Protocol HW-MVAD-01

Multi Center, Prospective, Non-Randomized, Single-Arm Trial Evaluating the Clinical Safety and Performance of the HeartWare MVAD® System for the Treatment of Advanced Heart Failure

Statistical Analysis Plan

Final Version 2.0 20SEP2017

Revision History

Version	Date	Revision Author	Comments
1.0	14MAY2015	[redacted]	Initial Document
2.0	20SEP2017	[redacted]	Updates for final analysis changes

Signature Page

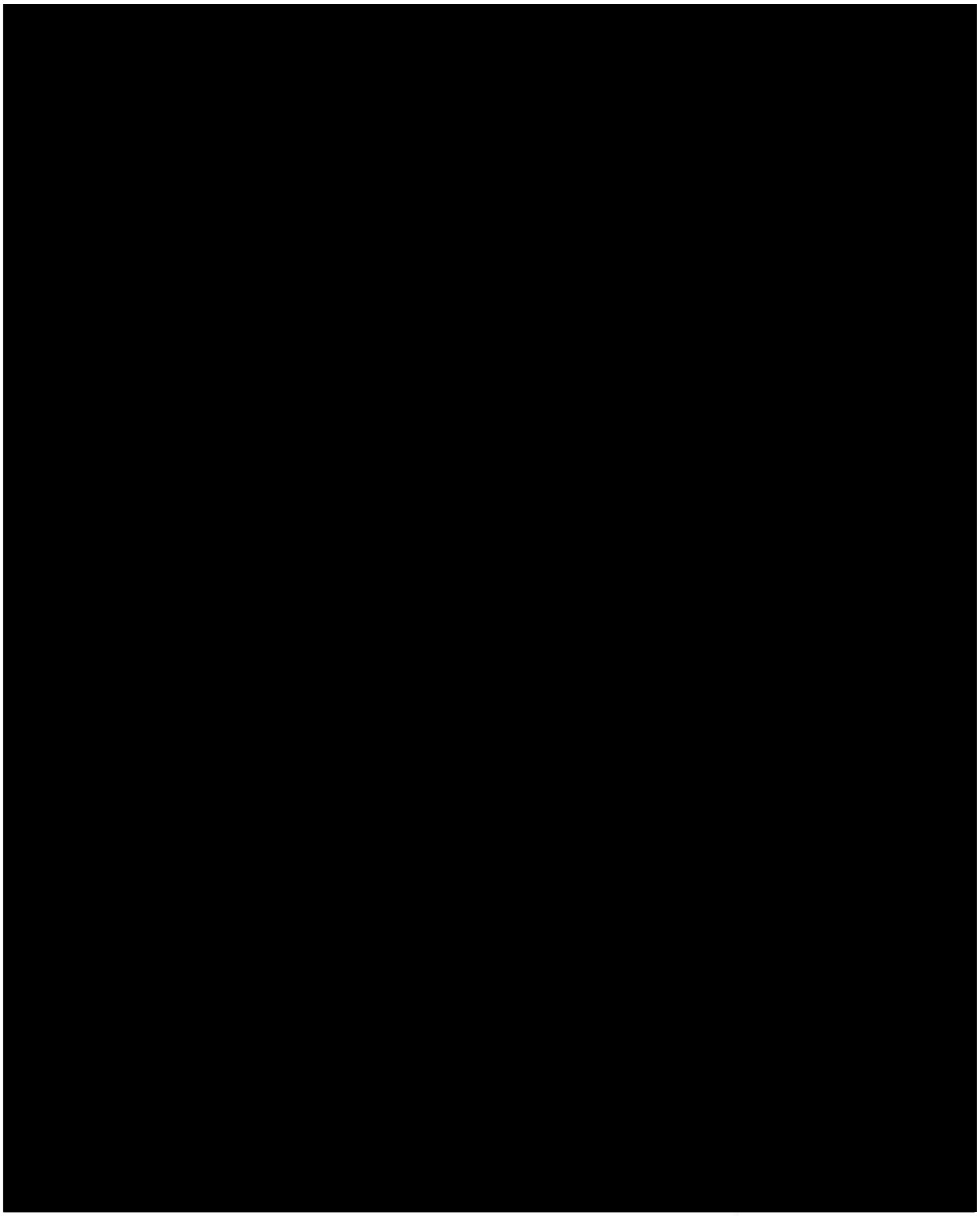

Table of Contents

In-Text Tables

1 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADE(s)	adverse device effect(s)
AE(s)	adverse event (s)
AHA	American Heart Association
ATC	anatomical therapeutic chemical
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BSA	body surface area
C	Celcius
CEC	Clinical Events Committee
CFB	change from baseline
CFR	code of federal regulations
CI	confidence interval
CIP	Clinical investigation plan
cm	centimeters
CNS	central nervous system
CRF	case report form
CSR	Clinical Study Report
CT	Computed Tomography
CVA	Cerebral Vascular Accident (stroke)
DD	device deficiencies
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
EU	European Union
F	Fahrenheit
FDA	Food and Drug Administration
g/dL	grams per deciliter
GCP	good clinical practice
HR	heart rate
hr(s)	hour(s)
HVAD	HeartWare ventricular assist device
IBPM	intensive blood pressure management plan
IC	Informed Consent
ICH	International Conference on Harmonisation
ICU	intensive care unit

INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
IPD	Important protocol deviations
IRB	institutional review board
ISHLT	International Society of Heart and Lung Transplantation
ITT	intent-to-treat
kg	kilograms
KCCQ	Kansas City Cardiomyopathy Questionnaire
KM	Kaplan-Meier
L/min	liters/ minute
LA	left atrial
LOS	length of stay
LOT	length of operative time
LV	left ventricular
LVAD	left ventricular assist device
LVEDD	left ventricular end diastolic diameter
LVEDV	left ventricular end diastolic volume
LVEF	left ventricular ejection fraction
LVESD	left ventricular end systolic diameter
LVESV	left ventricular end systolic volume
m	meters
MAP	mean arterial pressure
max	maximum
MedDRA	Medical dictionary for regulatory activities
mg	milligram
min	minimum
mL	milliliters
ms	milliseconds
MRS	Modified Rankin Scale
MVAD	miniaturized ventricular assist device
N	number of patients
NI	Non-inferiority
NIH	National Institutes of Health
NIHSS	National Institutes of Health Stroke Scale
NP	Nurse Practitioner
NYHA	New York Heart Association
PA	Physician's Assistent
PCWP	pulmonary capillary wedge pressure
PD	pharmacodynamic

PG	Performance goal
PK	pharmacokinetic
PP	per protocol
PVR	Pulmonary Vascular Resistence
RHC	right heart catherization
RN	Registered Nurse
RPM	revolutions per minute
RR	respiration rate
RVAD	right ventricular assist device
SADE	serious adverse device effect
SAE	serious adverse event
SAS®	(statistical analysis software)
SD	standard deviation
SOC	system organ class
SOP	standard operating procedures
SVO_2	Mixed Venous Oxygen Saturation
TEAE	treatment-emergent adverse event
TEMP	temperature
TIA	Transient Ischemic Attack
TTD	time to death
UADE	unanticipated adverse device effect
USADE	unanticipated serious adverse device effect
VAD	ventricular assist device
VAS	visual analogue scale
WHO	World Health Organization

2 INTRODUCTION

Heart failure is one of the leading causes of death in the developed world. It is estimated that 2-6% of the adults in the world suffer from heart failure with a higher prevalence in industrialized nations. There are up to 15 million cases in the European Union, approximately 5.3 million diagnosed cases in the United States, and up to 300,000 cases in Australia. Overall, 50% of patients with heart failure are dead within four years, while 40% who are hospitalized due to acute heart failure are readmitted or dead within one year. Improvements in medical treatments and longer life expectancies have expanded the potential heart failure patient population, consequently increasing the prevalence of the disease. Cardiac transplantation is currently the most effective therapy for advanced heart failure. However, the lack of available donor organs restricts this form of therapy to just over 3,700 patients/year worldwide, as reported to the International Society for Heart and Lung Transplantation (ISHLT) Transplant Registry.

Over the last decade, bridging to cardiac transplantation with implantable left ventricular assist device (LVAD) systems has gained wider clinical acceptance, and today LVADs are used to extend life expectancy for patients with advanced heart failure who deteriorate while awaiting a donor heart. Approximately 32% of the patients who receive heart transplants are bridged with ventricular assist devices. There are currently several devices approved for bridging to cardiac transplantation in the EU. The use of permanent LVADs as an alternative to transplantation has also been approved. This permanent use is known as destination therapy.

