SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Ventricular assist device
Device Trade Name:	HeartMate 3 Left Ventricular Assist System
Device Procode:	DSQ
Applicant Name and Address:	Thoratec Corporation 6035 Stoneridge Drive Pleasanton, CA 94588
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P160054/S008
Date of FDA Notice of Approval:	October 18, 2018

The original PMA P160054 was approved on August 23, 2017 where the HeartMate 3 Left Ventricular Assist System (LVAS) was 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. The SSED to support the indication is available on the CDRH website (https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160054B.pdf) and is incorporated by reference herein. The current supplement was submitted to expand the indication for the HeartMate 3 Left Ventricular Assist System to include long-term hemodynamic support.

II. INDICATIONS FOR USE

The HeartMate 3 Left Ventricular Assist System is indicated for providing short- and long-term mechanical circulatory support (e.g., as bridge to transplant or myocardial recovery, or destination therapy) in patients with advanced refractory left ventricular heart failure.

III. CONTRAINDICATIONS

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

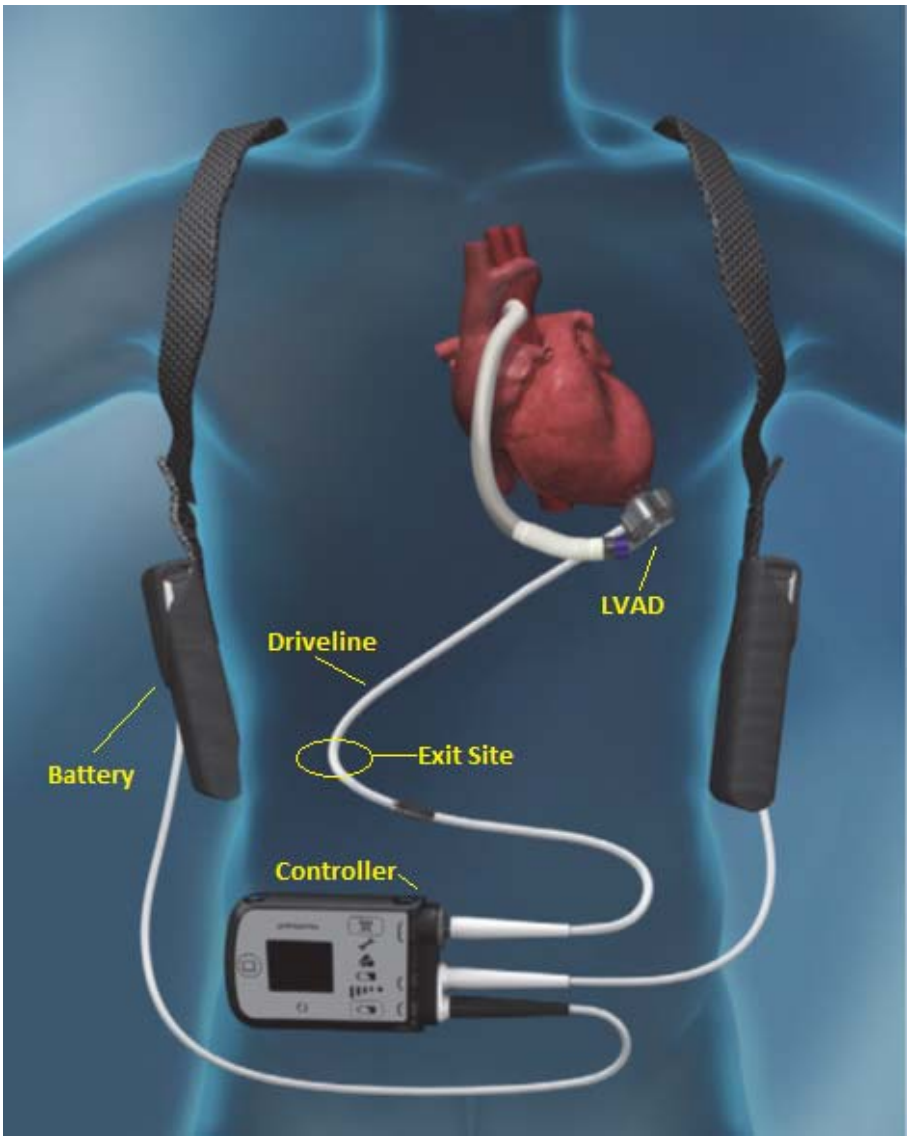
IV. WARNINGS AND PRECAUTIONS

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.

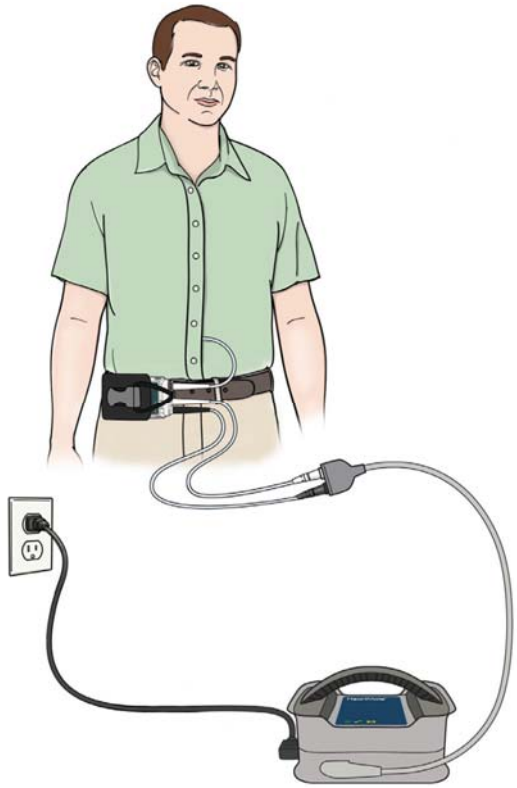
Figure 1: HeartMate 3 LVAS Implantable and External Components



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

There are several other alternatives for the treatment of end-stage heart failure, including: 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 other marketed mechanical circulatory support (MCS) devices. 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 for the long-term support indication in the following countries: All countries in the European Union, Australia, Brazil, Canada, Cayman Islands, Chile, Colombia, India, Israel, Kazakhstan, Lebanon, Malaysia, Mexico, Montenegro, Norway, Qatar, Saudi Arabia, Serbia, Singapore, Switzerland, Taiwan,

Thailand, Turkey and United Arab Emirates. 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)
- Device thrombosis

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

IX. SUMMARY OF NONCLINICAL STUDIES

A summary of previously reported preclinical studies can be found in the SSED for the original PMA (https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160054B.pdf).

Real-time reliability testing that was summarized in the original PMA continued, using the same devices in mock circulatory loops. The updated test results are summarized in Table 1.

Table 1: Summary of Real-Time 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 90% confidence at one year and 80% reliability with 80% confidence at 5 years.

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- and long-term hemodynamic support 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., bridge-to-transplant (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, which included ongoing ST Cohort subjects, 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 were the basis for the original PMA approval decision. A summary of the LT Cohort clinical study is presented below.

A. Study Design

Patients in the MOMENTUM 3 LT Cohort were treated between September 2014 and November 2015. The database for this PMA supplement reflected data collected through the 24-month follow-up visit (November 16, 2017) and included 366 subjects at 52 investigational sites.

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

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 all of the following inclusion criteria:

- Patient or legal representative has signed Informed Consent Form.
- Age ≥ 18 years.
- Body Surface Area (BSA) ≥ 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) ≤ 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 <u>not</u> 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 1 day, 1 week, discharge, 1 month, 3 months, 6 months, 12 months, 18 months and 24 months, postoperatively.

