SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generi Name:	Ventricular assist device
Device Trade Name:	HeartMate 3™ Left Ventricular Assist System
Device Procode:	DSQ
Applicnt's Name and Address:	Thoratec Corporation 6035 Stoneridge Drive Pleasanton, CA 94588
Date of Panel Recommendation:	None
Premarket Approval Applicantion (PMA) Number:	P160054
Date of FDA Notice of Approval:	August 23, 2017

II. INDICATIONS FOR USE

The HeartMate 3™ Left Ventricular Assist System (LVAS) is indicated for providing short-term hemodynamic support (e.g., bridge to transplant or bridge to myocardial recovery) in patients with advanced refractory left ventricular heart failure.

III. CONTRAINDICATIONS

The HeartMate™ 3 LVAS is contraindicated for patients who cannot tolerate, or who are allergic to, anticoagulation therapy.

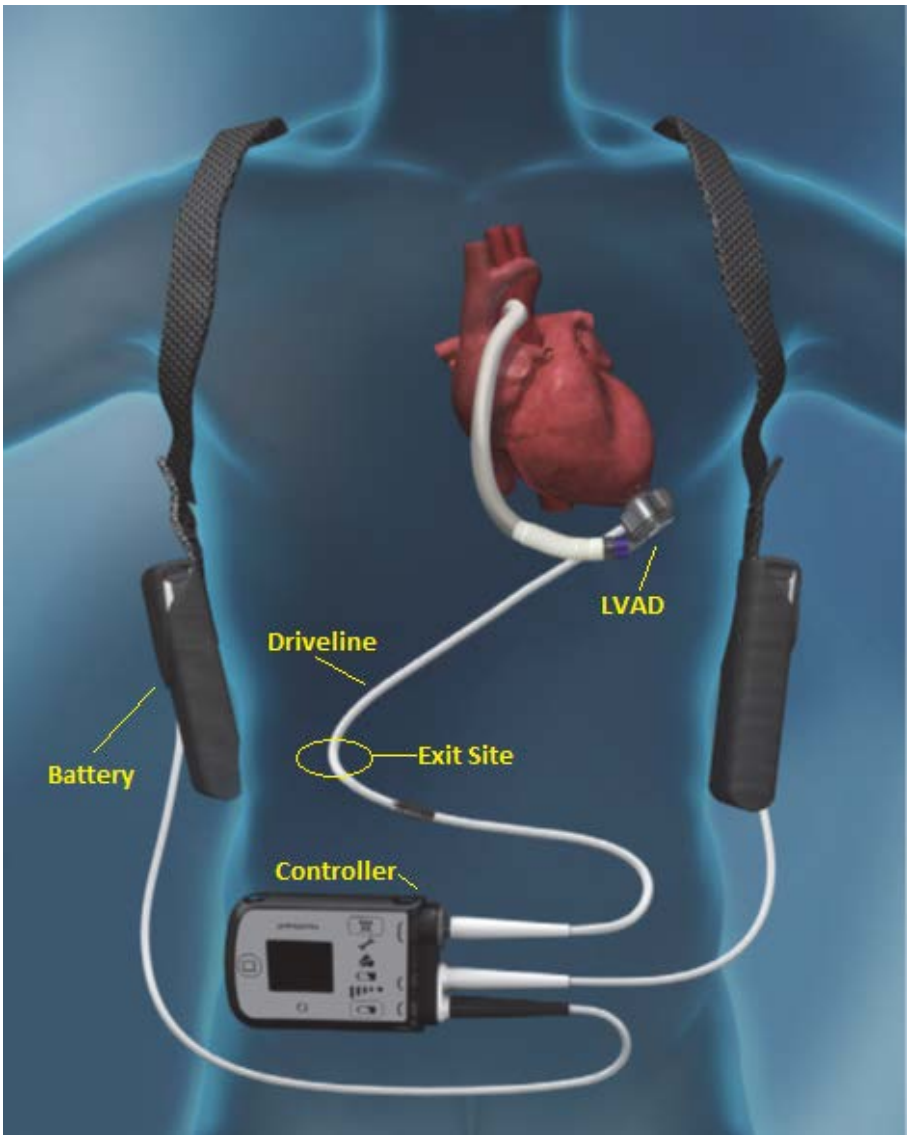
IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the HeartMate 3 LVAS labeling.

V. DEVICE DESCRIPTION

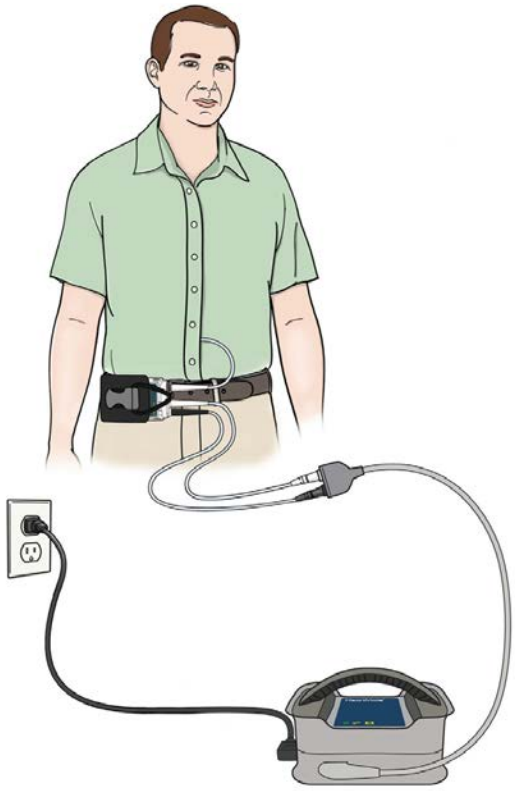
The HeartMate 3 LVAS consists of the HeartMate 3 left ventricular assist device (LVAD) and external components as shown in Figure 1. The HeartMate 3 LVAD is composed of an implanted centrifugal blood pump, an outflow graft with bend relief, an apical cuff, and a pump cable.

Figure 1: HeartMate 3 LVAS Implantable and External Components



The HeartMate 3 LVAD is connected via a percutaneous cable (driveline) to the microprocessor-based external System Controller. The System Controller is powered by either the Power Module (for hospital use) or the Mobile Power Unit that connects to the AC mains power, as shown in Figure 2, or by two (2) batteries that the patient carries. The System Controller performs all power handling and monitoring functions, including supplying power to the LVAD; communicating with the LVAD; storing system operating parameters; logging performance data; generating diagnostic information; producing visual and audible alarms; providing uninterrupted power to the LVAD during main power exchange; and displaying alarm messages, alarm history, and key operating parameters.

Figure 2: HeartMate 3 LVAS in Use with Mobile Power Unit (AC Power Supply)



VI. ALTERNATIVE PRACTICES AND PROCEDURES

The current standard of care for patients in end-stage heart failure includes four (4) treatment modalities: pharmacological therapy (ACE inhibitors and/or angiotensin II receptor blockers, beta blockers, aldosterone antagonists, diuretics, vasodilators, inotropes and recently, ivabradine and sacubitril/valsartan), cardiac transplantation, implantable cardioverter defibrillators (ICD) and cardiac resynchronization therapy (CRT), and mechanical circulatory support (MCS) devices. Heart transplantation is the primary treatment for advanced, refractory heart failure patients, but is limited as an option as donor heart availability remains relatively constant annually while the number of heart failure patients in need continues to increase. ICD and CRT therapy have become common and appropriate interventions for select patients whose symptoms continue to progress on optimal medical management. Several mechanical circulatory support alternatives are currently approved by FDA for the treatment of end-stage left ventricular heart failure, including the HeartMate II LVAS. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The HeartMate 3 LVAS is commercially available in the following countries: All countries in the European Union, Colombia, Egypt, India, Israel, Kazakhstan, Lebanon, Malaysia,

Mexico, Saudi Arabia, Switzerland, and Turkey. The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device:

- Death
- Bleeding
- Cardiac arrhythmia
- Localized infection
- Right heart failure
- Respiratory failure
- Device malfunctions
- Driveline infection
- Renal dysfunction
- Sepsis
- Stroke
- Other neurological event (not stroke-related)
- Hepatic dysfunction
- Psychiatric episode
- Venous thromboembolism
- Hypertension
- Arterial non-central nervous system (CNS) thromboembolism
- Pericardial fluid collection
- Pump pocket or pseudo pocket infection
- Myocardial infarction
- Wound dehiscence
- Hemolysis (not associated with suspected device thrombosis)

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

1. Biocompatibility Studies

The primary material of construction in the HeartMate 3 LVAS device is a titanium alloy, Ti6Al4V. The outflow graft is constructed of polyester vascular graft prostheses sealed with gelatin.

Toxicology and biocompatibility evaluations and testing for the HeartMate 3 LVAS were conducted in accordance with ISO 10993-1: Biological Evaluation of Medical Devices Part 1: Evaluation and Testing. Summaries of the test results are provided in Tables 1-4. Test samples for the studies consisted of patient-contacting (direct and indirect) portions of the devices and were produced from production equivalent units. All results were acceptable.

Table 1: Summary of Biocompatibility Testing - HeartMate 3 LVAD

Test	Purpose	Results
Cytotoxicity – minimal essential medium (MEM) elution	To determine if test article extracts cause cytotoxic effects and cell lysis.	The test article was non-cytotoxic with equivalent results to the negative control.
Sensitization – Guinea pig maximization	To evaluate the potential of a material or product to cause a sensitizing effect or allergenic reaction over an extended period of exposure.	The test article extracts did not elicit a sensitization response following an induction phase and a challenge phase.
Irritation/intracutaneous reactivity – rabbit intracutaneous reactivity	To determine if the test article extracts would cause local irritation in the dermal tissues of the test animals.	The injected test and control sites did not show significant dermal reactions over the observation periods.
Acute systemic toxicity	To determine if the test article extracts would cause acute systemic toxicity.	The respective test article extracts did not cause abnormal clinical signs indicative of toxicity, when tested in Swiss Albino mice.
Pyrogenicity - material mediated pyrogen test	To determine if the test article extracts causes a febrile response (temperature rise) in intravenously injected rabbits.	The rise in temperature was $\leq$ 0.5 ˚C and the test article was considered non-pyrogenic.
Sub-chronic toxicity	To determine if the test article extracts would cause systemic toxicity due to potential leachable components, when intravenously injected over 14 days in Albino mice.	The test article extract did not show any abnormal clinical signs in the test animals and was considered negative for signs of systemic toxicity due to leachable components.
Chronic toxicity	To determine if the test article extracts would cause systemic toxicity due to potential leachable components, when intravenously injected over 90 days in rats.	The test article extracts did not show a significantly greater biological reaction on the test animals as compared to the animals treated with the control article.
Hemocompatibility - ASTM hemolysis (direct contact and extract)	To determine the potential hemolytic activity on rabbit blood in response to the test article and its extract.	The test article and test article extracts showed hemolytic indexes of <5.0%.
Genotoxicity – AMES	To determine the potential mutagenic activity of a test sample extracts in strains of *Salmonella typhimurium*.	Test article extracts did not produce a two-fold or three-fold increase in the number of revertants in any of the 5 tester strains.
Genotoxicity – chromosomal	To determine whether the test article extracts would cause	Test article extracts did not induce statistically significant

Test	Purpose	Results
aberration	structural chromosome aberrations in Chinese Hamster Ovary cells.	increases in the number of structural chromosome aberrations compared to the negative control under both the activated and non-activated conditions.
Genotoxicity – mouse micronucleus	To determine the potential of the test article to induce micronuclei formation in immature polychromatic erythrocytes (PCE) present in the bone marrow of adult CD-1 mice.	Test article extract did not show a significant increase in the number of micronucleated PCEs as compared to the negative controls.
Implant	To verify the *in vivo* safety of the device when implanted in an animal model over a specified period of time.	There was no evidence of compromised hemodynamics, hemocompatibility, biocompatibility, hepatic function, or renal function, and no infection, or pathologic effects associated with the device over the tested period of time.
Chemical characterization	To identify and assess extractables utilizing exhaustive extraction conditions.	The risks estimated from each route of exposure and toxicological effects were deemed low for the HeartMate 3 LVAD. There were no leachables of toxicological concern after performing a chemical characterization testing utilizing exhaustive extractions (GC-MS, LC-MS, ICP-MS, FTIR) in conjunction with an assessment of extractables.