The HeartWare® Miniaturized Ventricular Assist System includes an implantable continuous, axial flow pump (MVAD® Pump) that was designed to provide flows up to 7 L/min in a small device that is both lightweight and simple to use. Due to its small size and mechanical simplicity, the MVAD® Pump may provide benefits not currently available with existing technology that require abdominal pump pockets.

Furthermore, the size of the MVAD® Pump may be suitable for patients who cannot tolerate an abdominal surgical procedure.

3 STUDY OBJECTIVES

This multi-center, prospective, non-randomized, single-arm trial will investigate the safety and performance of the HeartWare® Miniaturized Ventricular Assist Device (MVAD® Pump) system over 24 months in subjects with advanced heart failure. Secondary endpoints include the incidence of bleeding, incidence of major infections (per INTERMACS definitions), time to death, incidence of all device failures and device malfunctions, health status improvement, and functional status improvement. Safety measures will include the frequency and rates of adverse events, both overall and for each specific event, which will be collected throughout MVAD® Pump support.

This is a performance goal based trial concerning the primary endpoint and the first secondary endpoint. The primary endpoint is survival at 6 months (estimated to be 85%) based on a performance goal of 70%, with a one-sided significance level of 0.05. The initial Clinical Study Report (CSR) will be submitted with the 6 month data and will be submitted for CE Mark. The secondary endpoint is survival at 24 months (estimated to be 70%) based on a performance goal of 52.5%, with a one-sided significance level of 0.05. These data will be submitted for long term use labeling.

4 STUDY DESIGN

4.1 General Design

A summary of the study design is presented here; complete details are provided in the protocol.

This multi-center, prospective, non-randomized, single-arm trial will investigate the safety and performance of the HeartWare MVAD® system over 24 months in patients with advanced heart failure. Subjects who undergo explant will continue to have survival status assessed for 1 year after explant occurred. The study population will be selected from patients with chronic American Heart Association (AHA) Stage D/NYHA Class IIIB/IV heart failure who have failed optimal medical management.

After obtaining informed consent, all patients who meet inclusion/exclusion criteria will enter screening visit. All patients will be hospitalized following the implantation and to be evaluated for discharge based on the standard practice of each investigational site. A total of 60 patients will be enrolled, implanted with the MVAD® pump, and will be followed up for 24 months post implantation. Patients will be trained on managing the MVAD® pump which has been implanted prior to discharge from the hospital. Post implant, each patient will be scheduled to have a follow up visit at months 1, 3, 6, 12, 18, and 24 to assess the safety and performance of the device.

The performance of the MVAD® pump will be measured by the overall survival at 6 months and overall survival at 24 months, both to be presented as simple proportion and to be compared with the performance goal of 70% for 6-month survival and 52.5% for 24-month survival using one-sided tests at the 0.05 significance level. Additional parameters of interest include the incidence of major bleeding (per INTERMACS definition), incidence of major infections (per INTERMACS definition), time to death, incidence of all device failures and device malfunctions per INTERMACS definition, incidence of neurological dysfunction per INTERMACS definition, Health Status improvement, Functional status improvement, length of operative time, length of initial stay, re-hospitalizations, transplantations, and explants. Safety measures will include the frequency and rates of adverse events, overall and for each specific event, which will be collected throughout VAD support.

4.2 Discussion of Study Design

This is a multi-center prospective, non-randomized, single-arm study to assess the clinical safety and performance of the MVAD® pump for the treatment of advance heart failure. A multicenter study allows for scientific validity and generalization of the study findings. Since this is a single group study, the outcome of the study will be compared with the performance goal. A PG refers to a numerical value (point estimate) that is considered sufficient by FDA for use as a comparison for a safety and/or effectiveness endpoint.

4.3 Method of Assignment of Patients to Treatment Groups

In this single arm multi-center study, all patients will be implanted with the HeartWare MVAD® pump system.

4.4 Blinding

Not applicable.

4.5 Determination of Sample Size

The primary endpoint is survival at 6 months presented as a simple proportion (binomial rate). The survival rate at 6 months is estimated to be 85%, based on HeartWare's experience with the HVAD. This estimated rate will be compared to a performance goal (70%). A sample of 57 subjects is required to satisfy a one-sided significance level of 0.05 and a power greater than 80% (the lower bound of a one-sided 95% exact binomial confidence interval must exceed 70% for success). Three additional subjects (for a total of 60) will be implanted with the MVAD® pump to address for possible attrition due to lost to follow-up or withdrawal.

The first secondary endpoint is survival at 24 months presented as a simple proportion (binomial rate). The survival rate at 24 months is estimated to be 70%, based on HeartWare's experience with the HVAD. This estimated rate will be compared to a performance goal (52.5%). A sample of 57 subjects is required to satisfy a one-sided significance level of 0.05 and a power greater than 80% (the lower bound of an exact binomial confidence interval must exceed 52.5% for success). Three additional subjects (for a total of 60) will be implanted with the MVAD® pump to address for possible attrition due to lost to follow-up or withdrawal.

5 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

5.1 Changes in the Conduct of the Study

There were no changes in the conduct of the study at the time of preparing this statistical analysis plan.

5.2 Changes from the Analyses Planned in the Protocol/CIP

Due to the early stop of the protocol, fewer than 15 subjects were enrolled. As such, summary statistics are of little use. Therefore, case studies for each subject enrolled and followed will be presented and summary statistics are no longer planned.

6 BASELINE, EFFICACY AND SAFETY EVALUATIONS

6.1 Schedule of Evaluations

The assessments to be conducted at each scheduled visit are displayed in the following tables.

Table 1 Time and Event Schedule – Screening to Month 24

Event / Assessment	Screening/ Pre-implant 72 hours before Implant	Day 1-3/ During initial Hospitalization	Discharge	Month 1, 3 +/-7 days	Month 6 +14 days	Month 12,18 +/- 14 days	Month 24 +14 days
Informed Consent	X						
Inclusion/Exclusion	X						
Demographics	X						
Cardiovascular/ Medical history & Hospitalization/ INTERMACS Patient Profile	X						
Subject training (HeartWare MVAD® and BP Management)			X				
Urine Pregnancy Screen	X						
Safety Laboratory Chemistry and Hematology	X	X[1]		X	X	X	X
Hemodynamic Parameter/ Vital signs [2]	X	X		X	X	X	X
IBPM & Diary Assessments[2]			X	X	X	X	X
Echocardiogram [3]	X[3]			X	X	X	X
Implant Data		X[4]					
MVAD® Pump Parameters [5]		X		X	X	X	X
Log File Download			X	X	X	X	X
Driveline Care Assessment			X	X	X	X	X
NYHA Classification	X			X	X	X	X
6-Minute Walk	X			X	X	X	X
NIH Stroke Scale / Modified Rankin Scale [6]	X			X	X	X	X
Quality of Life Questionnaire (EuroQol EQ-5D-5L)	X			X	X	X	X
Kansas City Cardiomyopathy Questionnaire (KCCQ)	X			X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X

1 Day 3 only **2** Detailed schedules in Section 9.1.5 of CIP **3** Echocardiograms obtained within the 6 months prior to ICF may be used for screening
4 Implant=Day 1 **5** MVAD® Pump parameters will also be recorded daily post discharge until the patient's blood pressure is stable as defined in Section 9.1.5.2 and at any subsequent hospitalization **6** In addition obtain MRS and NIHSS at time of stroke and at 12 weeks and 24 weeks post-stroke (+/- 7 days)

Table 2 Time and Event Schedule – Follow-up after Explant of MVAD® Pump

Event / Assessment	Explant	Month 1 post explant +/-7 days	Month 6 post explant +/-30 days	Month 12 post explant +/-30 days
Visit Date / Survival Status		X	X	X
Concomitant Medications	X			
Adverse Events	X			

6.2 Time Point Algorithms

6.2.1 Relative Day

The date the device is implanted will be considered relative day 1, and the day before the device is implanted will be relative day -1. Relative days will be calculated as follows only when the full assessment date is known (i.e., partial dates will have missing relative days):

For days on or after the device is implanted:
Relative Study Day (Rel Day) = Date of Assessment – Date of implant + 1.

For days before the device is implanted:
Relative Study Day (Rel Day) = Date of Assessment – Date of implant.

6.2.2 Windows

For the purpose of statistical analysis, visits will be analyzed according to their scheduled time point. No windowing will be done. Unscheduleds visits will not be summarized but will be presented in the listings.

6.3 Baseline Assessments

Baseline is the last measurement before MVAD® Pump is implanted.

The following baseline assessments will be conducted pre-implant.

