be signed and dated by the authorized personnel attesting to the accurate completion of the eCRFs.

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 HM3 LVAS is now a commercially approved device. Commercial devices will comply with tracking provisions of Section 519(e) of the FD&C Act, 21 U.S.C. 360i(e) and in accordance with 21 CFR Part 821.Medical Device Tracking Requirements.

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, 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 the Sponsor, 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 the Sponsor:

- 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
- Sponsor Correspondence
- Annual/Semi-annual Regulatory Reports
- Documentation of Training
- Monitoring Visit Log
- Device Accountability (for devices used prior to October 25, 2018)
- 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 the 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

The Sponsor will submit Study progress reports as required by 21 CFR 812.150(b)(5) to all reviewing IRBs at least yearly. The Sponsor 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). The Sponsor 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 117.

The investigator must not dispose of any records relevant to this study without either (1) written permission from the Sponsor or (2) providing an opportunity for the Sponsor 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 the Sponsor 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 the Sponsor. Throughout the study, the Investigator shall provide the Sponsor 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 the Sponsor in order to allow the data to be pooled.

30 INSURANCE

The Sponsor 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 Clinical Events Committee (CEC):

An independent CEC comprised of experienced experts in the field, will review and adjudicate endpoint 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

The sites and the investigators include those who have been trained on the MOMENTUM 3 Clinical trial with the site having enrolled at least one patient in the MOMENTUM 3 study.

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 have

undergone training by the Sponsor or designee, and documentation of that training will have been maintained. The 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

The Sponsor is responsible for monitoring the study. The Sponsor 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, the Sponsor 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, the Sponsor 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.

31.6 Investigator and/or Study Site Termination/Suspension

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

The Sponsor 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, the Sponsor will notify the appropriate regulatory authority, and/or other participating centers as required by local and national regulations.

31.7 Early Study Termination

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

The study could be prematurely discontinued in the following cases:

- New findings about HM3 LVAS 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 the Sponsor

32 EMERGENCY CONTACTS

The Sponsor 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 STUDY VISIT SCHEDULE

Table 2 – Schedule of Events

	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)	180 Days Post Implant (+/- 30 days)	360 Days Post Implant (+/- 30 days)	720 Days Post Implant (+/- 30 days)	As Occurs
Inclusion/ Exclusion	X										
Enrollment	X										
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	
Physical Exam		X									
Vital Signs[2]		X		X[18]	X	X	X	X	X	X	
Hemodynamic Measurements[3]		X									
Laboratory Assessments		X			X	X	X	X	X	X	
Echocardiogram		X		X[14]	X	X	X	X	X	X	
ECG		X									
Modified Rankin Score[16]		X	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	
INTERMACS Profile[15]		X									
6 Minute Walk Test		X					X	X	X	X	
EQ-5D-5L		X					X	X	X	X	
KCCQ		X						X	X	X	
VO_2 Max[10]		X									
Blood & Urine Collection[17]		X			X		X	X			
Implant Data/CPB Time/Blood			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)	180 Days Post Implant (+/- 30 days)	360 Days Post Implant (+/- 30 days)	720 Days Post Implant (+/- 30 days)	As Occurs
Products											
HM3 Pump Parameters[7]			X		X	X	X	X	X	X	X[7]
Concurrent Procedures at Pump Implant			X								X
Subject Status					X	X	X	X	X	X	X
Subject Outcome					X	X	X	X	X	X	X
ICU Time						X					
Rehospitalizations							X	X	X	X	X
HM3 Pump Log Files[8]			X[13]	X[13]	X[13]	X[13]	X[13]	X[13]	X[13]	X[13]	X[13]
Adverse Events[4]			X		X	X	X	X	X	X	X
Device Malfunctions[4]			X		X	X	X	X	X	X	X
Operative Procedures[4]					X	X	X	X	X	X	X
Pump Replacements / Explants / Exchanges 4					X	X	X	X	X	X	X
Driveline Management Assessment					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] *HM3 Pump Parameters include: Pump Flow, Pump Speed, Pulsatility Index and Pump Power. In addition to defined scheduled collection of pump parameters, they must also be submitted when any pump-related or possibly related AE or malfunction occurs.*
[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] *Pump logs must be submitted when any pump-related or possibly related AE or malfunction occurs.*
[14] *Post-operative TEE is also acceptable; can be performed POD 0 (post-implant) + 2 days.*
[15] *INTERMACS profile to be assessed immediately prior to implantation*
[16] *Must be performed by an independent assessor; defined as an independent, trained, and certified clinician*
[17] Applies only to subjects participating in the optional Biobank substudy
[18] Blood pressure only