Table 2: Summary of Biocompatibility Testing - HeartMate 3 System Controller

Test	Purpose	Results
Cytotoxicity - agarose overlay	To determine if solid samples of the test article cause cytotoxic effects and cell lysis.	The test article was non-cytotoxic with equivalent results to the negative control.

Table 3: Summary of Biocompatibility Testing - HeartMate 3 Tunneler, Skin Coring Punch and Tunneling Adapter Assemblies

Test	Purpose	Results
Tunneler Assembly and Skin Coring Punch		
Cytotoxicity – minimal essential medium (MEM) elution	To determine if test article extracts cause cytotoxic effects and cell lysis.	The test article was non-cytotoxic with equivalent results to the negative control.
Tunneling Adapter Assembly		
Cytotoxicity – minimal essential medium (MEM) elution	To determine if test article extracts cause cytotoxic effects and cell lysis.	The test article was non-cytotoxic with equivalent results to the negative control.
Sensitization – Guinea pig maximization	Evaluate the potential of a material or product to cause a sensitizing effect or allergenic reaction over an extended period of exposure.	The test article extracts did not elicit a sensitization response following an induction phase and a challenge phase.
Irritation/intracutaneous reactivity – rabbit intracutaneous reactivity	To determine if the test article extracts would cause local irritation in the dermal tissues of the test animals.	The injected test and control sites did not show significant dermal reactions over the observation periods.
Acute systemic toxicity	To determine if the test article extracts would cause acute systemic toxicity.	The respective test article extracts did not cause abnormal clinical signs indicative of toxicity, when tested in Swiss Albino mice.
Pyrogenicity - material mediated pyrogen test	To determine if the test article extracts causes a febrile response (temperature rise) in intravenously injected rabbits.	The rise in temperature was $\leq$ 0.5 ˚C and the test article was considered non-pyrogenic

Table 4: Summary of Biocompatibility Testing - HeartMate 3 Modular Cable

Test	Purpose	Results
Cytotoxicity - agarose overlay	To determine test article extracts for cytotoxic effects and cell lysis.	The test article was non-cytotoxic with equivalent results to the negative control.
Sensitization – Guinea pig maximization	To evaluate the potential of a material or product to cause a sensitizing effect or allergenic reaction over an extended period of exposure.	The test article extracts did not elicit a sensitization response following an induction phase and a challenge phase.
Irritation/Intracutaneous reactivity	To determine if the test article extracts would cause local irritation in the dermal tissues of the test patients.	The injected test and control sites did not show significant dermal reactions over the observation periods.

2. *In Vitro* Verification Studies

The HeartMate 3 LVAD, Outflow Graft, Driveline, Apical Cuff, System Controller, and Surgical Tools were subjected to a variety of *in vitro* bench tests to verify that the design input requirements were met. The bench testing results of the HeartMate 3 LVAS components are summarized in Table 5.

Table 5: Summary of *In Vitro* Verification testing – HeartMate 3 LVAS

Test	Purpose	Results
LVAD		
Hydrodynamic performance	To verify LVAD flow-pressure capacity, flow estimation, power requirements, vibration resistance, mechanical shock resistance.	Passed
Computational fluid dynamics (CFD) analysis	To assess the hydraulic performance of the pump design and pump hemolytic and thrombotic potentials.	Passed
Torque strength	To verify the torque strength of the inflow cannula to the pump attachment.	Passed
Shock and vibration	To verify that LVAD maintains essential performance after being subjected to shock and vibration per ISO 14708-1 clause 23.	Passed
Leak test	To verify that there are no leaks at the joints.	Passed
LVAD start-up, speed control and voltage test	To demonstrate that that LVAD maintains set speed and voltage and starts on command.	Passed
Particulate release	To demonstrate that the average count of particles from samples is acceptable.	Passed
Pump physicals	To verify the pump size.	Passed
Outflow Graft		
Kink resistance	To demonstrate that the outflow graft is able to articulate without kinking.	Passed
Bend relief engagement	To demonstrate that the installation and removal force of the outflow graft bend relief and the pull-off force of the bend relief to the bend relief clip is acceptable.	Passed
Outflow graft length and diameter	To verify that the minimum length and the inner diameter of the outflow graft are acceptable.	Passed
Bend relief removal torque	To demonstrate that outflow graft bend relief torque required to disconnect the bend relief from the graft is acceptable.	Passed
Shock and vibration	To demonstrate that there is no leak at the joints after the graft is subjected to shock and vibration loads.	Passed

Test	Purpose	Results
Driveline		
Chemical resistance	To demonstrate that HeartMate 3 Driveline does not have electrical and mechanical damage after being subjected to cleaning agents.	Passed
Shock and static load test	To demonstrate that there is no mechanical or electrical damage for each Driveline tested.	Passed
Durability and water resistance	To demonstrate that the Driveline inline connectors remain functional and sealed areas are water resistant.	Passed
Impact and shear resistance	To demonstrate that the Modular Cable is not mechanically or electrically damaged after being subjected to impact resistance (UL 2556 clause 7.11) and shear force.	Passed
Flexibility and kink resistance	To demonstrate that Driveline is acceptable for use when subject to bending.	Passed
Torque test	To demonstrate that Driveline inline connector nut retraction and breakaway torque is acceptable.	Passed
Cut resistance	To demonstrate that the Modular Cable and percutaneous cable remain undamaged following incidental contact with a cutting tool.	Passed
Hi-pot test	To verify that Driveline withstands hi-pot test.	Passed
Insertion and removal force test	To verify that Driveline inline connector insertion and removal forces are acceptable.	Passed
Driveline inspection tests	To verify external features of the Driveline such as inline connector length, diameter, Modular Cable length, outer diameter and percutaneous length.	Passed
Apical Cuff		
Leak test	To demonstrate that water does not leak at the interface between the inlet cannula and apical cuff.	Passed
Inseparability test	To demonstrate that when apical cuff is locked into place by lock mechanism, it resists separation from the inflow.	Passed
Pull test	To demonstrate that the axial force required to remove the apical cuff should be low amount of force when no locking mechanism is engaged.	Passed
Rigidity test	To demonstrate that the apical cuff is rigid	Passed

Test	Purpose	Results
	enough to resist deformation.	
Particulate release	To demonstrate that particulate matter release is in compliance with EN 45502-1 subclause 14.2	Passed
System Controller		
Drop resistance, shock resistance and vibration	To verify that HeartMate 3 System Controller and Modular Cable satisfy the mechanical drop, shock and vibration requirements.	Passed
Performance testing and functionality testing	To verify that System Controller satisfies performance requirements such as thermal management, motor power, operating voltage, Controller electronics power and Controller power, and to verify Controller functionality such as Controller mating characteristics, Controller case requirements, power cable requirements, user interface and the 11 volt Li-Ion Backup Battery.	Passed
Pump power display	To demonstrate that Controller has the capability to measure and display LVAD power.	Passed
Overcurrent protection test	To verify that Controller is capable of restoring power to the LVAD within 100 ms of a short in the driveline.	Passed
Water and material ingress	To verify that HeartMate 3 System Controller connected with Modular Cable satisfies requirements such as water and material ingress, Modular Cable-Controller connector durability and Driveline electrical resistance.	Passed
User interface features	To verify System Controller user interface membrane switch features such as switch activation force and service life, visual indicator characteristics and liquid crystal display (LCD).	Passed
Insertion and extraction forces	To demonstrate that the System Controller and Modular Cable comply with the insertion and extraction forces specified in the design requirements.	Passed
Audio annunciator characteristics	To verify the audible annunciator characteristics of the System Controller.	Passed
Reusable Instruments – HeartMate 3 Outflow Pliers, HeartMate 3 Cuff Unlock Tool, and HeartMate 3 Tunneling Lance and Handle		
Functional testing	To test for functionality of the tools after	Passed

Test	Purpose	Results
	undergoing the pre-determined cleaning, disinfection and sterilization conditioning.	
Direct part marking testing	To demonstrate the Unique Device Identification number remains legible without exhibiting any signs of corrosion or damage after undergoing the pre-determined cleaning, disinfection and sterilization conditioning.	Passed
HeartMate 3 Tunneling Adapter		
Functional testing	To test for functionality of the tunneling adapter as well as attachment strength of the interfaces between the tunneling adapter, tunneling handle and lance.	Passed
HeartMate 3 LVAS - Electrical Safety and Electromagnetic Compatibility		
Electrical safety and electromagnetic compatibility testing	To demonstrate that HeartMate 3 LVAS complies with IEC 60601-1 and its collateral standards, including the requirements for electromagnetic compatibility (IEC 60601-1-2); to validate the use of the HeartMate 3 LVAS in ambulances and aircraft; to demonstrate HeartMate 3 LVAS compatibility with security and logistical systems (SLS), electrosurgical unit (ESU), electrocardiogram (EKG/ECG), defibrillators, ultrasound, and pacemaker and implantable cardioverter defibrillators (ICD).	Passed

3. *In Vitro* Long-Term Reliability Testing

The HeartMate 3 LVAD was subjected to real-time reliability testing, and the Driveline, Outflow Graft, and Connectors were subjected to accelerated reliability testing. The test results are summarized in Table 6.

Table 6: Summary of Reliability Testing

Test	Purpose	Results
LVAD reliability life testing	To test for the long-term, real-time reliability of the HeartMate 3 LVAD assembly to demonstrate 80% reliability with at least 80% confidence for a 5-year mission life	Results demonstrated that the HeartMate 3 LVAD achieved 94% reliability with 80% confidence at one year and 89% reliability with 80% confidence at two years.
Accelerated reliability	To perform accelerated	All acceptance criteria were

Test	Purpose	Results
testing	reliability testing on the HeartMate 3 Driveline, Outflow Graft and Connectors. The tests included subjecting the components to pre-determined conditioning, and testing for mechanical and/or electrical failures as specified by each sub-test.	met. No mechanical or electrical failures were identified.