- Informed Consent obtained
- Inclusion/Exclusion criteria
- Cardiovascular and general medical history including prior hospitalizations
- Demographics (age, race (where applicable), ethnicity (where applicable), gender, weight, height)
- Hemodynamic parameters
- Echocardiogram parameters
- Vital signs (heart rate [HR], respiration rate [RR], blood pressure [BP], and body temperature [TEMP])
- Clinical Laboratory tests (hematology, chemistry, pregnancy test (where applicable))
- NYHA Classification
- 6-Minute Walk
- NIH Stroke Scale
- Modified Rankin Scale
- Quality of Life Questionnaire (EuroQoL EQ-5D-5L)
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- INTERMACS Patient Profile
- Adverse Events (pre-implant and post informed consent (IC))
- Concomitant Medications (pre-implant)

6.4 Efficacy Variables

6.4.1 Primary Efficacy Variable – Overall Survival at 6 months

The primary efficacy variable is survival at 6 months after implant expressed as simple proportion of patients alive on the MVAD® pump divided by endpoint eligible patients. The overall survival at 6 months post implant simple proportion point estimate is n/N; where N is the total number of patients included in the analysis set; and n is the number of patients alive at Relative Study Day 183, lower bound of the 6 month visit.

Patients who are lost to follow-up or who withdraw consent prior to Relative Study Day 183 will be excluded from both denominator and numerator when computing the simple proportion. Patients with transplants, explants for recovery or exchanges (to a device other than the MVAD® Pump) prior to Relative Study Day 183 will be included in the denominator for this analysis, with status identified at time of procedure. If there are any patients who are eligible for analysis but for whom the primary endpoint cannot be assessed, they will be excluded from both denominator and numerator for this analysis.

6.4.2 Secondary Efficacy Variable – Overall Survival at 24 months

The secondary efficacy variable is survival at 24 months after implant expressed as simple proportion (patients alive on the MVAD® pump divided by endpoint eligible patients). The overall survival at 24 months post implant will be presented as a simple proportion; that is, the point estimate will be n/N; where N is the total number of patients included in the analysis set; and n is the number of patients alive by Relative Study Day 730 (lower bound of the 24 month visit).

Patients who are lost to follow-up or who withdraw consent prior to Relative Study Day 730 will be excluded from both denominator and numerator when computing the simple proportion. Patients with transplants, explants for recovery or exchanges (to a device other than the MVAD® Pump) prior to Relative Study Day 730 will be included in the denominator for this analysis, with status identified at time of procedure. If there are any patients who are eligible for analysis but for whom the primary endpoint cannot be assessed, they will be excluded from both denominator and numerator for this analysis.

6.4.3 Additional Efficacy Variables

6.4.3.1 Overall Survival (Time to Death)

Time to death (TTD) is defined as the time from date of implant until date of death on device (in days). If a patient had a transplant, explants for recovery, exchanges (to a device other than MVAD® Pump) prior to endpoint, and any withdrawal or lost to followup will be censored at the time of this event date. For each patient that remains alive on device, TTD

will be censored at the time of last contact date known to be alive (contacts considered in the determination of last contact date would include but not limited to scheduled visit dates, adverse event date, and last known alive date).

Time to Death (TTD) = Date of event/censor – Date of Implant + 1.

6.4.3.2 Health Status, as measured by EuroQol EQ-5D-5L

The EuroQol-5D-5L (EQ-5D-5L), an assessment of general well-being, will be utilized. Pre-implant assessment will be performed at screening/pre-implant (when feasible) and month 1, 3, 6, 12, 18, and 24.

The EQ-5D-5L includes a descriptive system that comprises 5 dimensions of health status and a VAS scale (referred to as EQ VAS) that records the respondent's self-rated health status. The 5 dimensions of health status are

- Mobility (M)
- Self-care (S)
- Usual activities (U)
- Pain/discomfort (P)
- Anxiety/depression (A)

The EQ VAS value and the change from baseline will be tabulated by time point.

The EQ VAS data at screening (baseline), at each post implant visit (post baseline), and change from baseline (visit value – baseline value) will be calculated for each patient.

6.4.3.3 Health Status, as measured by Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KCCQ, a disease specific 23-item, self-administered instrument that quantifies physical function, symptoms (frequency, severity, and recent change), social function, self-efficacy and knowledge and quality of life. Patients will complete the KCCQ at screening/pre-implant (when feasible) and month 1, 3, 6, 12, 18, and 24.

The KCCQ is composed of 15 questions. The questions are grouped to reflect clinically relevant domains: physical limitation (question 1a-1f), symptom stability (question 2), symptom frequency (questions 3, 5, 7, 9), symptom burden (questions 4, 6, 8), self-efficacy (questions 10, 11), quality of life (questions 12, 13, 14), and social limitation (question 15a15d). To facilitate interpretability, three summary scores were developed, overall summary score, total symptom score, and clinical summary score. Further details of the KCCQ determination is presented in the Appendix.

Scale scores for the total and for each domain (physical limitation, symptoms, selfefficacy, social limitation, quality of life, functional status, and clinical summary) will be calculated for each patient at each time point. The change from baseline (visit value – screening visit

value) will be calculated for each patient. The values and the change from baseline will be tabulated by time point.

6.4.3.4 Functional status, as measured by NYHA

Determination of NYHA classification will be performed by an independent assessor (defined as a physician or qualified physician assistant (PA), registered nurse (RN) or nurse practitioner (NP) not directly involved with this clinical trial). NYHA will be captured at screening/pre-implant and month 1, 3, 6, 12, 18, and 24. The number of patients by NYHA Class will be determined at each time point. The denominator will be the number of patients on the device at the given time point and completed the assessment form.

6.4.3.5 Functional status, as measured by 6-minute walk

Subjects will complete a six minute walk test at screening/pre-implant and month 1, 3, 6, 12, 18, and 24. Missing data in patients who did not perform the 6-minute walk due to early termination will not be imputed. Those patients will be excluded from the analysis. Missing data in patients who were medically unable to or indicated that they could not perform the 6-minute walk task will be imputed to zero (0). If a patient missed a visit or the associated CRF page was not filled out at a visit then no imputation will be done.

6.4.3.6 National Institutes of Health Stroke Scale (NIHSS)

NIHSS assessments will be obtained screening/pre-implant and month 1, 3, 6, 12, 18, and 24, by a trained individual. In addition to screening/pre-implant assessment, NIH Stroke Scale is required in the event of a stroke. After a stroke, a follow-up NIH Stroke Scale is required at 12 weeks (+/-7 days), and 24 weeks (+/-7 days) after the event to document any deficits. The total raw NIHSS score will be used for reporting purposes.

6.4.3.7 Modified Rankin Scale (MRS)

The Modified Rankin Scale (MRS) will be obtained screening/pre-implant and month 1, 3, 6, 12, 18, and 24, by a trained individual. MRS will be required in the event of a stroke. After a stroke, a follow-up MRS score is required at 12 weeks (+/-7 days), and 24 weeks (+/-7 days) after the event to document any deficits. An MRS score greater than 3 will be used to suggest the presence of neurological deficit after a stroke.

6.5 Drug Concentration Measurements and Pharmacokinetic Parameters

Not applicable to this study.

6.6 Safety Variables

6.6.1 Extent of Exposure and Compliance to Study Treatment

This is a device study; all qualified patients are to be implanted with the investigational device in the hospital. Timing of the implantation and associated parameters will be recorded on the CRFs.

6.6.2 Adverse Events

The investigator's verbatim term for all adverse events (AEs) will be mapped to system organ class (SOC) and preferred terms using the current version of the Medical Dictionary for Regulatory Activities (MedDRA).

An AE in this study is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs in subjects, users or other persons whether or not related to the investigational medical device. This includes events related to the investigational medical device. This includes events related to the procedures involved (any procedure in the clinical investigation plan). For users or other persons this is restricted to events related to the investigational medical device. From the time the informed consent form is signed adverse events will be collected. Only AEs occurring while on the device are considered treatment-emergent. In the event of an explant for transplant or recovery, adverse events will be collected until the induction of anesthesia for explant. AEs occurring after the device has been turned off in lieu of surgical explant will not be collected. In the event of an explant for an exchange for another HeartWare MVAD® system, adverse events will be collected throughout the subject's participation on the trial. In the event of an explant for exchange for a non HeartWare MVAD® system, adverse events will be collected until the induction of anesthesia for exchange.

In addition, INTERMACS-defined AEs occurring during the study will be recorded. The definition for all INTERMACS-defined AEs can be found in Appendix 17.9 of the protocol. The category of other adverse events will be those adverse events that were unable to be reported into an INTERMACS-defined adverse event category. For the INTERMACS-defined adverse events, the number of events per person-year will be calculated.