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 LT Cohort of the MOMENTUM 3 trial was a composite of survival to transplant, recovery, or 24 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 trial required that at least 75 HeartMate 3 LVAS subjects, each with at least 24 months (2 years) of support duration, be available at the time of PMA application.

The primary analysis was performed as intent to treat (ITT) and was performed at 24 months. The as treated (AT) analysis was performed as adjunctive analysis. Patients were considered a success if, within two years post implantation, they

- received a cardiac transplant that was not urgently required due to a device malfunction or adverse event;
- had the device explanted subsequent to myocardial recovery; or
- survived to 24 months 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 24 months 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 or adverse event of the device;
- withdrew from the study for any reason; or
- did not receive a HeartMate 3 LVAS or HeartMate II LVAS after randomization.

The HeartMate 3 LVAS was to be considered non-inferior to the HeartMate II LVAS 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 -10%. Additionally, if the HeartMate 3 LVAS was found to be non-inferior to the HeartMate II LVAS, the protocol specified that the primary composite endpoint would also be analyzed sequentially for superiority at a one-sided 0.025 level of significance.

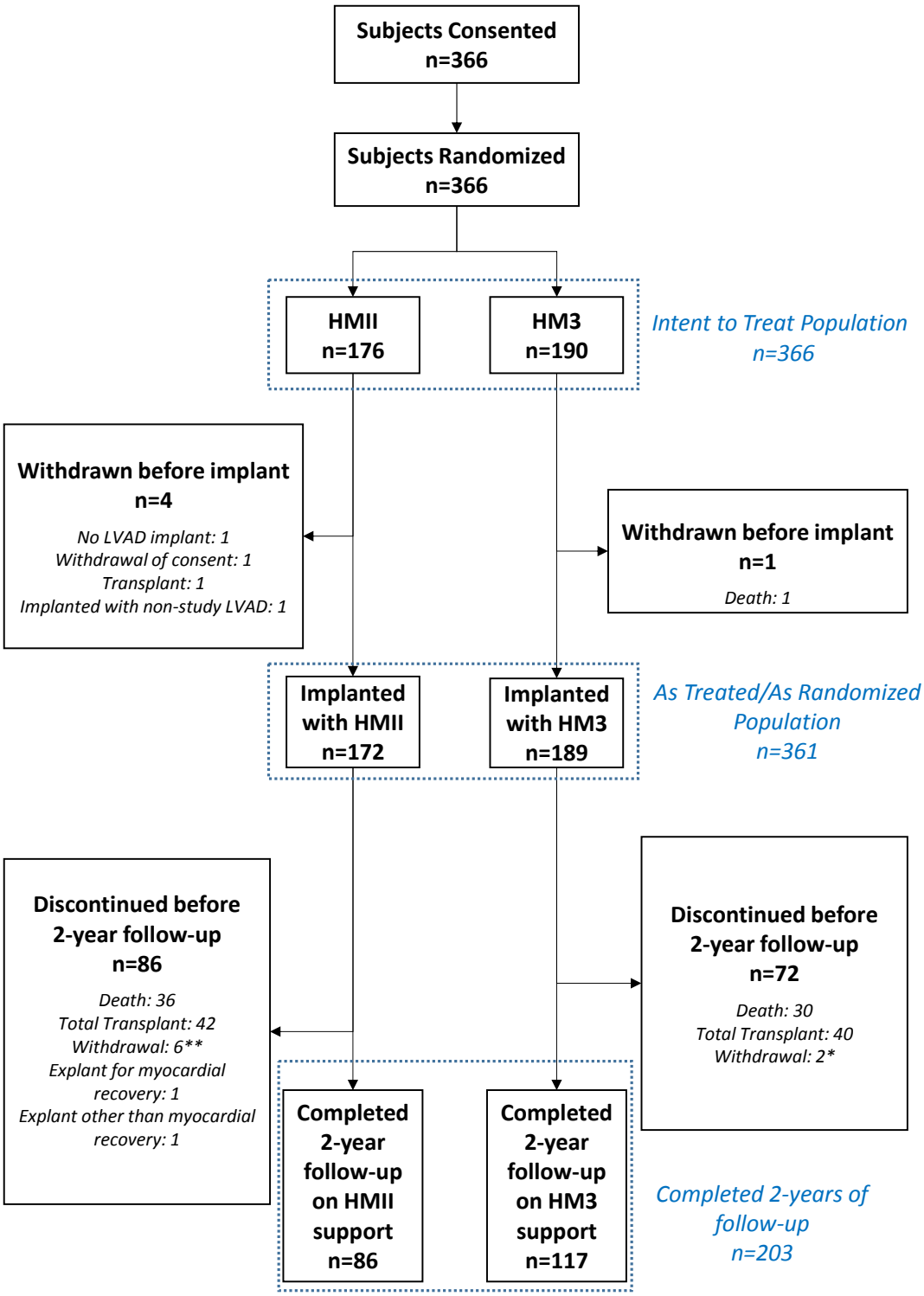
Secondary endpoints were evaluated descriptively, including adverse events, hospitalizations, reoperations, quality of life (EQ-5D-5L and KCCQ), functional status (NYHA Class and 6MWT), and device malfunctions. In addition, a number of subgroup analyses were prespecified including gender, race, Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile, and intended use of the device (BTT vs. DT). The secondary endpoints were evaluated using the AT population and were assessed at 24 months.

B. Accountability of PMA Cohort

At the time of database lock, of 366 subjects enrolled in the LT Cohort trial, 98.6% (361) of the subjects are available for analysis at the completion of the study (the 24-month post-operative visit). The disposition of the patients is shown in Figure. All 366 subjects were consented and randomized, 190 subjects to the HeartMate 3 arm and 176 subjects to the HeartMate II arm, which comprise the ITT population. Five (5) subjects 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 361 subjects, 189 in the HeartMate 3 arm and 172 in the HeartMate II arm. Eight (8) subjects were withdrawn after receiving a device, two (2) in the HeartMate 3 arm and six (6) in the HeartMate II arm. All withdrawals were pre-specified to be counted as endpoint failures for the primary analysis,

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



* (1) non-compliance, (1) explant to total artificial heart
** (1) withdrew consent, (5) exchange to a non-study or unassigned LVAD

C. Study Population Demographics and Baseline Parameters

The demographics and baseline characteristics of the study population, as summarized in Table 2, 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.

Overall, 96% of enrolled subjects had NYHA Class IV symptomatology, and 83% were INTERMACS Profile 2 or 3. The majority of subjects within the LT cohort had "DT" as the intended use before implantation.

Table 2: Patient Demographics and Baseline Characteristics (ITT Population)

Demographics and Baseline Characteristics	Summary Statistics*		p-Value†
	HeartMate II (n=176)	HeartMate 3 (n=190)	
Age – year	59 ± 12	61 ± 12	0.2288
Body-surface area – m^2	2.1 ± 0.3	2.1 ± 0.3	0.4938
Body-mass index – kg/m^2	28.4 ± 5.8	29.0 ± 6.2	0.3150
Weight – kg	87.5 ± 20.1	89.1 ± 20.9	0.4471
Male sex	143 (81%)	150 (79%)	0.6028
Ischemic cause of heart failure	88 (50%)	80 (42%)	0.1423
Race			
White	131 (74%)	127 (67%)	0.1358
Non-white	45 (26%)	63 (33%)	
Intended use			
Bridge to transplant (BTT)‡	42 (24%)	49 (26%)	0.9903
Possibly BTT: Likely to be eligible	17 (10%)	18 (9%)	
Possibly BTT: moderate likelihood	9 (5%)	9 (5%)	
Possibly BTT: unlikely to be eligible	2 (1%)	3 (2%)	
Destination therapy (DT)	106 (60%)	111 (58%)	
INTERMACS profile§			
1	4 (2%)	1 (1%)	0.5717
2	51 (29%)	61 (32%)	
3	91 (52%)	101 (53%)	
4	28 (16%)	24 (13%)	
5	2 (1%)	2 (1%)	
6 or 7	0 (0%)	0 (0%)	
Not provided‖	0 (0%)	1 (1%)	
NYHA Class¶			
Class I	0 (0%)	0 (0%)	0.1150
Class II	0 (0%)	0 (0%)	