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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 the Sponsor 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:

<u>Acute Renal Dysfunction</u>
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.

<u>Chronic Renal Dysfunction</u>
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.

   b. 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.

8. 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.

APPENDIX 7: BIOBANK SUBSTUDY CLINICAL INVESTIGATION PLAN

Serum, Plasma, and Urine Biobank of Continuous Flow LVAD Recipients

MOMENTUM 3 CAP SUBSTUDY CLINICAL INVESTIGATION PLAN

Sponsored By:

Thoratec, LLC
Pleasanton, CA

Thoratec is the sponsor of the MOMENTUM 3 and the MOMENTUM 3 CAP Trials and is a wholly owned subsidiary of Abbott.

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LIST OF ABBREVIATIONS

6MWT	6 Minute Walk Test
CAP	Continued Access Protocol
cc	Milliliter (cubic centimeter)
CRF	Case Report Form
CV	Cardiovascular
EDTA	Ethylenediaminetetraacetate
ELISA	Enzyme-linked Immunosorbent Assay
FDA	Food and Drug Administration
g	times gravity (also known as relative centrifugal force)
HF	Heart Failure
HM3	Heartmate 3
ICF	Informed Consent Form
IDE	Investigational Device Exemption
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
IRB	Institutional Review Board
LVAD	Left Ventricular Assist Device
LVAS	Left Ventricular Assist System
ml	Milliliter
QOL	Quality of Life
ul	Microliter
VAD	Ventricular Assist Device

1 STUDY SYNOPSIS

STUDY SYNOPSIS	
Title:	Serum, Plasma, and Urine Biobank of Continuous Flow LVAD Recipients: A MOMENTUM 3 Continued Access Protocol (CAP) Substudy
Acronym:	MOMENTUM 3 Biobank
Purpose:	The purpose of this study is to establish a biobank of serum, plasma, and urine from subjects in the MOMENTUM 3 CAP.
Objective:	***Primary Objective*** To establish a biobank of blood and urine samples at various time points pre- and post LVAD placement, which can be used for future assessment of cardiovascular (CV) specific biomarkers including potential analyses of coagulation system, HF biomarkers, etc. ***Exploratory Objectives*** • To correlate biomarkers with echocardiographic parameters • To find relationships between CV biomarkers and risk of thrombosis/bleeding • To find relationships between CV biomarkers and hospitalization/death
Endpoints:	The establishment of a biobank repository of MOMENTUM 3 CAP subject plasma, serum and urine samples.
Design:	This substudy is a longitudinal, multi-center, single-arm study exploring blood and urine expression levels of CV biomarkers in subjects who are undergoing LVAD implantation. Subjects will have urine and blood samples taken at baseline, 7, 30, and 180 days post-implant.
Devices Used:	HeartMate 3 Left Ventricular Assist System (LVAS)
Study Population	The study will include 200 subjects who are enrolled in the MOMENTUM 3 CAP, who elect to participate in the MOMENTUM 3 Biobank.