For each event, the potential etiology of the event will be determined by the investigator and categorized as:

1. Related to MVAD® Procedure
2. Related to MVAD® System
3. Undetermined
4. Subject Condition
5. Other

Any event categorized as related to MVAD® procedure or related to MVAD® system will be considered an adverse device event (ADE). Any event categorized as subject condition, undetermined or other will be considered a non adverse device event (non ADE).

For an event where the relationship is missing, the relationship will be considered related for analysis purposes.

6.6.2.1 Non Adverse Device Event (non ADE)

Adverse events not related to the use of the investigational medical device. This includes events reported due to the subject condition, not able to be determined to be related to the medical device, or other. A non adverse device event (non ADE) will be considered emergent if the onset of the event is on or after the start of anesthesia for the implant surgery.

6.6.2.2 Device or Procedure Related

Adverse Device Event (ADE)

Adverse events related to the use of the investigational medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunctions of the investigational medical device or as a result of a user error or intentional misuse. All ADEs are considered emergent.

Unanticipated/Unexpected Serious Adverse Device Event (USADE)

An USADE is an event which by its nature, incidence, severity or outcome has not been identified in the current Risk Management section of the Investigator's Brochure and Instructions for Use. The anticipated/expected adverse events are defined in Section 10.1.4 of the protocol. All USADE are considered emergent.

6.6.2.3 Serious Adverse Event

A serious adverse event (SAE) is an AE that led to death, led to serious deterioration in health that resulted in life-threatening illness or injury, in permanent impairment of a body structure or body function, in the patient's hospitalization or prolongation of existing hospitalization, in medical or surgical interventions to prevent life threatening illness, or led to fetal distress, fetal death or a congenital abnormality or birth defect.

This includes device deficiencies (DDs) that might have led to a serious adverse event if suitable action had not been taken, or intervention had not been made or if circumstances had been less fortunate.

A serious adverse device event (SADE) is an event that resulted in any of the consequences characteristic of a serious adverse event.

An unanticipated/unexpected serious adverse device effect (USADE) is an unanticipated/unexpected event that resulted in any of the consequences characteristic of a serious adverse event.

6.6.3 Clinical Laboratory Evaluations

Clinical laboratory tests are scheduled at the screening visit (baseline) within 72 hours prior to MVAD® pump implantation, Day 3 and at each post discharge clinical visit. Change from baseline to each visit will be defined as the visit value minus the baseline value. All clinical laboratory test results will be reported in or converted to Standard SI units for analysis. Clinical laboratory results will also be classified as normal (if value is within normal reference range) or abnormal (if value is either below (L) or above the normal reference range (H)).

6.6.4 Other Safety Variables

6.6.4.1 Vital Sign Measurements

Vital sign measurements (systolic and diastolic blood pressure, mean arterial pressure (MAP), heart rate, respiratory rate, and temperature) are scheduled at the screening visit (baseline), Days 1- 3 post implant, and month 1, 3, 6, 12, 18, and 24. Change from baseline to each visit will be defined as the visit value minus the baseline value. Blood pressure will be managed to maintain MAP as tolerated at ≤ 85 mmHg (using an automated cuff method) or ≤ 90 mmHg (using the Doppler/cuff method) for at least 3 months after discharge and continue until the subject is medically stable.

6.6.4.2 Hemodynamic parameters

Hemodynamic parameters are taken at screening visit (baseline), Days 1- 3 post implant, and month 1, 3, 6, 12, 18, and 24. The hemodynamic parameters include central venous pressure, SVO_2, right atrial pressure, systolic pulmonary artery pressure, mean pulmonary artery pressure, diastolic pulmonary artery pressure, PCWP, cardiac index, cardiac output, and PVR. All parameters are collected (if possible) at the screening (baseline) visit. Some parameters are available only during right heart catherization (RHC) monitoring, while others are not available due to RHC monitoring. In addition, some parameters may not be available in some patients who have a VAD implanted. Change from baseline to each visit will be defined as the visit value minus the baseline value.

6.6.4.3 Echocardiogram Parameters

Echocardiogram parameters are scheduled at screening visit (baseline) and month 1, 3, 6, 12, 18, and 24. The echocardiogram may be obtained within the 6 months prior to the informed consent and used as the screening visit measurements. The echocardiogram parameters

(continuous variables) include set speed (RPM), pump flow (L/min), pump power (Watts), aortic valve opening/min (min), aortic valve opening duration (ms), LVEF (%), LVEDD (cm), LVESD (cm), LVEDV (mL) and LVESV (mL). Change from baseline to each visit will be defined as the visit value minus the baseline value. Other echocardiogram parameters that are categorical variables are aortic valve opening (yes/no), aortic insufficiency (none/mild/moderate/severe), and commissural fusion (yes/no). Additional information recorded includes aortic regurgitation, mitral regurgitation, tricuspid regurgitation, LA dimension, LV wall thickness, and presence of LV thrombus.

6.6.4.4 Length of Operative Time

The length of operative time (LOT) will be derived. The length of operative time will be the number of hours from the time of surgery starts for the implant of the device until the time the surgery for implantation of the device is completed.

Length of operative time in hours = time of chest closure – time of chest incision

6.6.4.5 Length of Initial Hospital Stay

At discharge, length of stay (LOS) will be collected for LOS overall, LOS in ICU, and LOS in general ward. The length of initial hospital stay based on the LOS overall will be the number of days from the date of hospitalization prior to the device implantation until the date of discharge following device implantation.

Length of hospitalization in days = date of discharge – date of implantation +1

6.6.4.6 Hospitalization after the Initial Hospitalization for Implant (Re-hospitalization)

For each patient having a hospitalization (excluding planned procedures) after the initial hospitalization for implant, the length of stay will be collected for LOS overall, LOS in ICU, and LOS in general ward. For each patient, the number of hospitalizations after the initial hospitalization for the device implantation will be tallied. Also for each patient, the cumulative number of days hospitalized after the initial hospitalization for the device implantation will be determined for LOS overall, LOS in ICU and LOS in general ward. All re-hospitalizations will be summarized in the listings (including planned procedures).

6.6.4.7 Transplantation

The number of patients with a transplantation will be determined. The denominator will be the number of patients with a device implanted. The time to first transplantation will be calculated as the number of days the transplant occurred after the device implantation.

Time to first transplant in days = date of transplant – date of implantation +1

6.6.4.8 Explant

The number of patients with an explant of the device will be tallied. The denominator will be the number of patients with a device implanted. Also the time to explantation of the device will be the number of days from when the explant occurred after the device implantation.

Time to Explant in days = date of explant – date of implantation +1

The reason for explant will also be recorded.

6.7 Pharmacodynamics Parameters

Not applicable to this study.

7 STATISTICAL METHODS

7.1 General Methodology

All analysis will be performed using SAS® Version 9.2 or higher. Data will be summarized using descriptive statistics (number of patients [N], mean, standard deviation [SD], median, minimum, and maximum) for continuous variables and using frequency and percentage for discrete variables.

The primary and secondary efficacy analyses for survival (simple proportion) will be based on the lower bound of the one-sided 95% exact binomial confidence interval exceeding the performance goal. No other hypothesis testing will be performed.

Patient listings of all data from the case report forms (CRFs) as well as any derived variables will be presented.

7.2 Adjustments for Covariates

Site effects will be considered for the primary efficacy endpoint using site as a blocking variable. No other covariates are planned to be used in the analyses for this study.

7.3 Handling of Dropouts or Missing Data

Patients who are lost to follow-up or who withdraw consent prior to specified relative day will be excluded from both denominator and numerator when computing the simple proportion for the primary endpoint (survival at 6 months) and the first secondary endpoint (survival at 24 months). Patients who are lost to follow-up or who withdraw consent will, however, be eligible for the overall survival analysis.

Transplants, explants for recovery and exchanges (to a device other than the MVAD® Pump) will be eligible for survival analysis with their survival status identified at the time of the

procedure. Death with the MVAD® pump in place is the only event that will be considered a failure.

Patient-years and follow-up time are based on database-driven known time on MVAD® support (including post–exchange time). If a patient is on LVAD support at last known follow-up and a later date of death exists, the date of death must be considered the last follow-up for that patient. The patient is known to be alive and assumed to be on MVAD® support up to the date of death.

If a partial date is reported where the day is missing, then the day will be imputed as the first day of the month unless the month is the same month as the device is implanted then then the day will be that of implantation with the month and year remaining the same. If a partial date is reported where the month is missing, then the month will be imputed to January unless the year is the same year as the device is implanted then the month will be that of implantation with the year remaining the same. If a partial date where both the day and month is missing, follow details as stated previously.