4. Software Validation

The HeartMate 3 LVAD and the System Controller are software driven components of the system. The software development process complies with AAMI ANSI IEC 62304:2006, AAMI ANSI ES 60601-1:2005/(R)2012, A1:2012, c1:2009/(R)2012 and A2:2010/(R)2012.

5. Sterilization

The following HeartMate 3 system components are provided sterile: HeartMate 3 LVAD, Outflow Graft, Coring Knife, Apical Cuff, Thread Protectors, Skin Coring Punch, Tunneling Adapter, Modular Cable with Cap, and the System Controller. The sterilization method is 100% ethylene oxide (EO) and the sterilization process has been validated to provide a minimum sterility assurance level (SAL) of 10^{-6} in accordance with AAMI/ANSI/ISO 11135:2014. A validated post-sterilization aeration process assures that residual levels of EO and ethylene chlorohydrin (ECH) are within acceptable limits specified by ANSI/AAMI/ISO 10993-7:2008. The implant accessories, i.e., the Surgical Hand Tools and Tunneling Lance and Handle, are re-usable tools that are sterilized by the user.

6. Packaging and Shelf Life

Packaging integrity and shelf life testing was completed for each of the HeartMate 3 LVAS components per ASTM D4169-09 and AAMI ANSI ISO 11607-1: 2006. Shelf life has been established at 3 years for the HeartMate 3 LVAD, System Controller and Backup Battery, Apical Cuff, Modular Cable and Cable Cap, Skin Coring Punch, Thread Protectors, and Coring Knife, and at 5 years for the the Sealed Outflow Graft.

B. Animal Study

A chronic Good Laboratory Practice (GLP)-compliant animal study was conducted in a bovine model to verify that the HeartMate 3 LVAS did not pose any unacceptable safety risk in the animal for a minimum of 60 days. Safety of the HeartMate 3 device was assessed through the collection of the following in each study animal: pump data, vital signs, blood chemistries, hematology and coagulation profiles, plasma hemoglobin, and adverse events.

Full gross and histopathological assessment was performed on animals surviving to term. A summary of the chronic animal study is provided in Table 7.

Table 7: Summary of Chronic Animal Study

GLP chronic animal study – Implant duration: 60 days	
Sample size	10
Test articles	HeartMate 3 LVAS - HeartMate 3 Pump with Modular Cable, Outflow Graft, Apical Cuff, HeartMate 3 Controller, and Backup battery.
Technique	Left thoracotomy was performed to implant HeartMate 3 LVAS implantable components.
Results	Eight of the 10 animals survived to 60 days post implantation. Two animals expired on post-op day 0 due to complications unrelated to the HeartMate 3 device. No device malfunctions were reported. Of the nine adverse events reported, only one was determined to be device related: a driveline site infection.
Conclusion	Study data showed that there were no observed unacceptable safety risks associated with the use of the HeartMate 3 device.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study in the U.S. to establish a reasonable assurance of safety and effectiveness of the HeartMate 3 LVAS to provide short-term hemodynamic support (such as bridge to transplant, BTT; or bridge to myocardial recovery) in patients with advanced refractory left ventricular heart failure under IDE #G140113, entitled "Multi-Center Study of Maglev Technology in Patients Undergoing MCS Therapy with HeartMate 3" (MOMENTUM 3).

MOMENTUM 3 was an all-comers trial enrolling patients under a single set of entry criteria irrespective of the intended use of the device as short-term (e.g., BTT and bridge to cardiac recovery) or as long-term (e.g., destination therapy; DT) support. The trial consisted of three pre-specified cohorts as follows:

- A Short Term (ST) Cohort to establish the safety and effectiveness of the HeartMate 3 LVAS in providing short-term hemodynamic support.
- A Long Term (LT) Cohort to establish the safety and effectiveness of the HeartMate 3 LVAS in providing long-term hemodynamic support.
- A Long Term Durability Cohort to establish the long-term clinical durability of the HeartMate 3 LVAD.

The ST Cohort data from the MOMENTUM 3 trial was the basis for the premarket application (PMA) approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients in the MOMENTUM 3 ST Cohort were treated between September 2014 and October 2015. The database for this PMA reflected data collected through the 6-month

follow-up visit (April 13, 2017) and included 294 patients enrolled at 47 investigational sites.

The MOMENTUM 3 trial was a prospective, multicenter, randomized pivotal study comparing the HeartMate 3 LVAS with the HeartMate II LVAS. Patients were randomized in a 1:1 ratio to either HeartMate 3 or HeartMate II.

The MOMENTUM 3 trial was conducted under the oversight of several independent committees, including a Study Oversight Committee, which provided general trial oversight and leadership; a Clinical Events Committee (CEC), which adjudicated all adverse events per pre-established definitions; and a Data and Safety Monitoring Board (DSMB), which reviewed the trial data periodically to ensure that continuation of the trial did not present any unacceptable risk to the patients.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the MOMENTUM 3 trial was limited to patients who met the following inclusion criteria:

   - Patient or legal representative has signed Informed Consent Form.
   - Age $\geq$ 18 years.
   - Body Surface Area (BSA) $\geq$ 1.2 m^2.
   - New York Heart Association (NYHA) Class III with dyspnea upon mild physical activity or NYHA Class IV
   - Left Ventricular Ejection Fraction (LVEF) $\leq$ 25%.
   - Inotrope dependent OR cardiac index (CI) < 2.2 L/min/m^2, while not on inotropes and patient 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.
   - Females of child-bearing age must agree to use adequate contraception.

   Patients were not permitted to enroll in the MOMENTUM 3 trial if they met any of the following exclusion criteria:

   - Etiology of heart failure due to or associated with uncorrected thyroid disease, obstructive cardiomyopathy, pericardial disease, amyloidosis, or restrictive cardiomyopathy.
   - Technical obstacles which pose an inordinately high surgical risk, in the judgment of the investigator.
   - Existence of ongoing MCS other than IABP.
   - Positive pregnancy test.
   - Presence of mechanical aortic cardiac valve that will not be either converted to a bioprosthesis or oversewn at the time of LVAD implant.

- History of any organ transplant.
- Platelet count < 100,000 x 10^3/L (< 100,000/ml).
- Psychiatric disease/disorder, irreversible cognitive dysfunction or psychosocial issues that are likely to impair compliance with the study protocol and LVAS management.
- History of confirmed, untreated abdominal aortic aneurysm (AAA) > 5 cm in diameter within 6 months of enrollment.
- Presence of an active, uncontrolled infection.
- Intolerance to anticoagulant or antiplatelet therapies or any other peri/post-operative therapy that the investigator will require based upon the patient's health status
- Presence of any one of the following risk factors for indications of severe end organ dysfunction or failure:
    - An international normalized ratio (INR) ≥ 2.0 not due to anticoagulation therapy.
    - Total bilirubin > 43 μmol/L (2.5 mg/dl), shock liver, or biopsy proven liver cirrhosis.
    - History of severe chronic obstructive pulmonary disease (COPD) defined as the ratio of forced expiratory volume in one second to forced vital capacity (FEV1/FVC) < 0.7, and FEV1 < 50% predicted.
    - Fixed pulmonary hypertension with a most recent pulmonary vascular resistance (PVR) ≥ 8 Wood units that is unresponsive to pharmacologic intervention.
    - History of stroke within 90 days prior to enrollment, or a history of cerebrovascular disease with significant (> 80%) uncorrected carotid artery stenosis.
    - Serum Creatinine ≥ 221 μmol/L (2.5 mg/dl) or the need for chronic renal replacement therapy.
    - Significant peripheral vascular disease (PVD) accompanied by rest pain or extremity ulceration.
- Patient has moderate to severe aortic insufficiency without plans for correction during pump implant.
- 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).
- Planned bi-ventricular assist device support prior to enrollment.
- Patient has known hypo- or hyper-coagulable state such as disseminated intravascular coagulation and heparin induced thrombocytopenia (HIT)
- Participation in any other clinical investigation that is likely to confound study results or affect the study.
- Any condition other than heart failure that could limit survival to less than 24 months.

2. Follow-up Schedule

All patients were scheduled for follow-up examinations at Day 1, 1 week, discharge, 1 month, 3 months, 6 months, 12 months, 18 months and 24 months, postoperatively. Follow-up to support the ST indication was concluded at 6 months.

Preoperative baseline assessments included physical exam, patient demographics, blood chemistry, hemodynamics, medical and cardiac history, current medications, imaging tests, functional capacity as measured by the 6-minute walk test (6MWT) and NYHA classification, and quality of life as measured by EuroQoL 5D-5L (EQ-5D-5L) and Kansas City Cardiomyopathy Questionnaire (KCCQ). Postoperative assessments included current medications, patient status and outcome, blood chemistry, hemodynamics, imaging tests, functional status and quality of life. Pre-defined adverse events, reoperations, readmissions to the hospital and device malfunctions were reported as they occurred.

3. Clinical Endpoints

The primary endpoint for the ST Cohort of the MOMENTUM 3 trial was a composite of survival to transplant, recovery, or 6 months of LVAD support free of debilitating stroke or reoperation to replace the pump. Debilitating stroke was defined as a stroke with Modified Rankin Scale (MRS) > 3 assessed at 60 days after the event.

The primary analysis was performed as intent to treat (ITT) and was performed at exactly 180 days. Patients were considered a success if within 180 days post implantation, they receive a cardiac transplant that was not urgently required due to a device malfunction, had the device explanted subsequent to myocardial recovery, or survived to 180 days post implantation on LVAD support without experiencing a debilitating stroke (MRS > 3) or having the device replaced or exchanged. Patients were considered a failure if, within 180 days post implantation, they expired while on LVAD support, experienced a debilitating stroke, had the device replaced or exchanged, had a device explanted for a reason other than myocardial recovery, received an urgent transplant due to malfunction of the device, withdrew from the study for any reason, or did not receive a HeartMate 3 or HeartMate II after randomization.

The HeartMate 3 was to be considered non-inferior to the HeartMate II if the lower bound of the two-sided 95% confidence interval (CI) for the difference in the success rate between the two study arms (HeartMate 3 – HeartMate II) was greater than the non-inferiority margin of -10%. Additionally, if HeartMate 3 were found to be non-inferior to HeartMate II, the protocol specified that the primary composite endpoint would also be analyzed sequentially for superiority at a one-sided 0.025 level of significance.