STUDY SYNOPSIS	
Inclusion/Exclusion Criteria	***Inclusion Criteria*** 1. Subject or legally authorized representative has signed the Informed Consented Form (ICF) for the MOMENTUM 3 CAP 2. Subject or legally authorized representative has signed the ICF for the MOMENTUM 3 Biobank ***Exclusion Criteria*** 1. Inability to have pre-operative blood draw performed
Sample Collection	The current biostorage plan calls for 5 aliquots of serum, 10 aliquots of plasma (5 EDTA, 5 citrate) and 5 aliquots of urine. Each aliquot will be at least 1 ml, and up to 1.5 ml.
Sample Analysis	Once the biobank is established, the MOMENTUM 3 investigators will be able to submit proposals to utilize the biobank for sample analysis. A biobank subcommittee will evaluate and make assessments on these study proposals.

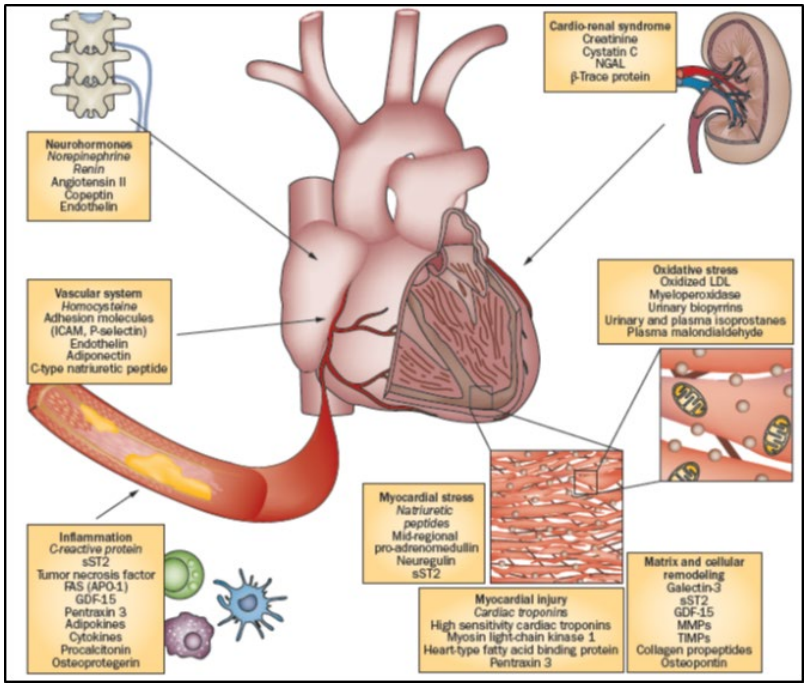
2 INTRODUCTION

Of the approximately 5.8 million Americans with heart failure (HF), up to 10% have stage D HF, defined as symptoms refractory to medical therapy. These patients face a grave prognosis, with mortality rates approaching 50%, and treatment options limited to cardiac transplantation, left ventricular assist devices (LVADs), and hospice care. Since transplantation is limited to <2% of advanced HF patients due to lack of sufficient donor organs and strict eligibility criteria, LVADs are increasingly being used to treat this patient population, and implantations exceeded heart transplants for the first time in 2012.

Whereas stage D HF can be the outcome of several etiologies of cardiac disease, it is characterized by excessive hemodynamic demands on the left ventricle that include further adverse remodeling. On a molecular level, this results in dysfunction in several interconnected biological pathways that promote disease progression (Figure 1) (1). Biomarkers representative of these processes are readily testable and reflect the degree of myocardial stress, fibrosis, fluid homeostasis, renal, and metabolomic dysfunction present in HF. Although less dramatic than cardiac replacement, LVAD therapy can restore normal cardiac hemodynamics and potentially lead to normalization of molecular measures of HF. However, few studies have comprehensively measured changes in HF biomarkers and metabolites in patients after LVAD support.

There are numerous reasons for improved understanding of molecular changes with LVAD placement in patients with HF; these include understanding risk factors for stroke, infection, bleeding, optimization of VAD interactions with the cardiovascular system, and the potential for myocardial recovery. Thus far, few studies have managed to study the molecular effect of LVAD support, leading to inadequate information about the biological interactions between the support device and the patient with advanced HF. This has likely hampered the development of better devices and the better management of current devices.