Missing data for other parameters will not be imputed for analysis unless defined in Section 6. Censoring for the efficacy endpoints is discussed in Sections 6.4.3.1. Missing adverse event dates will be imputed using partial date imputation rules as previously described in this Section.

7.4 Interim Analyses and Data Monitoring

To meet the trial's ethical responsibility to its subjects, results will be monitored by two independent groups that have no formal involvement with the subjects or the investigation, as follows:

1. DSMB – Data Safety Monitoring Board
2. CEC – Clinical Events Committee

The members of these committees shall function independently of HeartWare and the CRO.

The DSMB will review the study at key points during the conduct. Details of the DSMB safety review meetings will be detailed in a separate DMC Charter.

7.5 Multi-center Studies and Pooling of Centers

Patients will be pooled across sites for analysis of study endpoints.

Site effects will be performed for the primary endpoint using site as a blocking variable. Sites with at least 8 patients will retain their identities. Smaller sites will be ranked in decreasing order of size and cumulatively pooled until pooled sites of no less than 8 are achieved.

7.6 Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons or multiplicity will be made.

The family wise error rate has not been affected by multiplicity for two reasons: the distinction between primary and secondary for the hypothesized endpoints, and the expected correlation between the hypothesized endpoints.

Adjustments to the significance level are not necessary; however careful consideration will be used when making statements concerning the first secondary endpoint.

7.7 Use of an "Efficacy Subset" of Patients

Not applicable to this study.

7.8 Active-Control Studies Intended to Show Equivalence

Not applicable to this study.

7.9 Examination of Subgroups

No examination of the primary or secondary efficacy variable by subgroups is planned.

8 STATISTICAL ANALYSIS

8.1 Disposition of Patients

The number of patients enrolled, who received an implant, and who are evaluable will be summarized. The number of treated patients who completed the study, the number of patients who discontinued from the study and the reasons for discontinuing from the study will also be summarized. Patients who died prior to 24 months are considered achieving the endpoint and therefore they would be included in the 'completed the study' category.

8.2 Protocol Deviations

Important protocol deviations (IPDs) will be summarized. The HeartWare review team will identify IPD categories. The IPD specifications will be defined prior to the close of the database for the interim analysis. An overall IPD listing will be reviewed just prior to database closure for the interim analysis and database lock for final analysis. The HeartWare review team will approve all final IPD determinations. The HeartWare review team will consist of the clinical monitoring manager, clinical project manager, data manager, biostatistician, and regulatory representative. Once all IPD determinations are finalized and approved by the HeartWare review team, the database will be closed for statistical analysis. The number of patients in each IPD category will be summarized. All IPDs will be listed by patient.

8.3 Analysis Populations

8.3.1 Enrolled Population

All patients who signed informed consent will be included in this analysis set. This analysis set will be used only for patient accountability for disposition purposes.

8.3.2 Intent-to-Treat (ITT) Population

All patients who enroll in the study (i.e., have signed informed consent) and who undergo anesthesia for implantation will be included in this analysis set. This population will be the primary analysis population.

8.3.3 Per Protocol (PP) Population

Patients in the ITT Population who received HeartWare MVAD® will form the Per Protocol (PP) Population.

Efficacy analysis will be conducted for both ITT and PP analysis sets, differences in results using the two analyses will be carefully examined.

8.3.4 Safety Population

Patients in the ITT Population who received HeartWare MVAD® will form the Safety Population. This population will be used in all safety reporting and analysis.

8.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for ITT and PP populations.

Gender, race, and ethnicity will be summarized using counts and percentages. Age (years), height (cm), weight (kg), body surface area [BSA (m^2)], body mass index (BMI) (kg/m^2) will be summarized with descriptive statistics.

The number and percentage of patients with medical history events will be summarized. Cardiovascular history at baseline and comorbidities at baseline will be summarized separately. Vital signs collected at screening will be summarized with descriptive statistics. Smoking status will be summarized using counts and percentages.

The following implant data will be summarized.

1. Cardiopulmonary bypass (yes/no)
2. Total time on bypass
3. Surgical technique (sternotomy, thoracotomy, other)
4. Outflow graft location (ascending aorta, descending aorta, subclavian, other)
5. Any concomitant cardiac procedure (yes/no)
6. Intraventricular thrombus (none, present, not assessed, not applicable)

7. Transfusion in operating room (yes/no)
8. Driveline location (right upper quadrant, right lower quadrant, left upper quadrant, left lower quadrant)

The following discharge parameters will be summarized.

1. Discharge to (home, skilled nursing care facility, inpatient rehabilitation facility, hospice, other)
2. Days in ICU
3. Days in general ward

8.5 MVAD® Parameters

LVAD, including flow, speed, and power, will be tabulated by time point with descriptive statistics. This summary will be performed for PP population.

8.6 Prior and Concomitant Therapy

The World Health Organization (WHO) Drug Dictionary (version 16.0) will be used to classify medications by preferred term and WHO Anatomical Therapeutic Chemical (ATC) classification of ingredients.

Medications will be summarized using counts and percentages by WHO ATC classification of ingredients and by preferred term. This summary will be performed for ITT population.

Medications with start date and stop date prior to implant will be included in the prior medication summary. Medications taken during the study, including those started prior to implant, will be included in the concomitant medication summary.

8.7 Analysis of Efficacy Parameters

All primary and secondary efficacy analyses will be performed on ITT and PP populations.

8.7.1 Analysis of Primary Efficacy Variable – Overall Survival at 6 Months

The primary endpoint is survival at 6 months presented as a simple proportion (subjects alive on the MVAD® pump divided by endpoint eligible subjects). Transplants, explants for recovery and exchanges (to a device other than the MVAD® Pump) prior to 6 month follow-up will be eligible for endpoint analysis (with survival status identified at the time of the procedure). Trial failure is associated with events (death) on the MVAD® Pump. The survival incidence at 6 months is estimated to be 85%, based on HeartWare's experience with the HVAD. This estimate will be compared to a performance goal (PG_1). The null and alternative hypotheses are provided below:

$H_0: \pi_{MVAD1} \leq PG_1$

$H_A: \pi_{MVAD1} > PG_1$

π_{MVAD1} is the estimated proportion of survival in the treatment group. The performance goal at 6 months is 70%. Success is achieved if the lower bound of the one-sided 95% exact binomial confidence interval exceeds the performance goal.

A summary table will include number of patients alive and number of patients dead by study day 183 (the lower bound of the 6 month visit), the proportion for overall survival at 6 months, and the associated lower and the upper 90% exact binominal confidence intervals.

Sensitivity analysis will be performed to assess the impact of the missing data (See Section 8.7.5.1).

8.7.2 Analysis of Secondary Efficacy Variable – Overall Survival at 24 Months

The first secondary endpoint is survival at 24 months presented as a simple proportion (defined like the primary endpoint). The survival incidence at 24 months is estimated to be 70%, based on HeartWare's experience with the HVAD. This estimate will be compared to a performance goal (PG_2). The null and alternative hypotheses are provided below:

$H_0: \pi_{MVAD2} \leq PG_2$
$H_A: \pi_{MVAD2} > PG_2$

π_{MVAD2} is the estimated proportion of survival in the treatment group. The performance goal at 24 months is 52.5%. Success is achieved if the lower bound of the one-sided 95% exact binomial confidence interval exceeds the performance goal.

A summary table will include the number of patients alive and number of patients dead by study day 730 (the lower bound of the 24 month visit), proportion of overall survival at 24 months and the associated lower and the upper 90% exact binominal confidence intervals.

8.7.3 Analysis of Other Secondary Efficacy Variables

Analysis for overall survival (TTD), health status (KCCQ, EuroQoL EQ-5D-5L), and functional status (NYHA, 6 minute walk) will be performed on both the ITT and PP populations. Analysis for NIHSS and MRS will be performed on both the ITT and PP populations.

8.7.3.1 Overall Survival (TTD)

TTD will be derived from the Kaplan-Meier estimates and 95% confidence intervals will be calculated. The quartiles for Kaplan-Meier estimates will all be presented. Plot of the Kaplan-Meier curve will be provided. This analysis will be performed on both the ITT and PP populations.

8.7.3.2 Kansas City Cardiomyopathy Questionnaire (KCCQ)

KCCQ scale scores and change from baseline will be summarized by each scheduled visit using descriptive statistics, including 95% CI for the mean. Only patients that are currently on device at the given time point will be summarized.

8.7.3.3 EuroQol-5D-5L

The health status data will be tabulated by scheduled time point for each dimension and health profile with number and percentage in each category.