Demographics and Baseline Characteristics	Summary Statistics*		p-Value†
	HeartMate II (n=176)	HeartMate 3 (n=190)	
Class IIIB	4 (2%)	11 (6%)	
Class IV	172 (98%)	179 (94%)	
Baseline cardiovascular history			
Coronary artery disease	97 (55%)	102 (54%)	0.8338
Myocardial infarction	64 (36%)	63 (33%)	0.5828
Left ventricular aneurysm/repair	2 (1%)	2 (1%)	1.0000
Arrhythmias	129 (73%)	141 (74%)	0.9055
Supraventricular arrhythmias	91 (52%)	94 (49%)	0.6771
Ventricular arrhythmias	70 (40%)	84 (44%)	0.3988
Congenital heart disease	1 (1%)	1 (1%)	1.0000
Revascularization	76 (43%)	71 (37%)	0.2863
Valve replacement/repair	7 (4%)	18 (9%)	0.0400
Valve insufficiency	149 (85%)	166 (87%)	0.5460
CRT/CRT-D#	62 (35%)	75 (39%)	0.4495
Defibrillator (ICD/CRT-D)	123 (70%)	122 (64%)	0.2673
Pacemaker	11 (6%)	10 (5%)	0.8228
Ongoing IABP#	26 (15%)	25 (13%)	0.7628
Hypertension	119 (68%)	127 (67%)	0.9115
Baseline medical history			
Neurological history	37 (21.0%)	41 (21.6%)	1.0000
Transient ischemic attack (TIA)	11 (6.3%)	18 (9.5%)	0.3332
Cerebrovascular accident: Ischemic	17 (9.7%)	15 (7.9%)	0.5827
Cerebrovascular accident: Hemorrhagic	1 (0.6%)	0 (0%)	0.4809
Cerebrovascular accident: Not specified	2 (1.1%)	1 (0.5%)	0.6101
Seizure	2 (1.1%)	1 (0.5%)	0.6101
Neurological other	10 (5.7%)	12 (6.3%)	0.8295
Psychiatric history	47 (26.7%)	34 (17.9%)	0.0448
Psychosocial issues	9 (5.1%)	8 (4.2%)	0.8051
Substance abuse	11 (6.3%)	6 (3.2%)	0.2145
Gastrointestinal history	59 (33.5%)	74 (38.9%)	0.3277
Renal insufficiency	47 (26.7%)	38 (20.0%)	0.1385
Renal failure	7 (4.0%)	11 (5.8%)	0.4756
Cancer history	26 (14.8%)	30 (15.8%)	0.8846
Previous organ transplant history	0 (0%)	0 (0%)	---
Endocrine history	97 (55.1%)	110 (57.9%)	0.5995
Diabetes mellitus: Insulin-dependent	28 (15.9%)	26 (24.2%)	0.0516

Demographics and Baseline Characteristics	Summary Statistics*		p-Value†
	HeartMate II (n=176)	HeartMate 3 (n=190)	
Diabetes mellitus: Non insulin-dependent	41 (23.3%)	41 (21.6%)	0.7084
Hematopoietic/lymphatic history	30 (17.0%)	15 (13.2%)	0.3095

*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
‖Subject 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 366 evaluable subjects at the 24-month time point (190 HeartMate 3 subjects and 176 HeartMate II subjects), as summarized in Table 3. In both the ITT and AT analyses, the trial demonstrated non-inferiority of the HeartMate 3 LVAS as compared to the HeartMate II LVAS for the primary endpoint.

Once non-inferiority was demonstrated, the data were then analyzed to test for superiority of the HeartMate 3 LVAS to HeartMate II LVAS for the composite primary endpoint. The superiority test in both the ITT and AT populations resulted in a significant finding ($p < 0.0001$, one-sided), indicating that the HeartMate 3 LVAS was superior to the HeartMate II LVAS in terms of the composite primary endpoint.

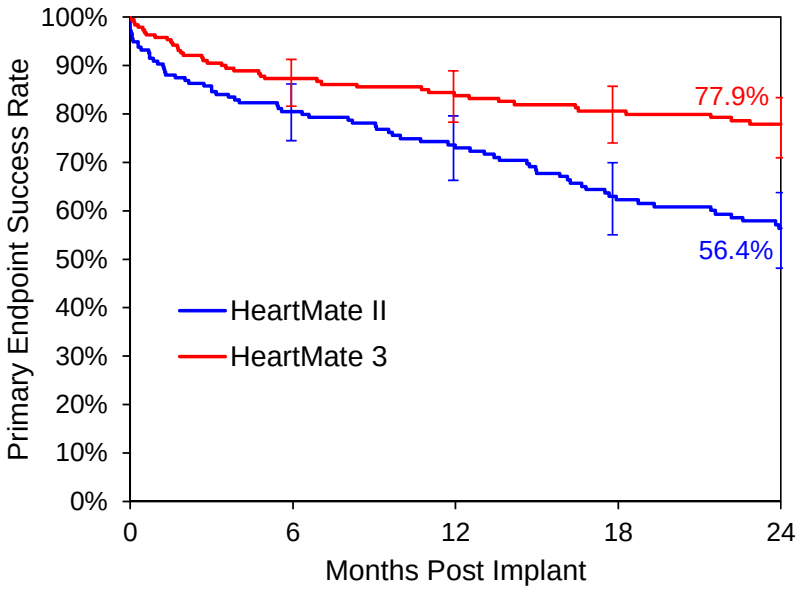
Table 3: Analyses of the Primary Endpoint

	Intent-to-Treat Analysis		As-Treated Analysis	
	HeartMate II	HeartMate 3	HeartMate II	HeartMate 3
Total # of patients	176	190	172	189
Alive free of debilitating stroke or device replacement	75	111	75	111
Elective transplant	30	40	30	40

	Intent-to-Treat Analysis		As-Treated Analysis	
	HeartMate II	**HeartMate 3**	**HeartMate II**	**HeartMate 3**
Explanted due to myocardial recovery	1	0	1	0
Total # of successes	106	151	106	151
Success rate at 24 months	60.2%	79.5%	61.6%	79.9%
Difference (HeartMate 3 – HeartMate II)	19.2%		18.3%	
Exact 95% confidence interval	[9.1%, 29.1%]		[8.0%, 28.2%]	
Non-inferiority limit	-10%		-10%	
Primary objective – non-inferiority				
Z-Score	6.0953		5.9051	
p-value	<0.0001		<0.0001	
Non-inferiority test	Passed		Passed	
Primary objective – superiority				
Z-Score	4.0229		3.8275	
p-value	<0.0001		<0.0001	
Superiority test	Passed		Passed	

The Kaplan-Meier curves reflecting the primary endpoint success rates are shown in Figure 3 and Figure 4 for the ITT population and AT population, respectively.