Figure 1 – Stage D HF Results in Dysfunction in Several Interconnected Biological Pathways that Promote Disease Progression (1)



1. Ahmad T, Fiuzat M, Felker GM, O'Connor C: Novel biomarkers in chronic heart failure. Nat Rev Cardiol 2012;9:347-59.

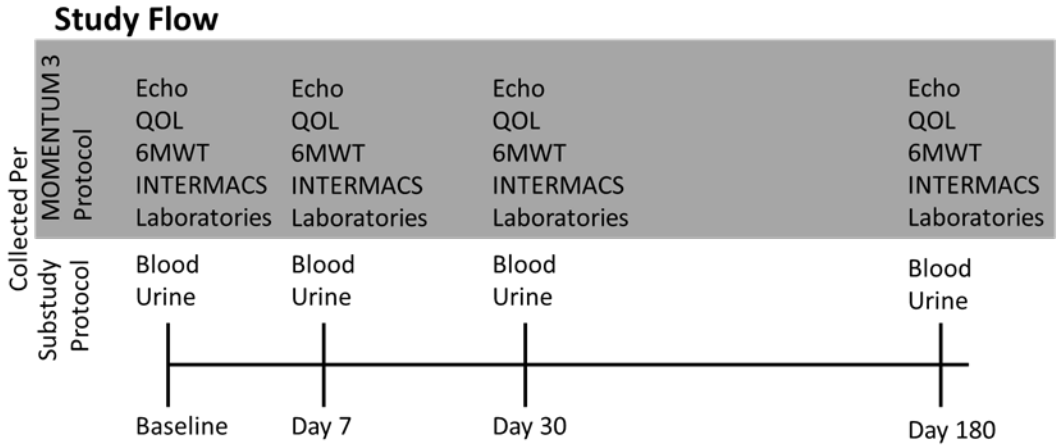
3 SUBSTUDY DESIGN

The proposed research will aim to address current gaps in knowledge in regards to molecular changes with LVAD placement by creating a biobank of blood and urine samples from a subset of subjects enrolled in the MOMENTUM 3 CAP. The MOMENTUM 3 CAP is a prospective, multicenter, single-arm, continuation of the MOMENTUM 3 IDE clinical trial. The long-term aim of this study is to assess longitudinally blood and urine biomarkers in subjects with stage D HF who are undergoing implantation of LVADs. This study design will allow for an exploration of the levels and variability of known biomarkers at different stages of mechanical circulatory support and allow for the discovery of novel markers in the future. This collection for future medical research is intended to expand the translational R&D capability of the Sponsor and will support future research aims that will advance our understanding of advanced HF and options for treatment.

4 STUDY COURSE AND DURATION

Enrollment in the MOMENTUM 3 Biobank is complete with 200 subjects. As shown below (Figure 2), subjects will have urine and blood samples drawn at key time-points that correlate with study visits to minimize hardship for the subject. Subjects will participate in the MOMENTUM 3 Biobank until completion of the day 180 follow up visit, until MOMENTUM 3 CAP outcome, or until the subject withdraws from the substudy.

Figure 2 – Study Flow - Blood (both plasma and serum) and urine samples will be collected to coincide with data obtained as part of the MOMENTUM 3 CAP.



5 STUDY POPULATION

The study population is a subset of the population that enrolled in the MOMENTUM 3 CAP who elect to participate in the MOMENTUM 3 Biobank. All sites participating in the MOMENTUM 3 CAP may be able to enroll subjects. Patients who do not receive the HM 3 implant or are not enrolled in the MOMENTUM 3 CAP will be withdrawn from the Biobank and their baseline samples will be discarded.