EQ VAS data and the change from baseline will be tabulated by scheduled time point using descriptive statistics, including the 95% CI for the mean. The EQ index value and the change from baseline will be tabulated by time point using descriptive statistics of sample size (N), mean, 95% CI for the mean, minimum, maximum, median, and standard deviations. Only patients that are currently on device at the given time point will be summarized.

8.7.3.4 6-Minute Walk

Results of the 6-minute walk at each scheduled visit and change from baseline to visit will be tabulated by time point using descriptive statistics, including 95% confidence intervals for the means.

8.7.3.5 NYHA Classification

Results of the NYHA classification at screening (baseline) and each scheduled post implant follow-up visits will be tabulated. Change from baseline in NYHA classification will also be summarized in a shift table.

8.7.3.6 NIH Stroke Scale

Results of the total raw NIHSS score at each visit and change from baseline to visit will be tabulated by scheduled time point using descriptive statistics, including 95% confidence intervals for the means. A table of change from stroke values to 12 weeks post-stroke and of change from stroke to 24 weeks post-stroke will be presented using descriptive statistics, including 95% confidence intervals for the means.

8.7.3.7 Modified Rankin Scale

Results of the MRS by category (MRS Score of 0, 1, 2, 3, 4, 5, and 6) at each scheduled visit will be tabulated using counts and percentages. A shift table of change from stroke to 12 weeks post-stroke and of change from stroke to 24 weeks post-stroke will be presented using counts and percentages.

8.7.4 Subgroup Analyses

No subgroup analyses of efficacy data are planned.

8.7.5 Exploratory Analyses

8.7.5.1 Sensitivity Analysis

If there are any patients implanted with MVAD® for whom the primary efficacy endpoint cannot be assessed, then a sensitivity analysis will be conducted, where patients with missing outcomes will be imputed as failures (death).

A simple proportion of overall survival at 6 months and exact binomial confidence intervals will be computed as described in the Analysis of Primary Efficacy Variable (Section 8.7.1).

8.8 Analysis of Safety

All safety analyses will be performed using the safety population. Formal inferential statistics will not be conducted.

8.8.1 Extent of Exposure and Compliance to Study Treatment

No formal tabulations are planned since all qualified patients will have received MVAD® system in the hospital.

8.8.2 Adverse Events

8.8.2.1 Adverse Events based on INTERMACS definition

The number and percentage of patients experiencing each specified AE using the INTERMACS definition will be summarized. Any AEs that are not treatment emergent will be listed only.

The incidence of AEs using the INTERMACS definition will be reported in the categories of bleeding (re-hospitalization, re-operation, gastrointestinal (GI)), cardiac arrhythmia (ventricular, supraventricular), device malfunction/failure, hemolysis, hepatic dysfunction, hypertension, infection (localized non-device, sepsis, driveline exit site), myocardial infarction, neurological dysfunction (CT confirmed ischemic cerebral vascular accident (CVA), CT confirmed hemorrhagic CVA, transient ischemic attack (TIA)), pericardial fluid collection, psychiatric episode, renal dysfunction (acute, chronic), respiratory dysfunction, right heart failure, arterial non-CNS thromboembolism, venous thromboembolism, wound dehiscence, and other event. In addition to the incidence rate, the number of events and the

event rate per patient year will be reported for each INTERMACS-defined adverse event. For the incidence rate, a patient will only be counted once per each INTERMACS-defined category and counted once per each INTERMACS-defined sub-category. The following summaries will be presented.

1. All Treatment Emergent Site-Reported AEs by INTERMACS-defined term
2. All Treatment Emergent Site-Reported ADEs by INTERMACS-defined term
3. All Treatment Emergent Site-Reported Non-ADEs by INTERMACS-defined term
4. All Treatment Emergent Site-Reported ADEs by INTERMACS-defined term – Related to MVAD System
5. All Treatment Emergent Site-Reported Serious AEs by INTERMACS-defined term
6. All Treatment Emergent Site-Reported Serious ADEs by INTERMACS-defined term
7. All Treatment Emergent Site-Reported Serious non-ADEs by INTERMACS defined term
8. All Treatment Emergent Site-Reported Serious ADEs by INTERMACS-defined term – Related to MVAD System
9. All Treatment Emergent Site-Reported AEs leading to outcome of fatal by INTERMACS-defined term
10. All Treatment Emergent Site-Reported AEs leading to exchange/explant of device by INTERMACS-defined term
11. All Treatment Emergent Adjudicated AEs by INTERMACS-defined term
12. All Treatment Emergent Adjudicated ADEs by INTERMACS-defined term
13. All Treatment Emergent Adjudicated Non-ADEs by INTERMACS-defined term
14. All Treatment Emergent Adjudicated ADEs by INTERMACS-defined term – Related to MVAD System
15. All Treatment Emergent Adjudicated Serious AEs by INTERMACS-defined term
16. All Treatment Emergent Adjudicated Serious ADEs by INTERMACS-defined term
17. All Treatment Emergent Adjudicated Serious non-ADEs by INTERMACS defined term
18. All Treatment Emergent Adjudicated Serious ADEs by INTERMACS-defined term – Related to MVAD System
19. All Treatment Emergent Adjudicated AEs leading to outcome of fatal by INTERMACS-defined term
20. All Treatment Emergent Adjudicated AEs leading to exchange/explant of device by INTERMACS-defined term

8.8.2.2 Adverse Events Categorized as Other in the INTERMACS-definition based on MedDRA

All adverse events (AE) that were categorized as ‘Other’ in the INTERMACS definition will be summarized by system organ class (SOC) and preferred term; events that are not treatment emergent will be listed only. A patient will only be counted once per system organ class and once per preferred term within a system organ class. Patient counts and percentages and event counts as well as event rate per patient year will be presented in the following summaries.

1. All Other Treatment Emergent Site-Reported AEs by SOC and preferred term
2. All Other Treatment Emergent Site-Reported ADEs by SOC and preferred term
3. All Other Treatment Emergent Site-Reported Non-ADEs by SOC and preferred term
4. All Other Treatment Emergent Site-Reported ADEs by SOC and preferred term – Related to MVAD System
5. All Treatment Emergent Site-Reported Serious Other AEs by SOC and preferred term
6. All Treatment Emergent Site-Reported Serious Other ADEs by SOC and preferred term
7. All Treatment Emergent Site-Reported Serious Other non-ADEs by SOC and preferred term
8. All Treatment Emergent Site-Reported Serious Other ADEs by SOC and preferred term – Related to MVAD System
9. All Other Treatment Emergent Site-Reported AEs leading to outcome of fatal by SOC and preferred term
10. All Other Treatment Emergent Site-Reported AEs leading to exchange/explant of device by SOC and preferred term

11. All Other Treatment Emergent Adjudicated AEs by SOC and preferred term
12. All Other Treatment Emergent Adjudicated ADEs by SOC and preferred term
13. All Other Treatment Emergent Adjudicated Non-ADEs by SOC and preferred term
14. All Other Treatment Emergent Adjudicated ADEs by SOC and preferred term – Related to MVAD System
15. All Treatment Emergent Adjudicated Serious Other AEs by SOC and preferred term
16. All Treatment Emergent Adjudicated Serious Other ADEs by SOC and preferred term
17. All Treatment Emergent Adjudicated Serious Other non-ADEs by SOC and preferred term
18. All Treatment Emergent Adjudicated Serious Other ADEs by SOC and preferred term – Related to MVAD System
19. All Other Treatment Emergent Adjudicated AEs leading to outcome of fatal by SOC and preferred term
20. All Other Treatment Emergent Adjudicated AEs leading to exchange/explant of device by SOC and preferred term

Adverse events potentially related to study device are defined as a subset of adverse events with a relationship to study device of either possible related or related. Events with missing relationship assessment will be included as potentially related to study device.

No statistical inference will be performed on adverse events.

Listings will be presented by patient for all adverse events as well as for each INTERMACS definition, UADEs, SAEs, adverse events associated with death, and adverse events leading to study device explant/exchange.

8.8.3 Clinical Laboratory Evaluations

Clinical laboratory test values at each scheduled visit and for change from baseline (screening) to visit will be summarized using descriptive statistics.

All clinical laboratory data will be presented in listings. Within each listing, laboratory values outside the normal ranges will be flagged as either high (H) or low (L). In addition, shift tables will be presented to display the shift in the normal range categories (L, normal [N], H) from baseline to the each visit.

8.8.4 Other Variables Related to Safety

8.8.4.1 Vital Signs

Vital sign measurements at each scheduled visit and change from baseline (screening) will be tabulated with descriptive statistics, including 95% confidence intervals for the means, by time point. A MAP value > 85 mmHg following discharge will be flagged in the listing.