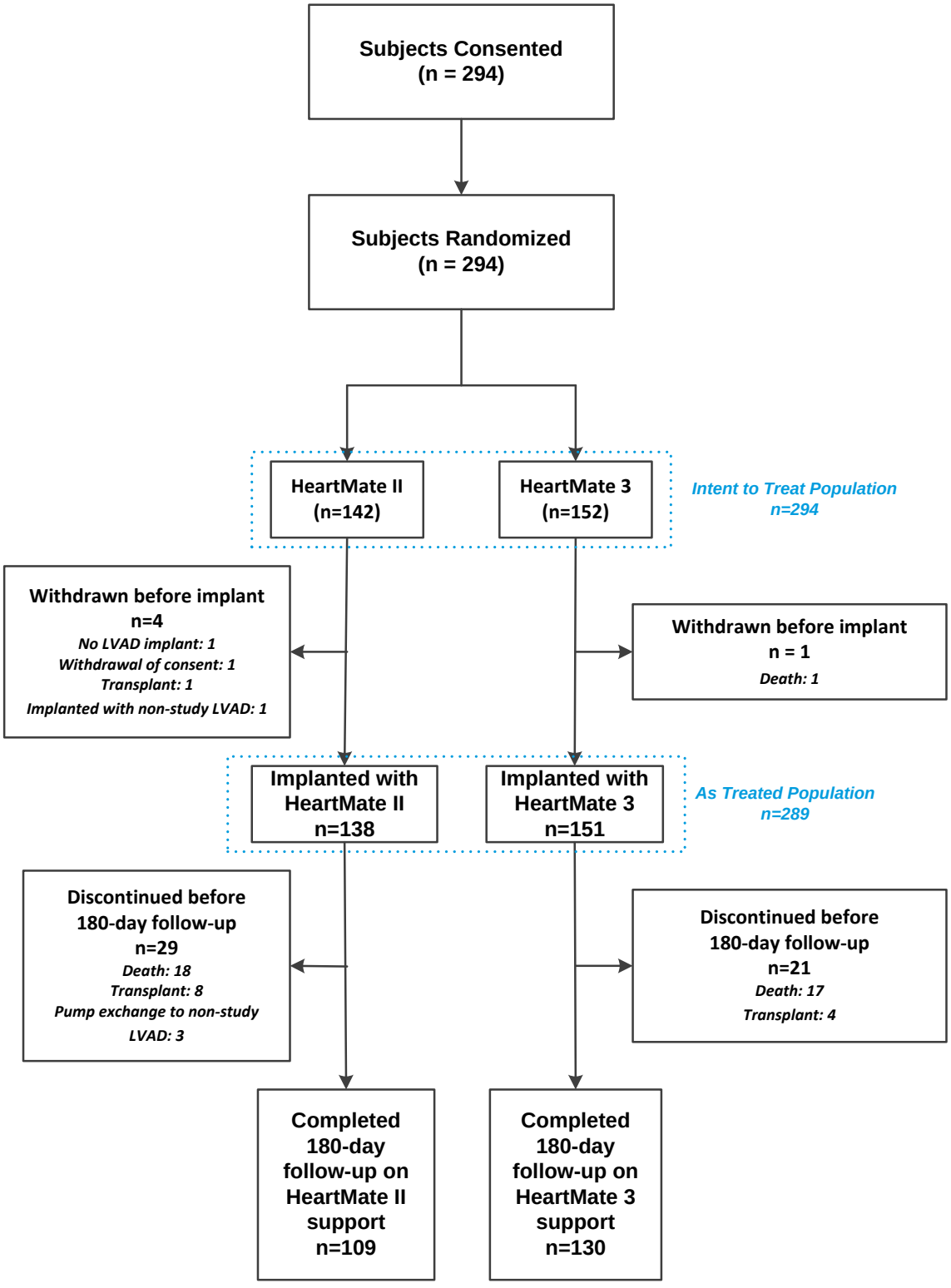
Secondary endpoints were evaluated descriptively, including adverse events, hospitalizations, reoperations, quality of life (EQ-5D-5L and KCCQ at 6 months), functional status (NYHA Class and 6MWT), and device malfunctions. In addition, a number of subgroup analyses were prespecified including gender, race, Interagency

Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile, or intended use of the device (BTT vs. DT). The secondary endpoints were evaluated using the As Treated (AT) population and were assessed at exactly 180 days except the quality of life and the functional status, which were assessed at 6 months (180 ± 30 days).

B. Accountability of PMA Cohort

At the time of database lock, of 294 patients enrolled in the ST Cohort trial, 98.3% (289) patients are available for analysis at the completion of the study, the 6-month post-operative visit. The disposition of the patients is shown in Figure 3. All 294 patients were consented and randomized, 152 patients to the HeartMate 3 arm and 142 patients to the HeartMate II arm, which comprise the ITT population. Five (5) patients were withdrawn after randomization but before receiving a device, one (1) in the HeartMate 3 arm and four (4) in the HeartMate II arm. As such, the AT population consists of 289 patients, 151 in the HeartMate 3 arm and 138 in the HeartMate II arm.

Figure 3: Disposition of MOMENTUM 3 Patients in the ST Cohort



C. Study Population Demographics and Baseline Parameters

The demographics and baseline characteristics of the study population, as summarized in Table 8, are typical for an LVAD study performed in the U.S. The two (2) study arms were well-balanced, with no significant difference in demographics, intended use, INTERMACS profile, functional status, exercise tolerance, or baseline inotropes.

Table 8: Patient Demographics and Baseline Characteristics (ITT Population)

Demographics and Baseline Characteristics	Summary Statistics[*]		p-Value[†]
	HeartMate II (n=142)	HeartMate 3 (n=152)	
Age – year	58.9 ± 12.0	60.3 ± 12.3	0.3076
Body-surface area – m^2	2.1 ± 0.3	2.1 ± 0.3	0.6428
Body-mass index – kg/m^2	28.5 ± 5.7	28.8 ± 5.6	0.6200
Weight – kg	87.4 ± 19.7	88.5 ± 20.0	0.6399
Male sex	114 (80.3%)	121 (79.6%)	1.0000
Ischemic cause of heart failure	73 (51.4%)	68 (44.7%)	0.3501
Race			
White	107 (75.4%)	104 (68.4%)	0.1973
Non-white	35 (24.6%)	48 (31.6%)	
Intended use			
Bridge to transplant (BTT)[‡]	37 (26.1%)	41 (27.0%)	0.9784
Possibly BTT: Likely to be eligible	16 (11.3%)	18 (11.8%)	
Possibly BTT: moderate likelihood	9 (6.3%)	7 (4.6%)	
Possibly BTT: unlikely to be eligible	2 (1.4%)	2 (1.3%)	
Destination therapy (DT)	78 (54.9%)	84 (55.3%)	
INTERMACS profile[§]			
1	4 (2.8%)	1 (0.7%)	0.7180
2	44 (31.0%)	50 (32.9%)	
3	69 (48.6%)	76 (50.0%)	
4	23 (16.2%)	22 (14.5%)	
5	2 (1.4%)	2 (1.3%)	
6 or 7	0 (0.0%)	0 (0.0%)	
Not provided[‖]	0 (0.0%)	1 (0.7%)	
NYHA Class[¶]			
Class I	0 (0.0%)	0 (0.0%)	0.3811
Class II	0 (0.0%)	0 (0.0%)	
Class IIIB	4 (2.8%)	8 (5.3%)	
Class IV	138 (97.2%)	144 (94.7%)	

Demographics and Baseline Characteristics	Summary Statistics*		p-Value†
	HeartMate II (n=142)	HeartMate 3 (n=152)	
Baseline cardiovascular history			
Coronary artery disease	79 (55.6%)	83 (54.6%)	0.9068
Myocardial infarction	53 (37.3%)	54 (35.5%)	0.8086
Left ventricular aneurysm/repair	1 (0.7%)	2 (1.3%)	1.0000
Arrhythmias	104 (73.2%)	113 (74.3%)	0.8946
Supraventricular arrhythmias	71 (50.0%)	74 (48.7%)	0.9071
Ventricular arrhythmias	59 (41.5%)	69 (45.4%)	0.5566
Congenital heart disease	1 (0.7%)	0 (0.0%)	0.4830
Revascularization	61 (43.0%)	59 (38.8%)	0.4789
Valve replacement/repair	6 (4.2%)	13 (8.6%)	0.1579
Valve insufficiency	121 (85.2%)	133 (87.5%)	0.6120
CRT/CRT-D#	51 (35.9%)	59 (38.8%)	0.6310
Defibrillator (ICD/CRT-D)	100 (70.4%)	101 (66.4%)	0.5306
Pacemaker	8 (5.6%)	9 (5.9%)	1.0000
Ongoing IABP#	21 (14.8%)	18 (11.8%)	0.4945
Hypertension	95 (66.9%)	103 (67.8%)	0.9014
Baseline medical history			
Neurological history	30 (21.1%)	36 (23.6%)	0.6752
Transient ischemic attack (TIA)	10 (7%)	16 (10.5%)	0.3124
Cerebrovascular accident: Ischemic	11 (7.7%)	11 (7.2%)	1.0000
Cerebrovascular accident: Hemorrhagic	1 (0.7%)	0 (0.0%)	0.4830
Cerebrovascular accident: Not specified	2 (1.4%)	1 (0.7%)	0.6113
Seizure	2 (1.4%)	1 (0.7%)	0.6113
Neurological other	9 (6.3%)	12 (7.9%)	0.6559
Psychiatric history	40 (28.2%)	28 (18.4%)	0.0533
Psychosocial issues	8 (5.6%)	8 (5.3%)	1.0000
Substance abuse	10 (7%)	5 (3.3%)	0.1868
Gastrointestinal history	48 (33.8%)	62 (40.8%)	0.2297
Renal insufficiency	36 (25.4%)	30 (19.7%)	0.2657
Renal failure	6 (4.2%)	10 (6.6%)	0.4461
Cancer History	22 (15.5%)	22 (14.5%)	0.8706
Previous organ transplant history	0 (0.0%)	0 (0.0%)	–
Endocrine history	76 (53.5%)	89 (58.6%)	0.4117
Diabetes mellitus: Insulin-dependent	22 (15.5%)	40 (26.3%)	0.0314
Diabetes mellitus: Non insulin-dependent	32 (22.5%)	30 (19.7%)	0.5704
Hematopoietic/lymphatic history	23 (16.2%)	22 (14.5%)	0.7468

Demographics and Baseline Characteristics	Summary Statistics*		p-Value†
	HeartMate II (n=142)	HeartMate 3 (n=152)	

*Continuous measures - Mean ± SD; categorical measures - no. (%)
†Continuous measures - Two-sample t-test; categorical measures - Fisher's exact test
‡BTT is defined as listed or planned to be listed within 24 hours
§https://www.uab.edu/medicine/intermacs/images/protocol_4.0/protocol_4.0_MoP/Appendix_O_Intermacs_Patient_Profile_at_time_of_implant.pdf
ISubject expired prior to INTERMACS assessment
¶ NYHA IIIB is defined per protocol as NYHA Class III with dyspnea upon mild physical activity; subjects who were inotrope-dependent were considered NYHA Class IV per protocol
#Abbreviations: ICD - implantable cardioverter defibrillator; CRT - cardiac resynchronization therapy device; CRT-D - cardiac resynchronization therapy device with defibrillator; IABP - intra-aortic balloon pump

D. Safety and Effectiveness Results

1. Primary Endpoint

The analysis of the primary endpoint was based on 294 evaluable patients at the 6-month time point, including 152 HeartMate 3 patients and 142 HeartMate II patients, as summarized in Table 9. The results show that in both the ITT and AT analyses, the trial met its primary endpoint and demonstrated non-inferiority of the HeartMate 3 as compared to the HeartMate II.