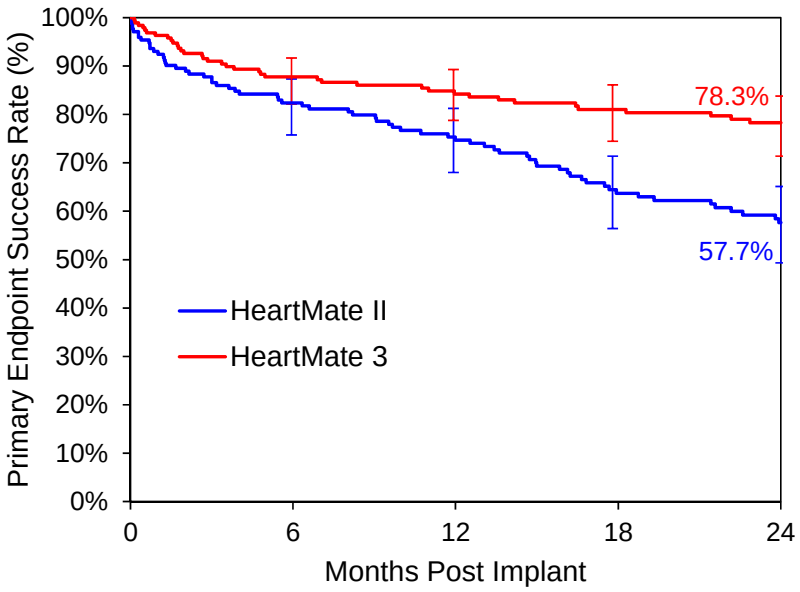
Figure 3: Kaplan-Meier Curve of the Primary Endpoint (ITT Population)



Number of subjects at risk:					
HeartMate II	176	134	114	90	75
HeartMate 3	190	161	141	122	111

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



Number of subjects at risk:

HeartMate II	172	134	114	90	75
HeartMate 3	189	161	141	122	111

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 primary composite endpoint outcome in relation to its components are presented in Table 4. The difference in the primary endpoint result between the two arms was primarily driven by a higher number of pump exchanges and urgent transplants in the HeartMate II arm.

Table 4: Outcomes Related to the Primary Composite Endpoint (AT Population)

Key Safety Outcomes*	HeartMate II (n=172)	HeartMate 3 (n=189)
Death	26	22
Debilitating stroke (MRS > 3)	7	11
Transplant due to device malfunction	8	0
Pump Exchange	21	3
Withdrawn (post implantation)	1	1
Withdrawn due to exchange with non-study device	2	1
Explanted other than myocardial	1	0

Key Safety Outcomes*	HeartMate II (n=172)	HeartMate 3 (n=189)
recovery		
Total Failure	**66 (38%)**	**38 (20%)**

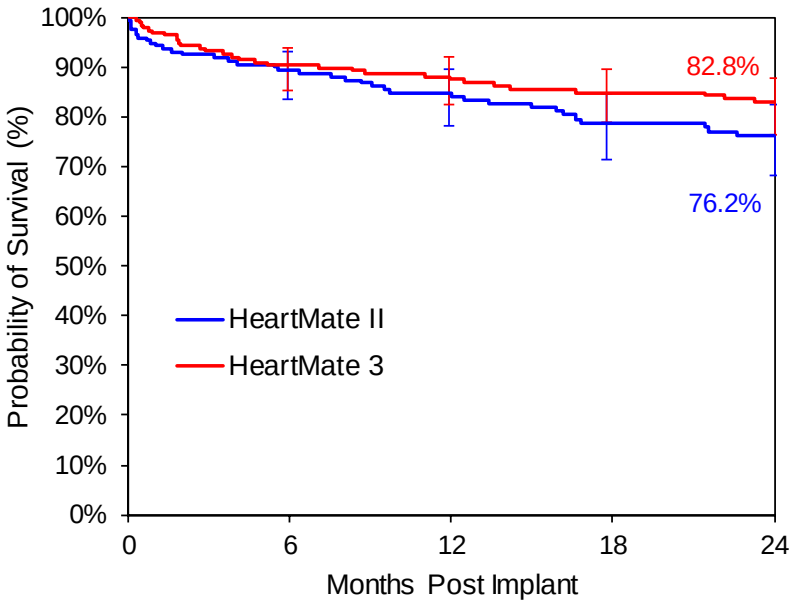
*For patients who experienced more than one endpoint event during the follow-up period (e.g., debilitating stroke prior to death), the event that occurred first is the failure event listed.

More detailed analyses of survival, debilitating stroke, and pump exchange are shown below:

Survival

The Kaplan-Meier curve for survival is shown in Figure 6. Survival at 24 months (data censored at the time of transplantation or device exchange) was similar in the two arms.

Figure 6: Kaplan-Meier Curve for Survival (AT Population)



Number of subjects at risk:

HeartMate II	172	141	121	98	86
HeartMate 3	189	165	146	127	117

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.

All deaths were reviewed and adjudicated by the CEC. A summary of patient deaths at 24 months in the AT population is provided in Table 5.

Table 5: Adjudicated Causes of Death (AT Population)

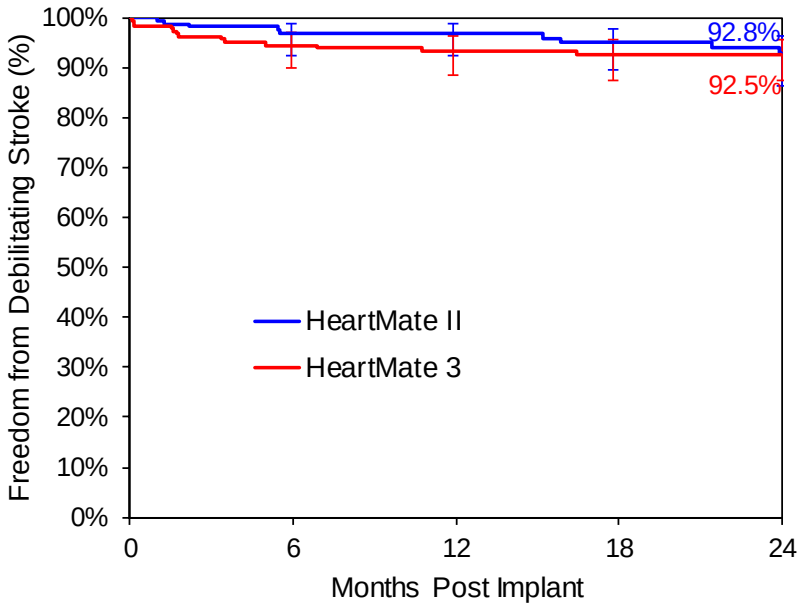
Adjudicated Cause of Death	Number of Events	
	HeartMate II (n=172)	HeartMate 3 (n=189)
Cardiopulmonary related		
Heart failure	0	1
Right heart failure	9	6
Respiratory failure	1	1
Ventricular arrhythmia	1	2
Brain related		
Stroke	6	6
Traumatic subdural hematoma (caused by a fall)	0	1
Anoxic brain injury (secondary to respiratory failure)	0	1
Intracranial hemorrhage (due to trauma)	1	0
Bleeding related		
Abdominal or gastrointestinal bleeding	2	1
Aortic dissection	1	0
Infection related		
Infection or sepsis	6	6
Pneumonia	1	0
Device-related		
Driveline disconnect*	0	2*
Pump thrombosis†	4†	0
Miscellaneous		
Cancer	0	2
Hepatic failure	2	0
Intravenous drug use	0	1
Unknown	2	0
Total	36	30

*One patient died as a result of disconnecting the driveline after receiving an alarm due to reversed power cable connections to the Mobile Power Unit. One patient died after an unintentional driveline disconnect occurred while changing the batteries.
†Three patients declined a pump exchange and died as a result of their worsening condition and heart failure. One patient also developed sepsis and renal failure and opted for comfort care only.

Debilitating Stroke

The Kaplan-Meier curve for freedom from debilitating stroke is shown in Figure 7.