8.8.4.2 Hemodynamic Parameters

Hemodynamic parameters at each scheduled visit and change from baseline (screening) will be tabulated with descriptive statistics, including 95% confidence intervals for the means, by time point.

8.8.4.3 Echocardiogram Parameters

Echocardiogram parameters that are continuous variables will be summarized using descriptive statistics, including 95% confidence intervals for the means, at each scheduled visit and change from baseline (screening) by time point. Categorical echocardiogram findings will also be tabulated by time point.

8.8.4.4 Length of Operative Time

Length of operative time in minutes will be summarized using descriptive statistics, including 95% confidence intervals for the means. The number and percentage patients with operative time will also be summarized by the following categories: 0 – <60 minutes, 60 – <120 minutes, 120 – <180 minutes, 180 minutes or more.

8.8.4.5 Length of Initial Hospital Stay

Length of initial hospital stay (LOS) overall, LOS in ICU, and LOS in the general ward will be summarized using descriptive statistics, including 95% confidence intervals for the

means. The number and percentage of patients with an initial hospital stay ≤ 7 days, 8-14 days, and > 14 days will also be summarized.

8.8.4.6 Re-Hospitalization

The number and percentage of patients with re-hospitalization after the initial hospitalization will be tabulated by category of stay: 1, 2, and 3 or greater. The number of re-hospitalizations will also be summarized using descriptive statistics. Cumulative length of re-hospitalization after initial hospital stay (overall LOS), LOS in ICU, and LOS in general ward will be summarized using descriptive statistics, including 95% confidence intervals for the means. Overall LOS, LOS in ICU, and LOS in general ward will also be summarized by counts and percentages for each of the following categories: <= 7 days, 8-14 days, and > 14 days.

8.8.4.7 Transplant

The number and percentage of patients with transplantation will be tabulated. Time to first transplantation relative to initial implant will be summarized using descriptive statistics, including 95% confidence intervals for the means. Also, the time to first transplantation relative to initial implant in the following categories will be tabulated:

- Transplant occurred ≤ 30 days after implant
- Transplant occurred ≤ 180 days after implant
- Transplant occurred > 180 days after implant

Time to first transplantation will be presented graphically as a Kaplan-Meier curve. If a patient had explants for recovery, exchanges (to a device other than MVAD® Pump) prior to transplantation, and any withdrawal or lost to follow-up will be censored at the time of this event date. For each patient that remains alive on device, time to first transplantation will be censored at the time of last contact date known to be alive (contacts considered in the determination of last contact date would include but not limited to scheduled visit dates, adverse event dates, and last known alive date).

8.8.4.8 Explant

Number and percentage of patients with an explantation will be tabulated. Time to first explantation relative to initial implant will be assessed using descriptive statistics (sample size (N), mean and 95% confidence intervals for the means, minimum, maximum, median, and standard deviation). Also the time to first explantation relative to initial implant in the following categories:

- Explant occurred ≤ 30 days after implant
- Explant occurred ≤ 180 days after implant

- Explant occurred > 180 days after implant

The number and percentage of patients who had their LVAD device replaced will be tabulated. The number and percentage of patients who received a new HeartWare MVAD® device will also be tabulated. The number and percentage for reasons for explanation will be tabulated. Since patients can have multiple explants, the reasons for explantation will include all reasons. Therefore the percentages may add up to more than 100%.

Time to first explantation will be presented graphically as a Kaplan-Meier curve. Any withdrawal or lost to follow-up will be censored at the time of this event date. For each patient that remains alive on device, time to first explantation will be censored at the time of last contact date known to be alive (contacts considered in the determination of last contact date would include but not limited to scheduled visit dates, adverse event dates, and last known alive date).

Time to first exchange will be presented graphically as a Kaplan-Meier curve. If a patient had transplant or explants for recovery, and any withdrawal or lost to follow-up will be censored at the time of this event date. For each patient that remains alive on device, time to first exchange will be censored at the time of last contact date known to be alive (contacts considered in the determination of last contact date would include but not limited to scheduled visit dates, adverse event dates, and last known alive date).

8.9 Pharmacodynamics

Not applicable to this study.

9 COMPUTER SOFTWARE

All analyses will be performed by Theorem Clinical Research using Version 9.2 or later of SAS® software. All summary tables and data listings will be prepared utilizing SAS® software.

The standard operating procedures (SOPs) of Theorem Clinical Research will be followed in the creation and quality control of all data displays and analyses.

10 REFERENCES

1. US Department of Health and Human Services Food and Drug Administration. Guidance for Industry Non-inferiority Clinical Trials. March 2010.

2. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol. 2000;35:1245–1255.

3. Leon MB, Smith CS, Mack M, Miller DC, Moses JW,Svensson LG, Tuzcu EM,Webb JB, Fontana GP,Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, and Pocock S for the PARTNER Trial Investigators. Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery. N Engl J Med 2010;363:1597-1607.

4. Reynolds MR, Magnuson EA,Lei Y, Leon MB, Smith CS, Svensson LG, Webb JG, Babaliaros VC, Bowers BS, Fearon WF, Herrmann HC, Kapadia S, Kodali SK, Makkar RR, Pichard AD, Cohen DJ, for the Placement of Aortic Transcatheter Valves (PARTNER) Investigators. Health-Related Quality of Life After Transcatheter Aortic Valve Replacement in Inoperable Patients With Severe Aortic Stenosis. Circulation. 2011; 124: 1964-1972.

5. EuroQol Group. EQ-5D-5L User Guide Basic Information on How to Use the EQ-5D-5L Instrument. Version 1.0 April 2011.

6. Levy WC, Mozaffarian D, Linker DT, Farrar DJ, Miller LW; REMATCH Investigators. Can the Seattle heart failure model be used to risk-stratify heart failure patients for potential left ventricular assist device therapy? J Heart Lung Transplant. 2009 Mar;28(3):231-6. PubMed PMID: 19285613

11 APPENDICES

11.1 APPENDIX 1: VARIABLE DEFINITIONS

- Body mass index (BMI; kg/m^2) is calculated as: weight (kg) / [height (m)]^2, rounded to one decimal place.

- Body surface area (BSA; m^2) is calculated using Mosteller formula as:
  $BSA= (H * W / 3600)^{0.5}$
  Where W = weight in kg and H= height in cm

- Weight will be displayed in kilograms (kg), height will be displayed in centimeters (cm), and temperature will be displayed in Celsius (C).

- Weights, heights, or temperatures recorded in alternate units will be converted to the units being displayed using standard conversion formulas.

- Length of Operative Time (mins) = time of chest closure –time of chest incision

- Length of Initial Hospital Stay (Days) = Date of discharge following device implantation – date of implant + 1

- For days on or after the device is implanted:
  Relative Study Day (Rel Day) = Date of Assessment – Date of implant + 1.

  For days before the device is implanted:
  Relative Study Day (Rel Day) = Date of Assessment – Date of implant.

- Days survived = Date of death/date of event for censoring – Date of implant + 1

- Days of hospitalization = Date of discharge from hospital – Date of admission + 1

- Cumulative days of hospitalization after initial hospitalization is the sum of the length of hospital stays after initial hospitalization.

- Days to explant = Date of explant – Date of initial implant + 1

- Days to transplant = Date of transplant – Date of initial implant + 1

- Change from baseline (CFB) = Visit value – Screening/Pre-Implant value

Calculation of adverse event rate per patient-year

1. Calculate the patient-years contributed by each patient. The time in the study starts at enrollment. The end date would be the last follow up date (end of study), unless the patient has an explant (when the pump is removed, turned off, or exchanged), dies, or is lost to follow-up prior to the end of study. The patient years are calculated as (date of explant or death or last follow up or end of study – date of enrollment + 1)/365.24. When the number of days is negative, the value will be missing for the patient-years.
2. Sum the patient-years across all patients in the study. Round to 2 decimal places. This is the denominator.
3. Sum the total number of events for a particular adverse event (prior to exchange). If a patient has patient-years that is missing, the AEs will not be counted for these patients (e.g., patients who have ongoing AEs that are entered into the database, an exchange after the AE but prior to enrollment).

4. The adverse event rate per patient-year = (Sum of the total number of events for the particular adverse event (prior to exchange))/(Sum of the patient-years across all patients in the study).