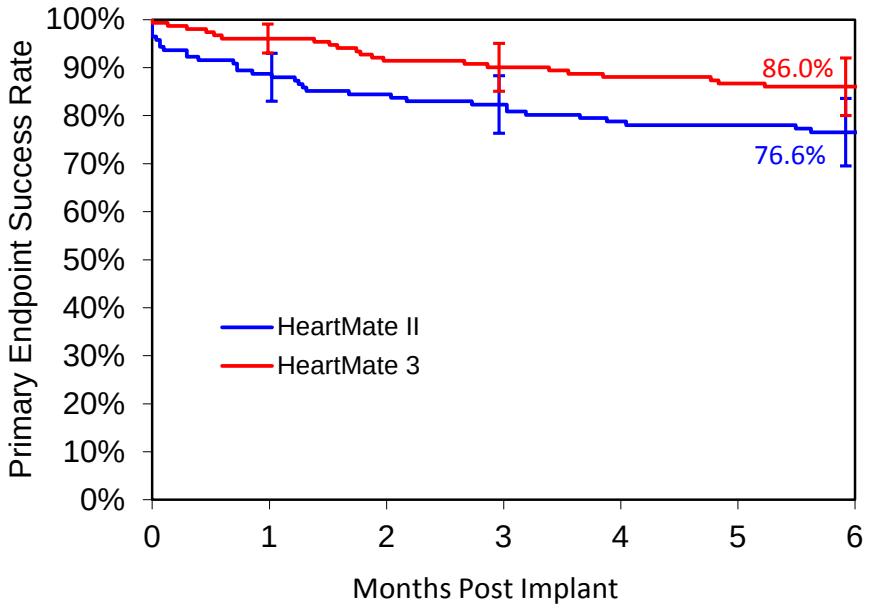
Once non-inferiority was demonstrated, the data were then analyzed to test the superiority of the HeartMate 3 compared to HeartMate II. The test in the ITT population resulted in a significant finding ($p = 0.019$, one-sided), indicating that the HeartMate 3 is superior to the HeartMate II. The difference between the two arms was primarily driven by a higher number of pump exchange and urgent transplants in the HeartMate II arm. However, the finding of superiority was not corroborated by the AT analysis and by a subsequent sensitivity analysis of patients who withdrew from the study. Based on the totality of the analyses, the superiority of the HeartMate 3 over the HeartMate II in terms of the primary endpoint cannot be claimed.

Table 9: Analyses of the Primary Endpoint

	Intent-to-Treat Analysis		As-Treated Analysis	
	HeartMate II	**HeartMate 3**	**HeartMate II**	**HeartMate 3**
Total # of patients	142	152	138	151
Alive free of debilitating stroke or device replacement	103	127	103	127
Elective transplant	6	4	6	4
Total # of successes	109	131	109	131
Success rate at 6 months	76.8%	86.2%	79.0%	86.8%
Difference (HeartMate 3 – HeartMate II)	9.4%		7.8%	
Exact 95% confidence interval	[-2.1%, 20.7%]		[-3.8%, 19.2%]	
Non-inferiority limit	-10%		-10%	
Primary objective – non-inferiority				
Z-Score	4.2031		3.9276	
p-value	<0.0001		<0.0001	
Non-inferiority test	Passed		Passed	
Primary objective – superiority				
Z-Score	4.3482		3.0912	
p-value	0.019		0.0394	
Superiority test	Passed		Failed	

The Kaplan-Meier curve of the primary endpoint is shown in Figures 4 and 5 for the ITT population and AT population, respectively.

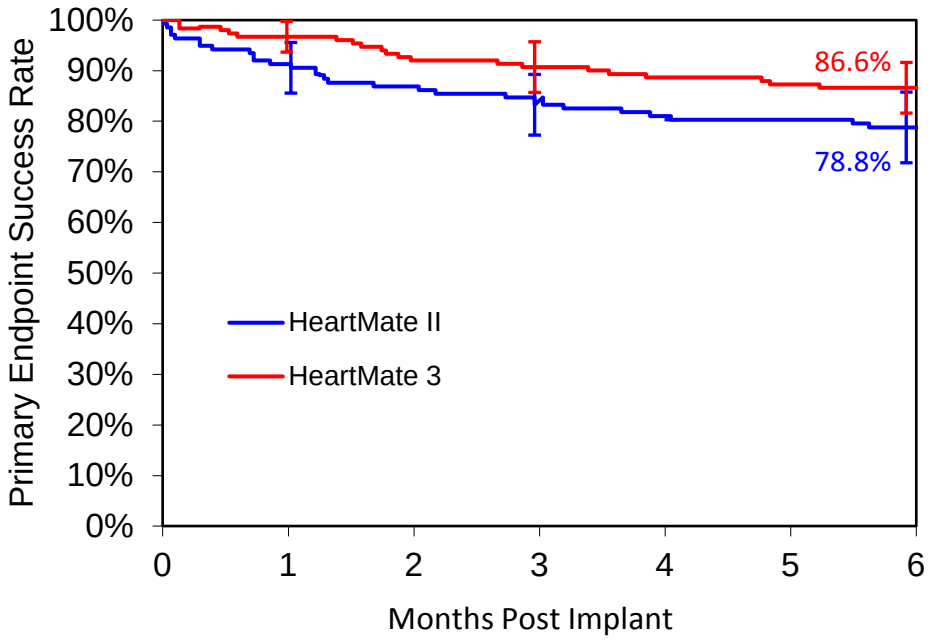
Figure 4: Kaplan-Meier Curve of the Primary Endpoint (ITT Population)



Number of subjects at risk:				
HeartMate II	142	125	116	103
HeartMate 3	152	146	135	127

Note: The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, these confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

Figure 5: Kaplan-Meier Curve of the Primary Endpoint (AT Population)



Number of subjects at risk

HeartMate II	138	125	116	103
HeartMate 3	151	146	135	127

Note: The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, these confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

The details of the outcomes related to the primary composite endpoint for the study are presented in Table 10.

Table 10: Outcomes Related to the Primary Composite Endpoint (AT Population)

Key Safety Outcomes*	HeartMate II (n=138)	HeartMate 3 (n=151)
Death	14	13
Debilitating stroke (MRS > 3)	4	6
Transplant due to device malfunction	2	0
Pump exchange	9	1
Total failures	**29 (21%)**	**20 (13%)**

*For patients who experienced more than one endpoint event during the follow-up period (e.g., debilitating stroke prior to death), the event that occurred first is the failure event listed.

2. Secondary Endpoints

Adverse Events

Table 11 lists all the pre-specified adverse events that occurred in the AT population; Table 12 lists the serious adverse events only. Serious adverse events are defined as those leading to death, congenital abnormality/birth defect, a life-threatening illness/injury that results in permanent disability, hospitalization/prolonged hospitalization, and/or intervention to prevent permanent injury or damage. All adverse events were adjudicated by the CEC for severity and relatedness to the device.

Table 9: All Adverse Events at 6 Months (AT Population)

Adverse Events	Summary Statistics*	
	HeartMate II (n=138)	**HeartMate 3 (n=151)**
Major infection	35% (48, 80)	42% (63, 96)
Localized	26% (36, 58)	30% (46, 57)
Sepsis	7% (9, 10)	9% (14, 19)
Driveline	7% (9, 11)	12% (18, 21)
Pump pocket or pseudo pocket	1% (1, 1)	1% (1, 1)
Pump or pump components	0% (0, 0)	0% (0, 0)
Bleeding	39% (54, 98)	33% (50, 100)
Bleeding requiring surgery	14% (19, 21)	10% (15, 15)
Gastrointestinal bleeding	15% (21, 36)	16% (24, 47)
Cardiac arrhythmia	38% (52, 68)	31% (47, 61)
Ventricular arrhythmia	20% (27, 37)	18% (27, 33)
Supraventricular arrhythmia	22% (30, 31)	15% (23, 27)
Both (ventricular and supraventricular arrhythmia)	0% (0, 0)	1% (1, 1)
Right heart failure	25% (34, 36)	30% (45, 49)
Right ventricular assist device (RVAD)	6% (8, 8)	3% (4, 4)
Respiratory failure	17% (24, 27)	22% (33, 44)
Renal dysfunction	9% (12, 12)	11% (17, 18)
Stroke	11% (15, 17)	8% (12, 12)
Hemorrhagic stroke	6% (8, 8)	3% (4, 4)
Ischemic stroke	7% (9, 9)	5% (8, 8)
Debilitating stroke	4% (5, 5)	6% (9, 9)
Other neurological event	6% (8, 8)	6% (9, 9)
Encephalopathy	1% (1, 1)	2% (3, 3)
Seizure	2% (3, 3)	3% (4, 4)
Transient ischemic attack (TIA)	1% (1, 1)	1% (1, 1)

Adverse Events	Summary Statistics*	
	HeartMate II (n=138)	HeartMate 3 (n=151)
Other†	2% (3, 3)	1% (1, 1)
Hepatic dysfunction	2% (3, 3)	5% (7, 7)
Psychiatric episode	6% (8, 9)	5% (7, 7)
Venous thromboembolism	5% (7, 7)	5% (8, 9)
Hypertension	6% (8, 9)	3% (4, 9)
Arterial non-cns thromboembolism	2% (3, 3)	2% (3, 3)
Pericardial fluid collection	4% (5, 5)	2% (3, 4)
Myocardial infarction	1% (1, 1)	1% (1, 1)
Wound dehiscence	1% (2, 2)	1% (1, 1)
Hemolysis (not associated with suspected device thrombosis)	1% (2,2)	1% (1, 1)
Suspected device thrombosis	10% (14, 18)	0% (0, 0)
Other adverse events	37% (51, 84)	50% (76, 134)

*% patients (# patients, # events)

†Other includes anoxic brain injury, traumatic brain injury, and intracranial bleed due to trauma.