Figure 7: Kaplan-Meier Curve for Freedom from Debilitating Stroke (AT Population)



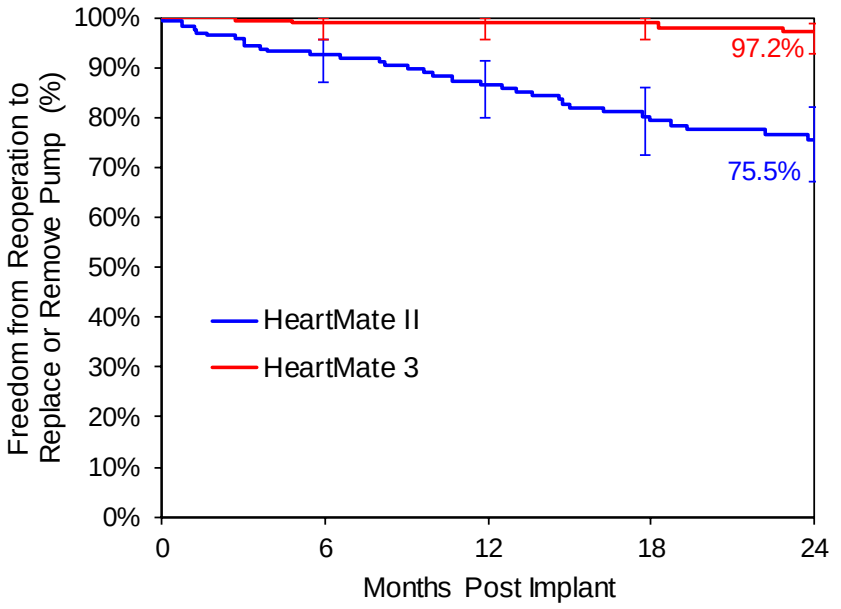
Number of subjects at risk:					
HeartMate II	172	139	121	97	84
HeartMate 3	189	162	142	123	114

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.

Pump Exchange or Removal

The Kaplan-Meier curve for freedom from pump exchange or removal is shown in Figure 8. The majority of device exchanges were precipitated by suspected pump thrombosis in the HeartMate II arm. Twenty (20) of the 35 (57%) suspected pump thrombosis events were confirmed.

Figure 8: Kaplan-Meier Curve for Freedom from Reoperation to Replace or Remove Pump (AT Population)



Number of subjects at risk:

HeartMate II	172	135	114	90	76
HeartMate 3	189	164	145	126	114

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.

Table 6: Summary of Suspected Device Thrombosis Events (AT Population)

	Summary Statistics	
	HeartMate II (n=172)	**HeartMate 3 (n=189)**
Total Patients	27/172 (16%)	2/189 (1%)
Total Events	33	2
Mean time to first event (days)	195	216
Signs and Symptoms		
Hemolysis	28/33 (85%)	1/2 (50%)
Worsening heart failure	20/33 (61%)	2/2 (100%)
Abnormal pump parameters	18/33 (55%)	2/2 (100%)

Action Taken/Outcome		
Device exchange to assigned study device	16/33 (48%)	0/2 (0%)
Device exchange to non-assigned study device	2/33 (6%)	0/2 (0%)
Device exchange to non-study device	3/33 (9%)	0/2 (0%)
Urgent transplant	4/33 (12%)	0/2 (0%)
Death	4/33 (12%)	0/2 (0%)
Returned Product Assessment Results		
Confirmed	20/33 (61%)	0/2 (0%)
Not confirmed	1/33 (3%)	0/2 (0%)
Inconclusive	3/33 (9%)	0/2 (0%)
Device not returned	9/33 (27%)	2/2 (100%)

2. Secondary Endpoints

Adverse Events

Table 7 lists the pre-specified adverse events that occurred in the AT population; Table 8 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 7: All Adverse Events at 24 Months (AT Population)

Adverse Events	**Summary Statistics***	
	HeartMate II (n=172)	**HeartMate 3 (n=189)**
Major infection	55% (94, 206, 0.85)	55% (104, 217, 0.74)
Localized	35% (60, 114, 0.47)	37% (70, 108, 0.37)
Sepsis	14% (24, 28, 0.12)	14% (26, 37, 0.13)
Driveline	20% (34, 59, 0.24)	24% (45, 68, 0.23)
Pump or pump components	1% (2, 2, 0.01)	0% (0, 0, 0.00)
Pump pocket or pseudo pocket	1% (2, 2, 0.01)	1% (2, 2, 0.01)
Bleeding	52% (90, 206, 0.85)	43% (81, 187, 0.64)
Bleeding requiring surgery	17% (30, 34, 0.14)	12% (23, 29, 0.10)
Gastrointestinal bleeding	27% (47, 100, 0.41)	27% (51, 107, 0.37)

Adverse Events	Summary Statistics*	
	HeartMate II (n=172)	HeartMate 3 (n=189)
Cardiac arrhythmia	41% (70, 105, 0.43)	38% (71, 108, 0.37)
Ventricular arrhythmia	23% (39, 64, 0.26)	24% (45, 67, 0.23)
Supraventricular arrhythmia	21% (36, 37, 0.15)	18% (33, 40, 0.14)
Both (ventricular and supraventricular arrhythmia)	0% (0, 0, 0.00)	1% (1, 1, 0.00)
Right heart failure	28% (48, 53, 0.22)	32% (60, 73, 0.25)
Right ventricular assist device (RVAD)	5% (8, 8, 0.03)	3% (6, 6, 0.02)
Respiratory failure	23% (39, 46, 0.19)	24% (45, 61, 0.21)
Renal dysfunction	11% (18, 18, 0.07)	13% (25, 29, 0.10)
Stroke	19% (33, 43, 0.18)	10% (19, 22, 0.08)
Hemorrhagic stroke	9% (16, 17, 0.07)	4% (8, 8, 0.03)
Ischemic stroke	13% (23, 26, 0.11)	6% (12, 14, 0.05)
Debilitating stroke	5% (9, 11, 0.05)	7% (13, 15, 0.05)
Other neurological event	9% (15, 16, 0.07)	12% (22, 25, 0.09)
Encephalopathy	2% (3, 3, 0.01)	3% (6, 6, 0.02)
Seizure	2% (3, 3, 0.01)	3% (5, 5, 0.02)
Transient ischemic attack (TIA)	4% (6, 6, 0.02)	3% (6, 8, 0.03)
Other†	2% (3, 4, 0.02)	3% (6, 6, 0.02)
Hepatic dysfunction	4% (7, 7, 0.03)	4% (8, 8, 0.03)
Psychiatric episode	7% (12, 16, 0.07)	5% (10, 13, 0.04)
Venous thromboembolism	4% (7, 7, 0.03)	5% (10, 11, 0.04)
Hypertension	12% (20, 25, 0.10)	6% (11, 17, 0.06)
Arterial non-CNS thromboembolism	3% (5, 5, 0.02)	2% (4, 4, 0.01)
Pericardial fluid collection	5% (9, 10, 0.04)	2% (4, 5, 0.02)
Myocardial infarction	1% (2, 2, 0.01)	1% (1, 1, 0.00)
Wound dehiscence	1% (2, 2, 0.01)	1% (2, 2, 0.01)
Hemolysis (not associated with suspected device thrombosis)	2% (3, 3, 0.01)	1% (1, 1, 0.00)
Suspected device thrombosis	16% (27, 33, 0.14)	1% (2, 2, 0.01)
Other adverse events	56% (97, 215, 0.89)	70% (133, 332, 1.14)

*% patients (# patients, # events, events/patient-year)

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

Table 8: Serious Adverse Events at 24 Months (AT Population)