11.2 APPENDIX 2: KCCQ Determination

There are 10 summary scores within the KCCQ, which are calculated as follows:

Physical Limitation

The Physical Limitation score corresponds to questions 1a through 1f. Responses to questions 1a through 1f should be coded numerically as follows:

1 = Extremely Limited
2 = Quite a bit Limited
3 = Moderately Limited
4 = Slightly Limited
5 = Not at all Limited
6 = Limited for other reasons or did not do the activity

If the responses to questions 1a through 1f are not values 1, 2, 3, 4 or 5 then the response is set to missing. Note that a response of 6 (Limited for other reasons or did not do the activity) is treated as a missing value. If at least three responses to questions 1a-1f are not missing, then the physical limitation score is computed by calculating the mean response and standardizing the result as follows:

Physical Limitation = 100*(Mean Response – 1)/4

Symptom Stability
The Symptom Stability score corresponds to question 2. Responses to question 2 should be coded numerically as follows:

1 = Much Worse
2 = Slightly Worse
3 = Not Changed
4 = Slightly Better
5 = Much Better
6 = I’ve had no symptoms over the last 2 weeks

If the response is 6 (no symptoms over last 2 weeks) then set the response to 3 (not changed). If question 2 is not missing then the symptom stability score is computed by standardizing the result as follows:

Symptom Stability = 100*(Response – 1)/4

Symptom Frequency

The Symptom Frequency score corresponds to questions 3, 5, 7 and 9. The responses should be coded sequentially (1, 2, 3…) in order of increasing health status as follows:

Question 3

1 = Every Morning
2 = 3 or more times per week, but not every day
3 = 1-2 times a week
4 = Less than once a week
5 = Never over the past 2 weeks

Questions 5 and 7

1 = All of the time
2 = Several times per day
3 = At least once a day
4 = 3 or more times per week, but not every day
5 = 1-2 times per week
6 = Less than once a week
7 = Never over the past 2 weeks

Question 9

1 = Every night
2 = 3 or more times a week, but not every day
3 = 1-2 times a week
4 = Less than once a week
5 = Never over the past 2 weeks

If three or more responses are missing then symptom frequency cannot be computed and will be missing. Otherwise, the symptom frequency is computed by calculating the mean of the standardized responses and multiplying by 100 as follows:

Symptom Frequency = 100*Mean((Q3 – 1)/4, (Q5 – 1)/6, (Q7 – 1)/6, (Q9 – 1)/4)

Symptom Burden

The Symptom Burden score corresponds to questions 4, 6 and 8. The responses should be coded numerically as follows:

1 = Extremely Bothersome
2 = Quite a bit Bothersome
3 = Moderately Bothersome

4 = Slightly Bothersome
5 = Not at all Bothersome
6 = I've had no swelling (fatigue, shortness of breath)

If a response is 6 (none) then set the response to 5 (not at all). If at least one response is present then symptom burden score is computed by calculating the mean response and standardizing the result as follows:

Symptom Burden = 100*(Mean Response – 1)/4

Total Symptom

The Total Symptom score is calculated as the mean of the symptom frequency score and symptom burden score.

Self-Efficacy

The Self-Efficacy score corresponds to questions 10 and 11. The responses should be coded numerically as follows:

Question 10:
1 = Not at all sure
2 = Not very sure
3 = Somewhat sure
4 = Mostly sure
5 = Completely sure

Question 11:
1 = Do not understand at all
2 = Do not understand very well
3 = Somewhat understand
4 = Mostly understand
5 = Completely understand

If at least one question response is present then the self-efficacy score may be computed by standardizing the mean response as follows:

Self-Efficacy = 100*(Mean Response – 1)/4

Quality of Life

The Quality of Life score corresponds to questions 12, 13 and 14. The responses should be coded numerically as follows:

Question 12:

1 = It has extremely limited my enjoyment of life
2 = It has limited my enjoyment of life quite a bit
3 = It has moderately limited my enjoyment of life
4 = It has slightly limited my enjoyment of life
5 = It has not limited my enjoyment of life at all

Question 13:

1 = Not at all satisfied
2 = Mostly dissatisfied
3 = Somewhat satisfied
4 = Mostly satisfied
5 = Completely satisfied

Question 14:

1 = I felt that way all of the time
2 = I felt that way most of the time
3 = I have occasionally felt that way
4 = I have rarely felt that way
5 = I have never felt that way

If at least one question response is present then the quality of life score may be computed by standardizing the mean response as follows:

Quality of Life = 100*(Mean Response – 1)/4

Social Limitation

The Social Limitation score corresponds to questions 15a through 15d. These responses should be coded numerically as follows:

1 = Severely Limited
2 = Limited Quite a bit
3 = Moderately Limited
4 = Slightly Limited
5 = Did Not Limit at All
6 = Does not apply or did not do for other reasons

If the responses to questions 15a through 15d are not values 1, 2, 3, 4 or 5 then the response is set to missing. Note that a response of 6 is treated as a missing value. If at least two question responses are present then the social limitation score may be computed by standardizing the mean response as follows:

Social Limitation = 100*(Mean Response – 1)/4

Clinical Summary Score

The Clinical Summary score is calculated as the mean of the physical limitation score and total symptom score.

Overall Summary Score

The Overall Summary score is calculated as the mean of the physical limitation score, total symptom score, quality of life score and social limitation score.

11.3 APPENDIX 3: EuroQol 5D-5L Determination

The EQ-5D™ has two parts. The first part is a descriptive system that classifies respondents into one of 243 distinct health states. The descriptive system consists of the following five dimensions:

1. Mobility (MO).
2. Self-care (SC).
3. Usual activities (UA). 4. Pain/discomfort (PD).
5. Anxiety/depression (AD).

Each dimension has five possible levels (i.e., 1 to 5), representing "no problems," "slight problems", "moderate problems", "severe problems", and "unable to/extreme problems" respectively. Respondents are asked to choose one level that reflects their "own health state today" for each of the five dimensions. This health state classifier can describe 3125 unique health states that are often reported as vectors ranging from 11111 (full health) to 55555 (worst health).

The second part is a 20-cm visual analog scale (EQ-VAS) that has endpoints labeled "best imaginable health state" and "worst imaginable health state" anchored at 100 and 0, respectively. Respondents are asked to indicate how they rate their own health by drawing a line from an anchor box to that point on the EQ-VAS which best represents their own health on that day. Hence, the EQ-5D™ produces three types of data for each respondent:

1. A profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor (e.g., 11121, 33211)
2. A population preference-health index value based on the descriptive system.
3. A self-reported assessment of health status based on the EQ-VAS.

Missing values should be left blank. The index value will not be calculated when responses are missing for one or more of the dimensions.

11.4 APPENDIX 4: STATISTICAL ANALYSIS AND PROGRAMMING DETAILS

Exact binomial confidence intervals:

- *Make sure the outcome variable is coded properly since BINOMIAL option computes the binomial proportion and confidence limits for the first level of the variable. For example, if outcome is coded 'alive vs dead' the output will have test statistics and confidence limits for survival. If the outcome is coded 'death vs survival', then output will have test statistics and confidence limits for the mortality.*
- *Make sure appropriate alpha is specified since the procedure always produces 2sided confidence limits.*
    - *To obtain 1-sided 95% confidence limits, specify alpha=0.10*
    - *To obtain 2-sided 95% confidence limits, specify alpha=0.05*

The following is example syntax of SAS code to produce the 2-sided 90% exact binomial confidence intervals.

```
PROC FREQ DATA=sur6;
      WEIGHT n;
      TABLE outcome / BINOMIAL ALPHA=0.10;
      EXACT BINOMIAL;
      OUTPUT OUT out=bio BIN;
Run;
```

Where n *is total number of patients with outcome of alive and total number of patients with outcome of dead at 6 months. Outcome = Alive or Dead*

For hypothesis of primary endpoint,

```
Data result; Set
      bio;
      If round(XL_BIN, 0.01) > 0.70 then NI='Pass'; else NI='Fail';
Run;
```

For hypothesis of secondary endpoint,

```
Data result; Set
      bio;
      If round(XL_BIN, 0.01) > 0.52.5 then NI='Pass'; else
NI='Fail';
Run;
```

Kaplan-Meier (KM) Survival Analysis:

The SAS procedure LIFETEST will be used for Kaplan-Meier survival analysis.

- *Censored = 1 for all patients survived, patients with transplant or explant, patients discontinued without event of death or lost to follow-up*
- *Censored = 0 for all patients died.*

The following code will be used:

```
ods listing close;
ods output CensoredSummary=censor  quartiles = _qt;
    PROC LIFETEST DATA = surv TIMELIM=n;
TIME surdays*censored(1);     run; ods
listing; ods output close;
```

• Option TIMELIM is the maximum observation period • surdays= number of days survived post implant • dataset censor contains number of patients censored for this analysis • data _qt contains KM 25% quartile, median, and 75% quartile estimates of time to death