Table 10: Serious Adverse Events at 6 Months (AT Population)

Adverse Events	Summary Statistics*	
	HeartMate II (n=138)	HeartMate 3 (n=151)
Major infection	30% (41, 67)	37% (56, 84)
Localized	22% (31, 49)	28% (42, 49)
Sepsis	7% (9, 10)	9% (14, 19)
Driveline	4% (5, 7)	10% (15, 17)
Pump pocket or pseudo pocket	1% (1, 1)	1% (1, 1)
Pump or pump components	0% (0, 0)	0% (0, 0)
Bleeding	37% (51, 90)	30% (45, 85)
Bleeding requiring surgery	14% (19, 21)	10% (15, 15)
Gastrointestinal bleeding	15% (21, 34)	15% (23, 45)
Right heart failure	25% (34, 36)	30% (45, 49)
Right ventricular assist device (RVAD)	6% (8, 8)	3% (4, 4)
Cardiac arrhythmia	33% (46, 58)	26% (39, 50)
Ventricular arrhythmia	20% (27, 37)	18% (27, 33)
Supraventricular arrhythmia	15% (21, 21)	9% (14, 16)
Both (ventricular and supraventricular arrhythmia)	0% (0, 0)	1% (1, 1)
Respiratory failure	17% (24, 27)	22% (33, 44)

Adverse Events	Summary Statistics*	
	HeartMate II (n=138)	**HeartMate 3 (n=151)**
Renal dysfunction	9% (12, 12)	11% (17, 18)
Stroke	11% (15, 17)	8% (12, 12)
Hemorrhagic stroke	6% (8, 8)	3% (4, 4)
Ischemic stroke	7% (9, 9)	5% (8, 8)
Debilitating stroke	4% (5, 5)	6% (9, 9)
Other neurological event	6% (8, 8)	6% (9, 9)
Encephalopathy	1% (1, 1)	2% (3, 3)
Seizure	2% (3, 3)	3% (4, 4)
Transient ischemic attack (TIA)	1% (1, 1)	1% (1, 1)
Other†	2% (3, 3)	1% (1, 1)
Hepatic dysfunction	2% (3, 3)	5% (7, 7)
Venous thromboembolism	5% (7, 7)	4% (6, 7)
Psychiatric episode	5% (7, 7)	3% (5, 5)
Arterial non-cns thromboembolism	2% (3, 3)	2% (3, 3)
Hypertension	1% (1, 1)	2% (3, 3)
Pericardial fluid collection	3% (4, 4)	2% (3, 4)
Myocardial infarction	1% (1, 1)	1% (1, 1)
Wound dehiscence	1% (2, 2)	1% (1, 1)
Hemolysis (not associated with suspected device thrombosis)	1% (2, 2)	1% (1, 1)
Suspected device thrombosis	10% (14, 18)	0% (0, 0)
Other adverse events	35% (48, 75)	48% (73, 117)

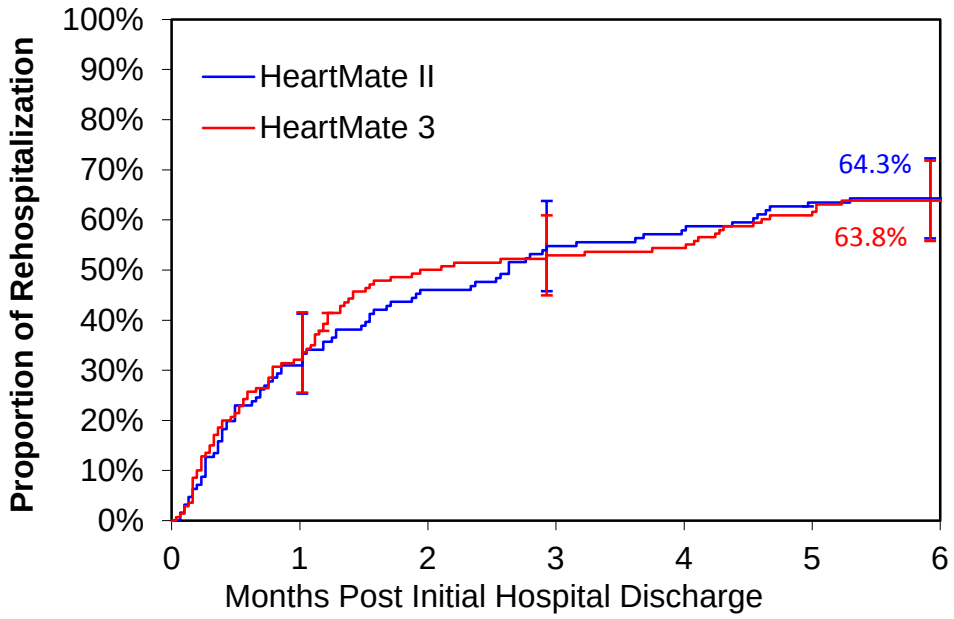
*% patients (# patients, # events)

†Other includes anoxic brain injury, traumatic brain injury, and intracranial bleed due to trauma.

Rehospitalizations

Eighty-nine (89) of the 140 HeartMate 3 patients (64%) discharged from the hospital reported a total of 178 readmissions as compared to 81 of the 126 discharged HeartMate II patients (64%) reporting a total of 159 readmissions. The Kaplan-Meier plot of rehospitalization is shown in Figure 6.

Figure 6: Rehospitalization Following Discharge from Implantation Surgery



Number of Subjects at Risk:				
HeartMate II	126	87	57	43
HeartMate 3	140	95	65	42

Note: The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, these confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion

Reoperations

All surgical procedures that occurred after the initial implantation surgery are summarized in Table 13. Cardiac transplants due to device malfunctions are included as a reoperation; elective cardiac transplants are not. Forty-six (46) of the 151 HeartMate 3 patients (30.5%) required a total of 74 reoperations by 6 months post implantation, as compared to 52 of the 138 HeartMate II patients (37.7%) requiring a total of 87 reoperations. A large number of peri-implant reoperations were due to mediastinal exploration and delayed chest closure.

Table 13: Reoperations at 6 Months

Operation	HeartMate II	HeartMate 3
Mediastinal exploration	19	15
Delayed chest closure	5	17
Replace/exchange device	11	1
RVAD implantation or removal	10	8
Cardiac transplant	2	0
Other – cardiac/vascular	10	3
Gastrointestinal	9	7
Respiratory	7	10
Other	14	13
Total	**87**	**74**

Device Malfunctions

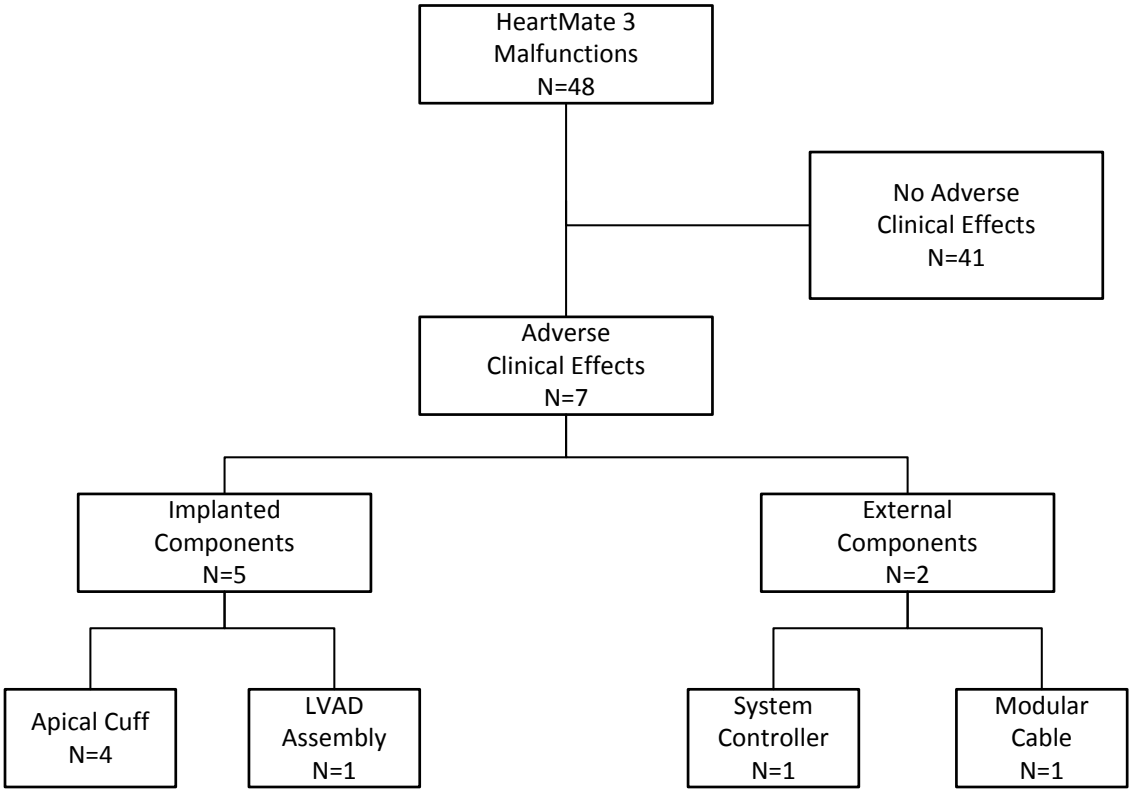
At 6 months, 40 of the 151 (26%) HeartMate 3 patients reported 48 suspected device malfunctions; 29 of the 138 (21%) HeartMate II patients reported 46 suspected device malfunctions, as summarized in Table 14. The majority of malfunctions in both arms involved external components, most commonly the System Controller.

Table 14: Suspected Device Malfunctions at 6 Months

	#Patients	%Patients	Events
HeartMate II (n=138)	29	21.0%	46
HeartMate 3 (n=151)	40	26.5%	48

The details of the 48 suspected HeartMate 3 device malfunctions are shown in Figure 7.

Figure 7: Suspected HeartMate 3 LVAS Malfunctions



Functional Status

Functional status was assessed by the NYHA class and the 6-minute walk test (6MWT), as shown in Figures 8 and 9. All patients were in NYHA Class III or IV at baseline, the proportion decreased to 23% in the HeartMate 3 arm and to 17% in the HeartMate II arm at 6 months. The average 6MWT distance increased from 164 m at baseline to 300 m at 6 months in the HeartMate 3 arm; the same distance increased from 128 m to 335 m in the HeartMate II arm.