Adverse Events	Summary Statistics*	
	HeartMate II (n=172)	HeartMate 3 (n=189)

Adverse Events	Summary Statistics*	
	HeartMate II (n=172)	HeartMate 3 (n=189)
Major infection	50% (86, 178, 0.74)	50% (94, 182, 0.62)
Localized	31% (53, 98, 0.40)	33% (63, 87, 0.30)
Sepsis	14% (24, 28, 0.12)	14% (26, 37, 0.13)
Driveline	16% (27, 47, 0.19)	20% (38, 55, 0.19)
Pump or pump components	1% (2, 2, 0.01)	0% (0, 0, 0.00)
Pump pocket or pseudo pocket	1% (2, 2, 0.01)	1% (2, 2, 0.01)
Bleeding	51% (87, 196, 0.81)	41% (78, 172, 0.59)
Bleeding requiring surgery	17% (30, 34, 0.14)	12% (23, 29, 0.10)
Gastrointestinal bleeding	27% (47, 97, 0.40)	27% (50, 105, 0.36)
Right heart failure	28% (48, 53, 0.22)	32% (60, 73, 0.25)
Right ventricular assist device (RVAD)	5% (8, 8, 0.03)	3% (6, 6, 0.02)
Cardiac arrhythmia	37% (63, 93, 0.38)	33% (63, 94, 0.32)
Ventricular arrhythmia	23% (39, 64, 0.26)	24% (45, 67, 0.23)
Supraventricular arrhythmia	14% (24, 25, 0.10)	12% (22, 26, 0.09)
Both (ventricular and supraventricular arrhythmia)	0% (0, 0, 0.00)	1% (1, 1, 0.00)
Respiratory failure	23% (39, 46, 0.19)	24% (45, 61, 0.21)
Renal dysfunction	11% (18, 18, 0.07)	13% (25, 29, 0.10)
Stroke	19% (33, 43, 0.18)	10% (19, 22, 0.08)
Hemorrhagic stroke	9% (16, 17, 0.07)	4% (8, 8, 0.03)
Ischemic stroke	13% (23, 26, 0.11)	6% (12, 14, 0.05)
Debilitating stroke	5% (9, 11, 0.05)	7% (13, 15, 0.05)
Other neurological event	9% (15, 16, 0.07)	12% (22, 25, 0.09)
Encephalopathy	2% (3, 3, 0.01)	3% (6, 6, 0.02)
Seizure	2% (3, 3, 0.01)	3% (5, 5, 0.02)
Transient ischemic attack (TIA)	4% (6, 6, 0.02)	3% (6, 8, 0.03)
Other†	2% (3, 4, 0.02)	3% (6, 6, 0.02)
Hepatic dysfunction	4% (7, 7, 0.03)	4% (8, 8, 0.03)
Venous thromboembolism	4% (7, 7, 0.03)	4% (8, 9, 0.03)
Psychiatric episode	6% (11, 12, 0.05)	3% (6, 9, 0.03)
Arterial non-CNS thromboembolism	3% (5, 5, 0.02)	2% (4, 4, 0.01)
Hypertension	5% (8, 9, 0.04)	4% (8, 9, 0.03)
Pericardial fluid collection	5% (8, 9, 0.04)	2% (4, 5, 0.02)
Myocardial infarction	1% (2, 2, 0.01)	1% (1, 1, 0.00)
Wound dehiscence	1% (2, 2, 0.01)	1% (2, 2, 0.01)
Hemolysis (not associated with suspected device thrombosis)	2% (3, 3, 0.01)	1% (1, 1, 0.00)

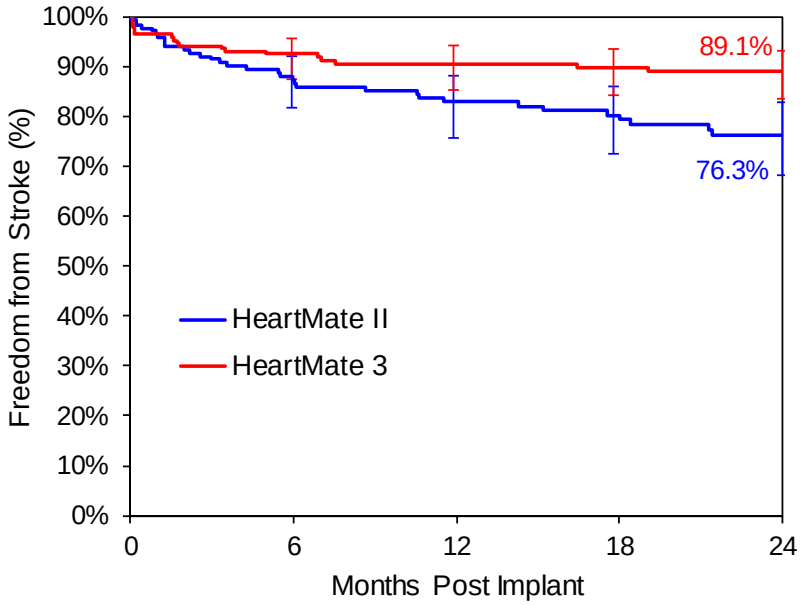
Adverse Events	Summary Statistics*	
	HeartMate II (n=172)	HeartMate 3 (n=189)
Suspected device thrombosis	16% (27, 33, 0.14)	1% (2, 2, 0.01)
Other adverse events	54% (93, 196, 0.81)	67% (126, 296, 1.02)

*% patients (# patients, # events, events/patient-year)
†Other includes anoxic brain injury, traumatic brain injury, and intracranial bleed due to trauma.

Stroke

The Kaplan-Meier curve for freedom from stroke is shown in Figure 9.

Figure 9: Kaplan-Meier Curve for Freedom from Stroke (AT Population)



Number of subjects at risk:

HeartMate II	172	127	104	85	73
HeartMate 3	189	159	138	120	111

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.

A summary of the stroke events within 24 months post implantation is presented in Table 9. Ten percent (10%) of the HeartMate 3 and 19% of the HeartMate II subjects experienced at least one stroke event. Among all stroke events that occurred with

HeartMate 3, 68% (15/22) were debilitating, as compared to 26% (11/43) of HeartMate II stroke events.

Table 9: Summary of Strokes within 24 months Post Implant (AT Population)

	HeartMate II (n=172)	HeartMate 3 (n=189)
Total Subject with Stroke	33/172 (19%)	19/189 (10%)
Hx of stroke or TIA	9/33 (27%)	6/19 (32%)
Hx of atrial fibrillation	12/33 (36%)	11/19 (58%)
Total Stroke Events	43	22
Ischemic	26/43 (60%)	14/22 (64%)
Hemorrhagic	17/43 (40%)	8/22 (36%)
Debilitating (MRS > 3)	11/43 (26%)	15/22 (68%)
INR Level		
Subtherapeutic INR (INR < 2.0)	16/34 (47%)	12/18 (67%)
Supratherapeutic INR (INR > 3.0)	8/34 (24%)	0/18 (0%)

Device Malfunctions

At 24 months, 86 of the 189 (46%) HeartMate 3 patients reported 143 suspected device malfunctions; 62 of the 172 (36%) HeartMate II patients reported 96 suspected device malfunctions, as summarized in Table 10. The majority of suspected malfunctions in both arms involved external components, most commonly the System Controller. Among the total number of suspected device malfunctions at 24 months, the suspected malfunction events of implanted components were more frequent in HeartMate II (26/96, 27%) than in HeartMate 3 (12/143, 8%), while those of external components were more frequent in HeartMate 3 (131/143, 92%) than in HeartMate II (70/96, 73%), as summarized in Table 11.