5.1 Inclusion Criteria

1. Subject or legally authorized representative has signed the Informed Consented Form (ICF) for the MOMENTUM 3 CAP
2. Subject or legally authorized representative has signed the ICF for the MOMENTUM 3 Biobank

5.2 Exclusion Criteria

1. Inability to have pre-operative blood draw performed

6 OBJECTIVES

6.1 Primary Objective

To establish a biobank of blood and urine samples at various time points pre- and post LVAD placement, which can be used for future assessment of CV specific biomarkers including potential analyses of coagulation system, HF biomarkers, etc..

6.2 Exploratory Objectives

- To correlate biomarkers with echocardiographic parameters
- To find relationships between CV biomarkers and risk of thrombosis/bleeding
- To find relationships between CV biomarkers and hospitalization/death

7 RISKS

The current study is without intended or anticipated medical benefit for the participating subjects, but will contribute to a better understanding of biomarkers in different LVAD populations. No investigational drug will be tested during this study. This study requires participation in the MOMENTUM 3 CAP.

Risks from the phlebotomy procedures include infection, bleeding, localized bruising, blood clot formation, and discomfort at the venipuncture site. The total blood draw volume, at each time point, will be 29 ml in addition to the blood draw volume requirements of the MOMENTUM 3 CAP. The blood draws associated with this protocol may be performed in tandem with blood draws associated with the MOMENTUM CAP, further reducing incremental risks.

8 ETHICAL CONSIDERATIONS

8.1 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 must 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 the Sponsor.

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

8.2 IRB Review

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

The Sponsor will comply with all IRB 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 the Sponsor for approval, prior to submitting to the IRB. Copies of the IRB submission and approval, including the approved ICF, must be forwarded to the Sponsor prior to the enrollment of subjects into the study. Sites will submit study progress reports in writing to the Sponsor and the IRB

as required. Sites will submit to the 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 the Sponsor and maintained on file at the study site.

8.3 Confidentiality

No individually identifiable/confidential subject data collected as part of this study will be released beyond the Sponsor. 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 the Sponsor.

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

The Sponsor will comply with all IRB 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 the Sponsor for approval, prior to submitting to the IRB. Copies of the IRB submission and approval, including the approved ICF, must be forwarded to the Sponsor prior to the enrollment of subjects into the study. Sites will submit study progress reports in writing to the Sponsor and the IRB as required. Sites will submit to the 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 the Sponsor and maintained on file at the study site.

9 BIOBANK SAMPLES

The current biostorage plan calls for 5 aliquots of serum, 10 aliquots of plasma (5 EDTA, 5 citrate) and 5 aliquots of urine. Each aliquot will be at least 1 ml, and up to 1.5 ml.

9.1 Optimization of Samples

For any given sample type there will be a range of possibility with respect to how many biomarkers can be run. Sample volumes required for different a single biomarker will vary from ~10 ul to up to ~250 depending on the platform utilized. For multiplex biomarker panels, up to 10 markers can be run simultaneously on 10-25 ul on a Meso Scale Discovery platform. If standard ELISA kits are used, sample volume is generally in the range of 50 ul and up to100 ul, and this is obligatorily a single biomarker. If biomarkers are run on an FDA approved commercially available autoanalyzer (i.e., NT-proBNP on a Roche Elecsys), generally, 250ul is required due to the dead space volume in the machine.

Sample quality will decrease with each additional freeze thaw cycle (this is particularly true with sodium citrate plasma samples). Thus the scientific quality of the data will decrease if simple thaw, test, re-freeze is the strategy employed (i.e. 4 autoanalyzer runs would be possible but depending on the markers number 2, 3, 4 will have declining value). However, with good planning this can be avoided: For example, if a plan is made for 30 novel protein markers on 4 multiplex chips, 5 markers by standard ELISA, 2

markers sent for auto analyzer runs simultaneously then a 1 ml cryovials of sample could support 37 individual biomarkers with 200ul for additional assays or future storage. Thus depending on the strategy employed to utilize the samples, each sample type with the current biobanking strategy of 5 aliquots could support as few as 5 biomarkers or as many as >250 biomarkers.