Figure 8: NYHA Class over Time

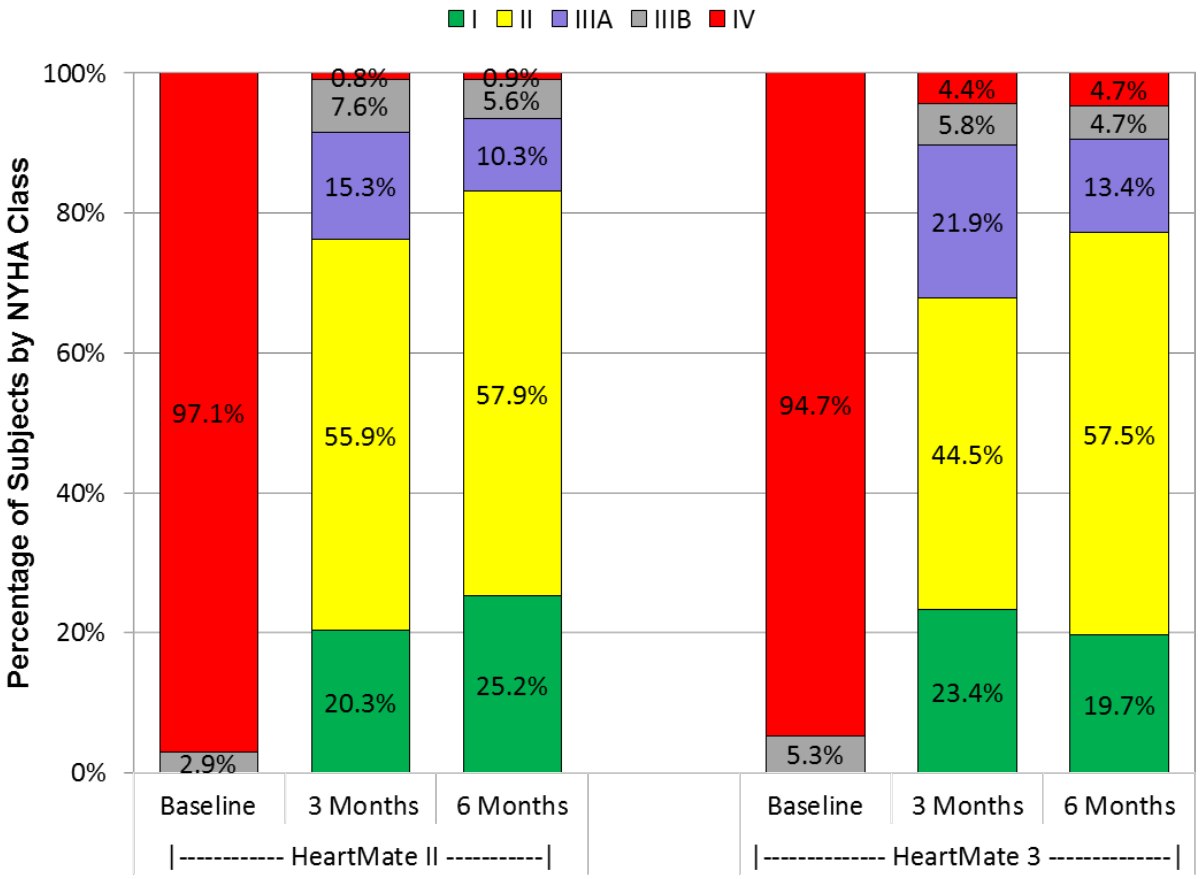
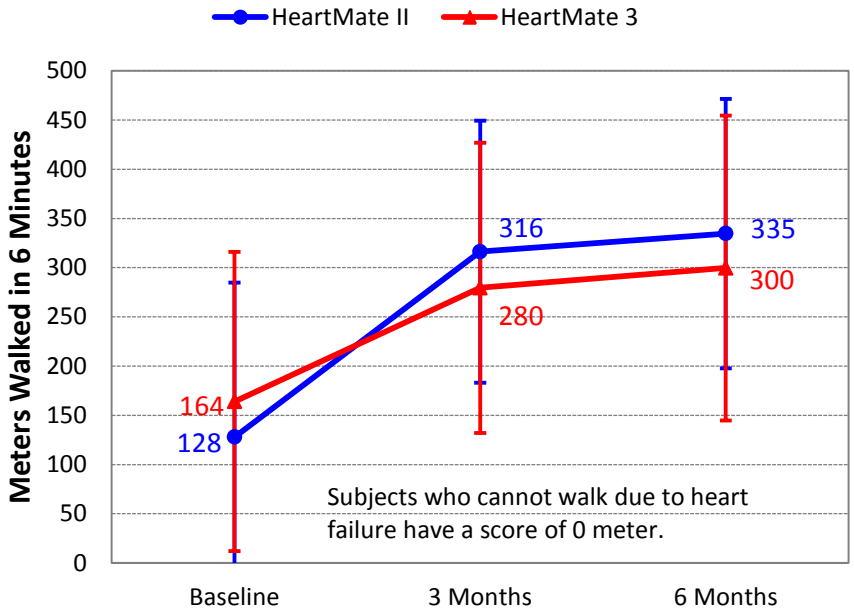


Figure 9: 6MWT Distance over Time



Quality of Life

The quality of life was assessed by the EQ-5D-5L and the KCCQ questionnaires, as summarized in Figures 10-13. Patients in both arms showed comparable improvements in the total EQ-5D-5L Score, the EQ-5D-5L Visual Analog Score, the KCCQ Overall Summary Score, and the KCCQ Clinical Summary Score over time.

Figure 10: Total EQ-5D-5L Score over Time (AT Population)

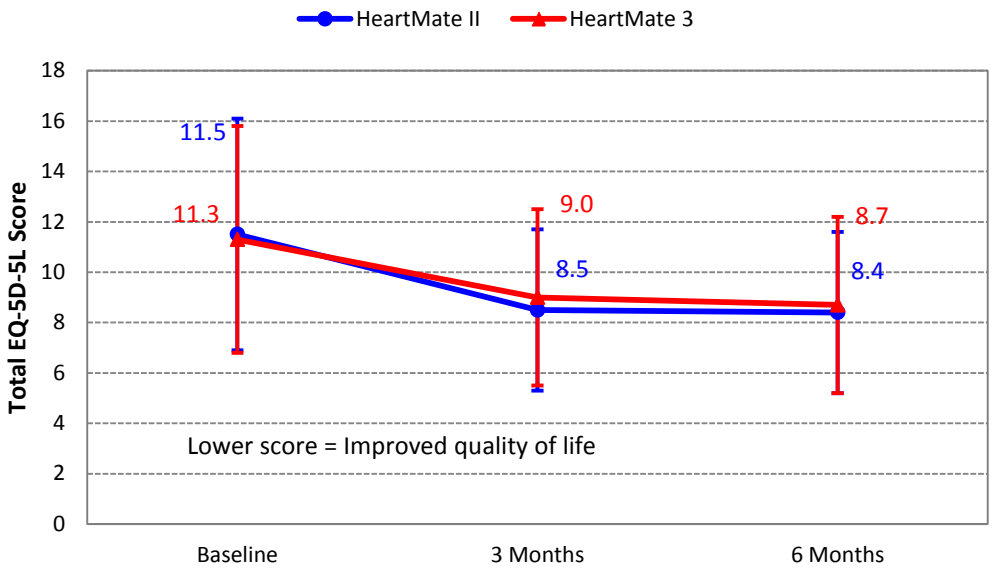


Figure 11: EQ-5D-5L Visual Analog Score over Time (AT Population)

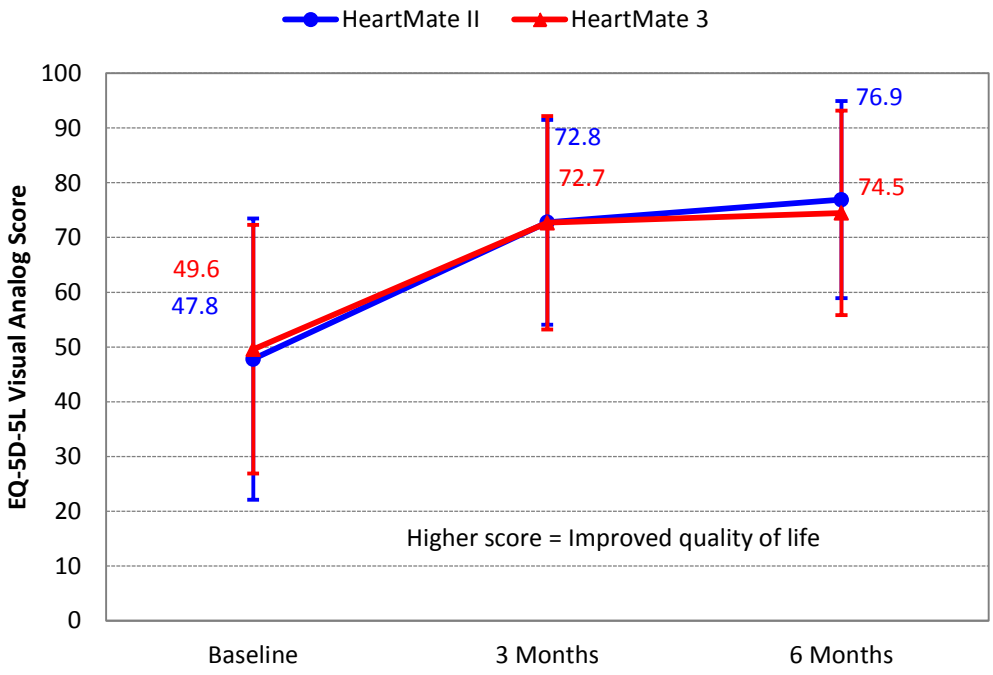


Figure 12: KCCQ Overall Summary Score over Time (AT Population)

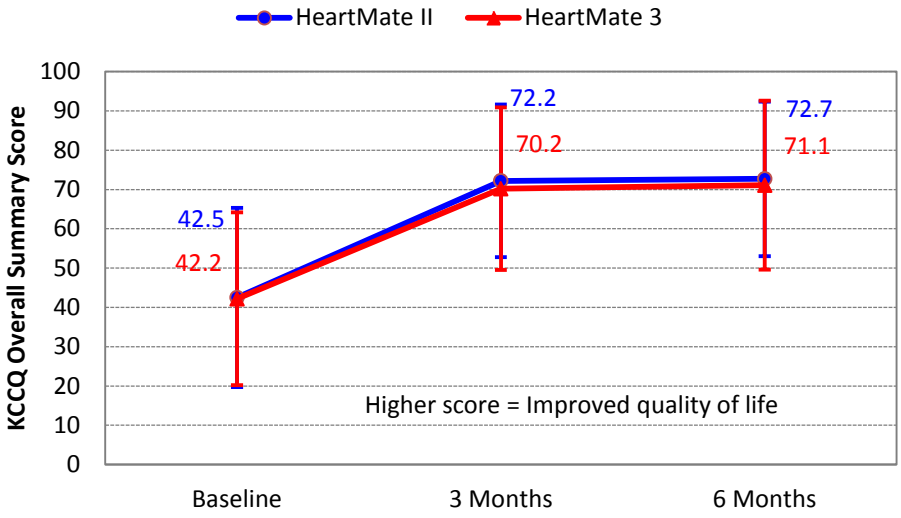
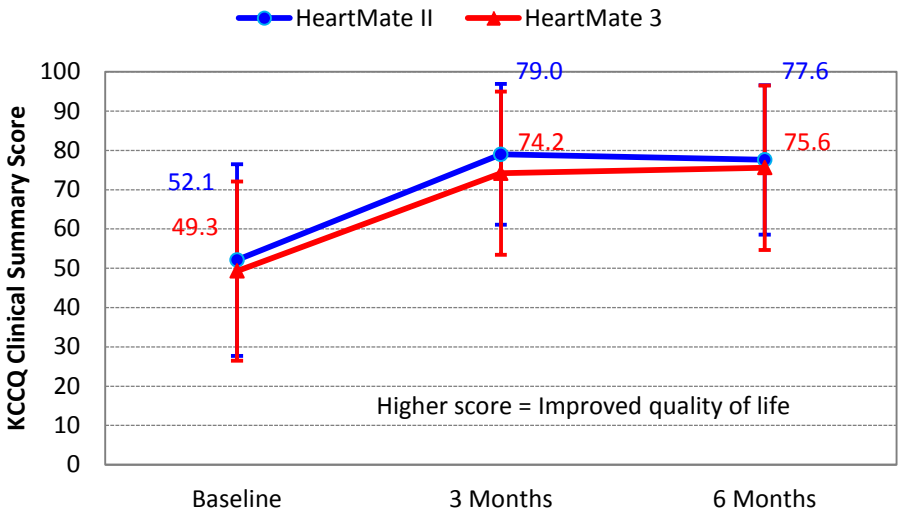


Figure 13: KCCQ Clinical Summary Score over Time (AT Population)



3. Subgroup Analyses

Prespecified sub-group analyses showed no major clinical differences in outcomes based on gender, race, INTERMACS profile, or intended use of the device (BTT vs. DT).

4. Other Results

Causes of Death

To determine cause-specific death, all deaths were reviewed and adjudicated by the CEC. A summary of patient deaths at 6 months in the AT population is provided in Table 15.