Table 10: Total Device Malfunctions at 24 Months

	Device Malfunctions*		
	#Patients	%Patients	#Events
HeartMate II (n=172)	62 (50)	36% (29%)	96 (75)
HeartMate 3 (n=189)	86 (70)	46% (37%)	143 (107)

*Suspected (confirmed)

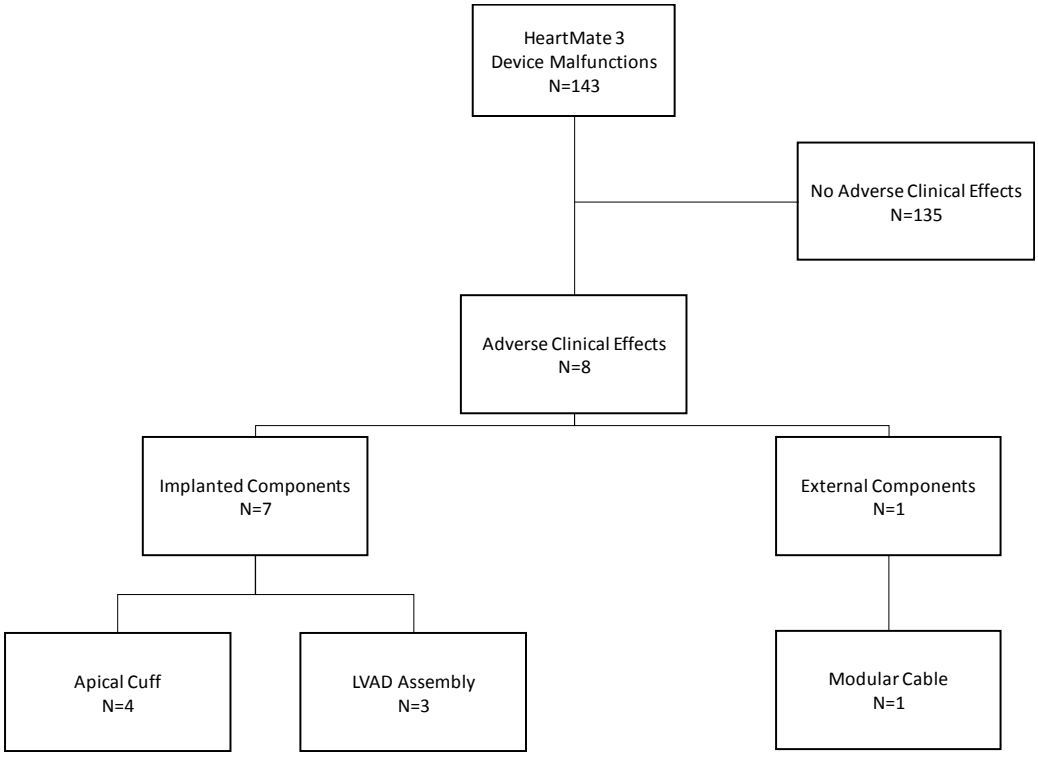
Table 11: Device Malfunctions by Implanted and External Components at 24 Months

	Device Malfunctions*					
	Implanted Components			External Components		
	#Patients	%Patients	#Events	#Patients	%Patients	#Events
HeartMate II (n=172)	23 (19)	13% (11%)	26 (22)	49 (38)	28% (22%)	70 (53)
HeartMate 3 (n=189)	12 (7)	6% (4%)	12 (7)	79 (65)	42% (34%)	131 (100)

*Suspected (confirmed)

The characterizations of the 143 suspected HeartMate 3 device malfunctions are shown in Figure 10.

Figure 10: Suspected HeartMate 3 LVAS Malfunctions



Rehospitalizations

In the AT analysis population, 93% (160/172) of the HeartMate II subjects and 94% (177/189) of the HeartMate 3 subjects were discharged from the hospital following implant surgery, as shown in Table 12. Among discharged subjects, 147 (91.9%) HeartMate II subjects and 156 (88.1%) HeartMate 3 subjects required hospital readmission during their 2-year follow-up period.

Table 12: Hospital Readmissions within 24 Months Post Implantation (AT Population)

	# Subjects Discharged Post Implant	# Subjects Readmitted	% Readmission	# Readmissions
HeartMate II (n=172)	160	147	91.9%	545
HeartMate 3 (n=189)	177	156	88.1%	579

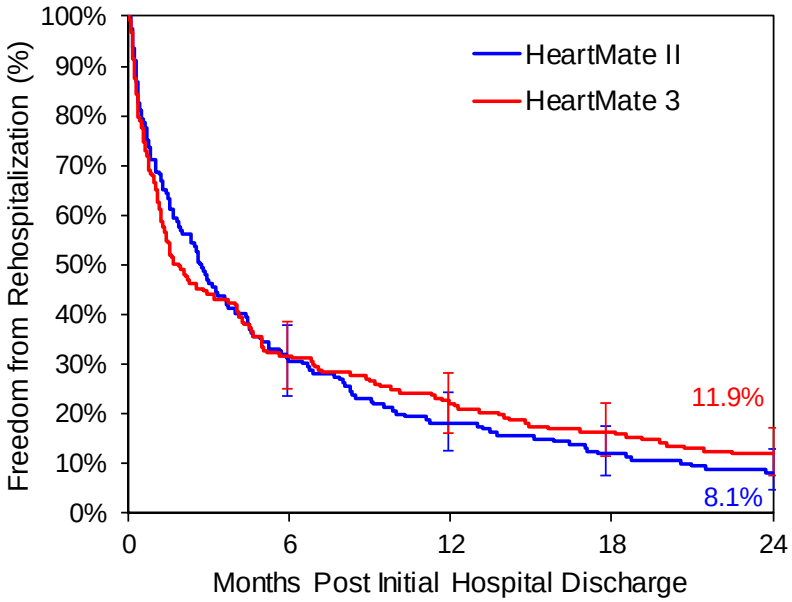
The reasons for the readmissions are shown in Table 13. Readmission for the management of defined adverse events accounted for a majority of rehospitalizations in both arms (74.1% HeartMate II vs. 74.4% HeartMate 3).

Table 13: Reasons for Readmission (AT Population)

	HeartMate II (n=172)	HeartMate 3 (n=189)
Adverse Event	404	431
Alarms	3	6
Anticoagulation Maintenance	8	19
Other	58	55
Pain	8	8
Routine or Scheduled Testing	5	5
Suspected Device Malfunction	15	5
Transplant or Transplant Evaluation	38	41
Weaning Protocol	0	2
Worsening Heart Failure	6	7
Total	**545**	**579**

The time-to-event analysis of rehospitalization is shown in Figure 11.

Figure 11: Rehospitalization Following Discharge from Implantation Surgery



Number of subjects at risk:					
HeartMate II	160	50	29	19	13
HeartMate 3	177	56	40	29	21

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 14. Cardiac transplants due to device malfunctions are included as a reoperation; elective cardiac transplants are not. Forty-three percent (43%; 82/189) of HeartMate 3 subjects and 56% (97/172) of HeartMate II subjects required at least one reoperation by 24 months post implantation. Secondary mediastinal procedures and device-related infection management procedures were most common and with similar rates in both arms. Device exchange or removal (urgent transplant) were observed more frequently in HeartMate II subjects.

Two subjects in the HeartMate 3 arm required reoperation because of outflow graft twisting that became clinically evident with low flow alarms on post-operative day 567 and 687, respectively.