9.2 Potential Biomarkers

DNA will not be collected as part of this study. Blood and urine will be drawn at the pre-specified times for the measurement of blood and urine markers of coagulation dysfunction, fibrosis, inflammation, and endothelial dysfunction likely including but not limited to:

- NT-pro-BNP
- NP-proANP,
- NTproCNP
- Troponin T
- hs-cTnT
- Thrombomodulin
- hs-CRP
- ST2
- MR-proADM
- Copeptin
- GDF-15
- P-selectin
- PAI-1
- sST2
- IF-ɣ
- IL-1
- IL-1ra
- IL-2
- IL-3
- IL-4
- IL-5
- IL-6
- IL-7
- IL-8
- IL-10
- IL-17
- IL-18
- TNF
- TGF
- CRP
- KIM-1
- Cystatin-C
- Osteopontin
- Adiponectin
- TNFR1
- NFR2
- sVCAM-1
- Eotaxin
- sICAM-1
- FABP
- MMP-12
- MMP-32
- MMP-3
- MMP-7
- MMP-8
- MMP-9
- FABP
- FAS
- VEGF
- VEGFR1
- Galectin-3
- tPA
- vWF
- TIE-2
- uPA
- Osteoprotegerin
- YKL-40
- MPO
- Thrombospondin-1
- Eotaxin
- Endoglin
- Endothelian-1
- Endostatin
- Renin
- sFLt- 1
- Kallikrein-5
- Tenscin C
- TIMP-1
- FGF-21
- FGF-23
- TIMP-3
- syndecan-1
- syndecan -4
- TIMP-4
- Angiotensin II
- Uric acid
- LDH
- PIIINP
- PICP
- CITP
- NGAL
- Creatinine
- Albumin
- Metabolites

APPENDIX A: PLASMA & SERUM SAMPLE COLLECTION, PROCESSING, AND SHIPPING PROCEDURE

Timing of Sample Collection and Types of Samples Collected
Samples will be collected from subjects at four time-points: day 0 (baseline), day 7, day 30, day 180)
Samples collected at each time-point will include 29cc whole blood and 10cc urine. Samples will be collected as follows:

1. Whole blood (a total of 29cc) will be collected into each of the following containers:
   a. One 10cc **purple** top tube with EDTA additive*
   b. Two 4.5cc **blue** top tubes containing sodium citrate additive*
   c. One 10cc **red** top tube with no additive*
   *Sites may use different volume and amounts of tubes as long as the total plasma/serum sample to be banked remains the same.
2. 10cc of urine will be collected into a screw-top urine container.

Preparation of Freezer Boxes
Batches of freezer box kits will be provided to each study site. A kit consists of:

1. Freezer box with label indicating subject number and time-point
2. Cryovials
3. Pre-printed strip of barcoded labels

There will be labels on the sides of the box indicating the specimen type that goes in each row. The labels corresponding to specimen type and aliquot number (column) should be applied to the supplied cryovials. For example, a label that indicates “Urine” and specimen number 12460.3 should be placed in the “Urine” row, in column #3.

It is important to label cryovials BEFORE samples are collected, as when they are applied to frozen tubes, they often fall off, resulting in useless samples that must be discarded. If not all vials are filled for a given sample type, empty vials should be left in the box and returned to the central laboratory when the box with frozen samples is shipped back.

Blood Collection Procedure
Venipuncture technique:

1. Draw blood using a butterfly needle.
2. Ensure that each tube is filled completely.
3. Fill tubes in the proper order to ensure that additives do not cross-contaminate:
   - Purple top tube (One tube)
   - Blue top tube (Two tubes)
   - Red top tube (One tube)
4. Invert the purple and blue tubes with several gentle inversions to ensure proper mixing of additives.