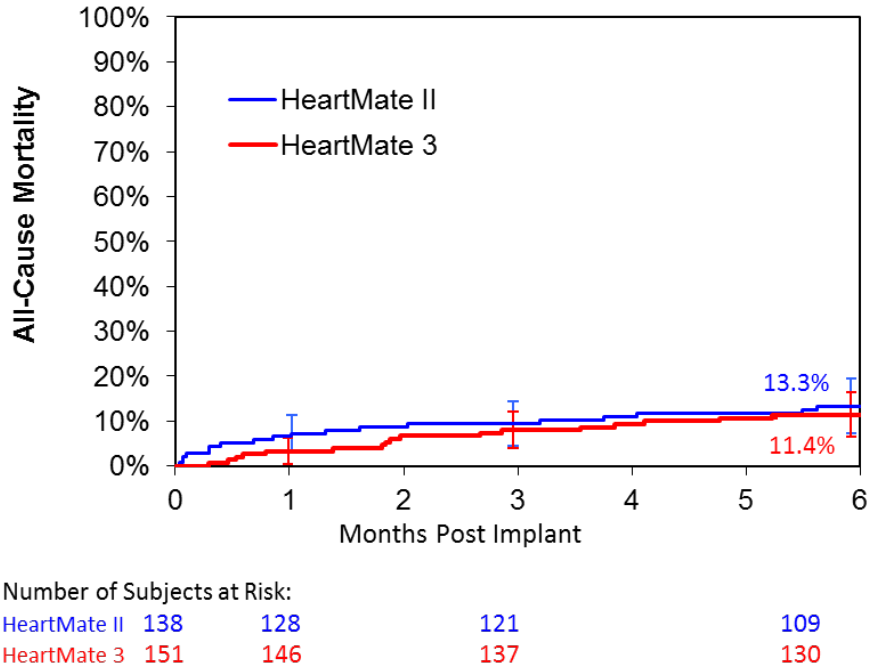
Table 15: Adjudicated Causes of Death (AT Population)

Adjudicated Cause of Death	Number of Events	
	HeartMate II (n=138)	HeartMate 3 (n=151)
Cardiopulmonary		
Right heart failure	9	4
Respiratory failure	0	1
Ventricular fibrillation	1	0
Brain related		
Stroke	3	5
Traumatic subdural hematoma (caused by a fall)	0	1
Anoxic brain injury (secondary to respiratory failure)	0	1
Bleeding		
Abdominal bleeding	1	0
Aortic dissection	1	0
Gastrointestinal bleeding	0	1[*]
Infection		
Sepsis	0	2
Pneumonia	1	0
Device-related		
Driveline disconnect	0	1[†]
Pump thrombosis	1[‡]	0
Miscellaneous		
Hepatic failure	1	0
Metastatic cervical cancer	0	1
Total	18	17

[*]Patient died as a result of GI bleeding associated with surgery for an obstructed bowel.
[†]Patient died as a result of disconnecting the driveline after receiving an alarm due to reversed power cable connections to the Mobile Power Unit.
[‡]Patient died of worsening heart failure secondary to pump thrombosis after declining a pump exchange.

The Kaplan-Meier curve of all-cause mortality for the AT population is shown in Figure 14.

Figure 14: All-Cause Mortality (AT Population)



Note: The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, these confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

Competing Outcomes Analysis

Plots of the competing outcomes (ongoing on LVAS support, expiration, transplantation, exchanged to non-study device) are provided in Figures 15 and 16 for the HeartMate II and HeartMate 3, respectively.

Figure 15: Competing Outcomes of HeartMate II Patients at 6 Months

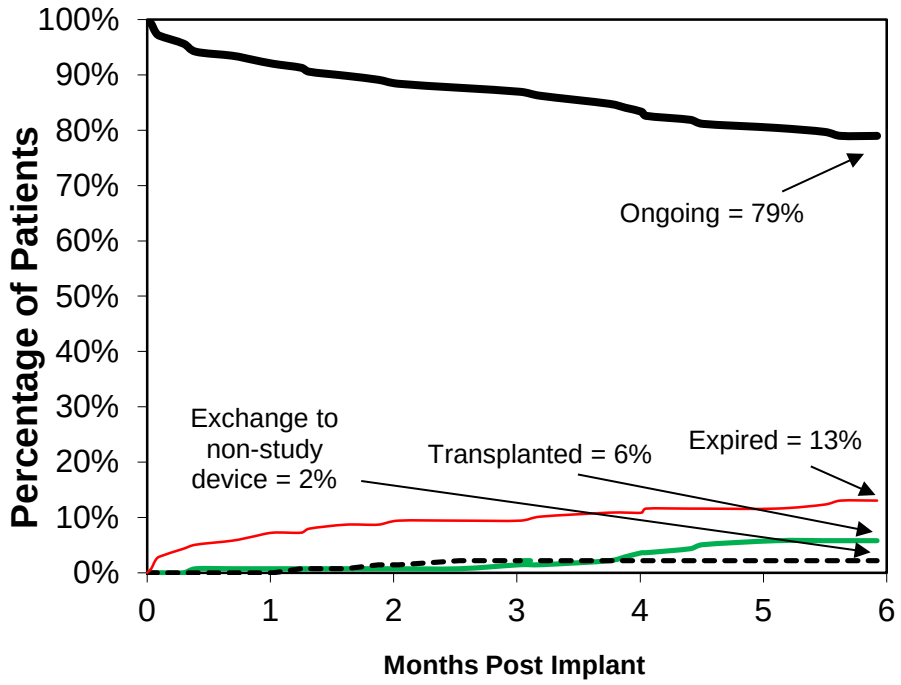
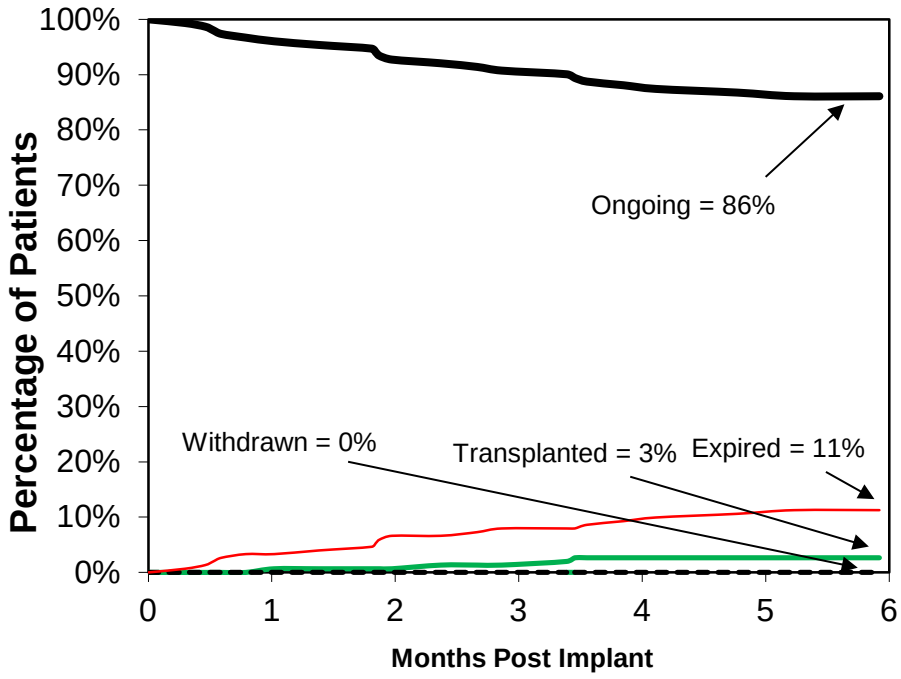


Figure 16: Competing Outcomes of HeartMate 3 Patients at 6 Months



5. Pediatric Extrapolation

In this premarket application, existing clinical data were not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 59 principal investigators of which none was a full-time or part-time employee of the sponsor and nine (9) had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None
- Significant payment of other sorts: 9
- Proprietary interest in the product tested held by the investigator: None
- Significant equity interest held by investigator in sponsor of covered study: None

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory Systems Device panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

At 6 months post implantation, 86% of patients in the HeartMate 3 arm achieved success in the composite primary endpoint as compared to 77% of patients in the HeartMate II arm, thus demonstrating non-inferiority of HeartMate 3 to HeartMate II (ITT: 95% CI of risk difference = -2.1%, $p<0.0001$). The numerical difference in the primary endpoint between the two arms was mainly driven by a clinically significantly higher number of pump exchanges and urgent transplants in the HeartMate II arm (7.8%) as compared to the HeartMate 3 arm (0.7%). The overall survival rate at 6-months post implantation was comparable between the HeartMate 3 (89%) and HeartMate II arms (87%).

Patients in both arms showed comparable improvement in functional status at 6 months relative to baseline. The percent of patients who were in NYHA Class III/IV decreased from 100% at baseline to 23% at 6 months in the HeartMate 3 arm and from 100% at baseline to 17% at 6 months in the HeartMate II arm. The average 6MWT distance increased from 164 m at baseline to 300 m at 6 months in the HeartMate 3 arm as compared to 128 m at baseline and 335 m at 6 months in the HeartMate II arm. Patients in both arms also showed comparable improvement in quality of life from baseline to 6 months as measured by EQ-5D-5L and KCCQ.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above. The serious adverse events that occurred in more than 5% of the patients in the clinical trial included: death (HeartMate 3: 11.3% vs. HeartMate II: 13.0%), major infection (37% vs. 30%), bleeding (30% vs. 37%), right heart failure (30% vs. 25%), cardiac arrhythmias (26% vs. 33%), respiratory failure (22% vs. 17%), renal dysfunction (11% vs. 9%), stroke (8% vs. 11%; debilitating stroke: 6% vs. 4%), and other neurological events (6% vs. 6%). There were no suspected pump thrombosis events in the HeartMate 3 arm at 180 days post implantation, while 10% of the patients in the HeartMate II arm experienced suspected pump thrombosis. The incidence of serious driveline infections was higher in the HeartMate 3 arm (10%) as compared to that in the HeartMate II arm (4%).

C. Benefit-Risk Determination

The probable benefits of the HeartMate 3 LVAS for patients with advanced refractory left ventricular heart failure included an 86% chance of survival free from debilitating stroke and without the need for a reoperation to replace the pump at 6 months. As compared to the HeartMate II LVAS, the HeartMate 3 LVAS was associated with a significantly lower risk of pump thrombosis.

The probable risks of the HeartMate 3 LVAS included serious adverse events such as death, major infection, bleeding, right heart failure, cardiac arrhythmias, respiratory failure, renal dysfunction, stroke, and other neurological events. The risks of the HeartMate 3 LVAS, as evidenced by types and incidences of adverse events, are generally comparable to those of the HeartMate II LVAS, with the exception of driveline infection.

1. Patient Perspectives

   This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support that for patients with advanced refractory left ventricular heart failure, the probable benefits of implanting the HeartMate 3 LVAD outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the HeartMate 3 LVAS in providing short-term hemodynamic support (e.g., BTT or bridge to myocardial recovery) in patients with advanced refractory left ventricular heart failure.

XIII. CDRH DECISION

CDRH issued an approval order on August 23, 2017.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to health from use of the device: See indications, contraindications, warnings, precautions, and adverse events in the device labeling.

Post-approval requirements and restrictions: See approval order.