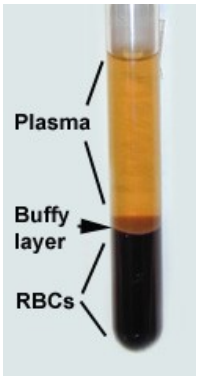
Blood can also be collected from a central line. An initial discard of 5 mL of blood from the line should be performed prior to collecting blood for research. Blood should be collected using new, clean syringes (one for the blue and purple tubes, and one for the red tube) using the order of draw and mixing protocols indicated above.

Blood Specimen Processing Procedure

Red top tubes should be stored upright at room temperature until clotting is observed. Purple and blue top tubes should be stored upright in a refrigerator for up to 1 hour after collection. Samples should be processed as quickly as possible after collection. Importantly, purple and blue tubes can be processed even before the red top tube has clotted.

1. Place blood collection tubes with rubber stoppers directly into centrifuge. Use bucket lids.
2. Centrifuge at 1000g x 10 min, ideally at 4°C.
3. For each sample type to be obtained, transfer only the clear liquid on top of the cell layer into the cryovials. Do not transfer any cells into the cryovials. If more than the required volume (5 mL) of clear liquid (serum or plasma) is present for any of the three blood sample types, the extra should be pipetted into the cryovials rather than thrown out. When pipetting extra, pipet up to 0.5 mL into each cryovial, starting from the last cryovial (vial #5).
4. While pipetting the plasma, place the spun serum tube on ice for 10 minutes in order to enhance clot retraction and maximize the amount of serum retrieved.
5. Using a micropipette, transfer 1 mL of plasma from the purple tube into each of five 1.5 mL cryovials labeled **PlasmaP**. Change the micropipette tip between sample types.
6. Using a micropipette, transfer 1 mL of plasma from the blue tube into each of five 1.5 mL cryovials labeled **PlasmaB**. Change the micropipette tip between sample types.
7. Using a micropipette, transfer 1 mL of serum from the red tube into each of five 1.5 mL cryovials labeled Serum. If fibrin clots cause difficulty pipetting the serum, there are two methods that can be used:
   a. (Preferred) Remove fibrin clot using wooden sticks and then pipet the serum into the cryovials.
   b. If no wooden sticks are available, the supernatant can be decanted and then re-spun.

   Never re-centrifuge a tube that contains cells.
8. Screw caps of cryovials onto aliquots and freeze the samples. Cryovials should be distributed in the box according to the box map.
9. Specimens should be stored at -80 degrees C until shipped to the central lab. If this is not possible, temporary storage at -20 degrees C is acceptable.



Urine Collection Procedure

Subject should be instructed to urinate into a clean disposable urinal (if male) or a hat (if female). 10cc of this urine should be poured into the "spot" screw-top urine container. Urine mixed with stool is not acceptable for specimen collection. If the subject has an indwelling urinary catheter, a sample can be obtained from the catheter reservoir.

Urine Specimen Processing Procedure

Urine specimens should be stored on ice or in a refrigerator until ready to be processed; they should be processed as quickly as possible after collection.

1. Transfer 6 mL of urine into a conical centrifuge tube using a transfer pipet.
2. Centrifuge at 1000g x 10 min, ideally at 4 degrees C.
3. Using a micropipette, transfer 1.5 mL of urine into each of five 1.5mL cryovials labeled Urine. Do not disturb the pellet at the bottom of the centrifuge tube.
4. Cryovial caps should be screwed on tightly. Cryovials should be distributed in the box according to the box map.

5. Specimens should be stored at -80 degrees C until shipped to the central lab. If this is not possible, temporary storage at -20 degrees C is acceptable.

Specimen Retention at the Core Lab

Frozen specimens will be maintained at -80 degrees C at the central laboratory until all testing has been completed and the results analyzed to determine no re-testing of samples is required. Sample volumes remaining after the full battery of testing covered in this protocol is completed may be retained (at the central laboratory or at another location), discarded, or used for additional testing at the discretion of the study sponsor.