Table 14: Reoperations at 24 Months (AT Population)

Operation	HeartMate II (n=172)	HeartMate 3 (n=189)
Replace/exchange device	24	3
LVAD Implant (other than HeartMate 3 or HeartMate II)	4	0
Outflow graft replacement	0	1
Heart transplant due to device malfunction	8	0
Device explant	2	1
Chest or abdominal related		
Delayed chest closure	10	22
Mediastinal exploration or evacuation	37	26
Other abdominal or chest exploration	6	3
Gastrointestinal related		
Surgery for gastrointestinal bleeding	5	8
Other gastrointestinal surgery	11	9
Cardiovascular related		
Pericardial fluid collection	6	1
Valve or vascular surgery	13	13
RVAD implant or removal	10	12
Infection related		
Tissue debridement or wound management	27	6
Driveline surgery	17	26
Miscellaneous		
Respiratory surgery	13	14
ICD revision or replacement	9	19
Orthopedic surgery	8	1
Other*	16	13
Total	**226**	**178**

*Includes aborted heart transplant (n=1), biopsy (n=4), craniotomy (n=3), dialysis catheter implant (n=1), eye surgery (n=5), genitourinary surgery (n=4), hematoma evacuation (n=2), hernia repair (n=6), and oral surgery (n=3).

At 24-month follow-up, the percent of days out of a hospital were similar between HeartMate 3 and HeartMate II subjects (90.3% vs. 91.4%), as shown in Table 15.

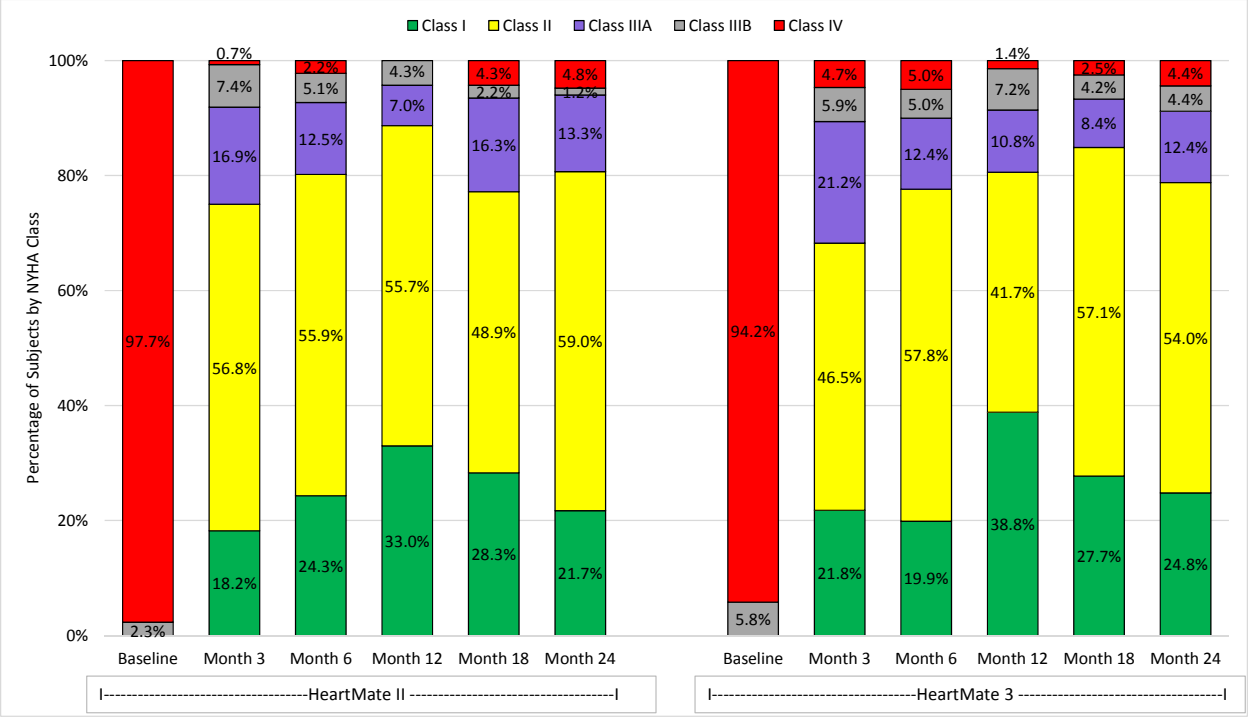
Table 15: Days Spent In and Out of the Hospital at 24 months Post Implant (AT Population)

	N	Total Days of Support	Index Hospitalization	Rehospitalization Days	Days out of Hospital	Percent of Days Out of Hospital
HeartMate II	172	88420	3564	4995	79861	90.3%
HeartMate 3	189	106481	4835	4315	97331	91.4%

Functional Status

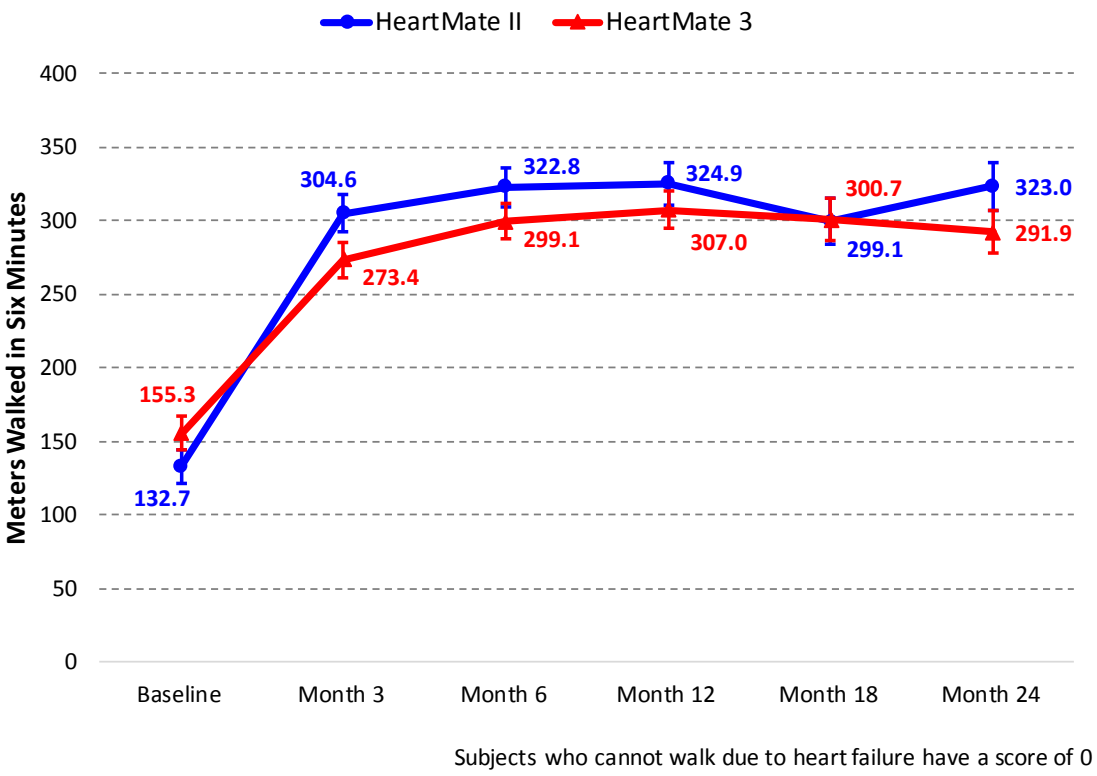
Functional status was assessed by NYHA classification and the 6MWT. Ninety-six percent (96%) of subjects were in NYHA Class IV at baseline. HeartMate 3 and HeartMate II subjects experienced a similar and durable improvement in symptomatology to predominantly Class I or II after LVAD implantation, as shown in Figure 12.

Figure 12: NYHA Class over Time



Durable clinically significant improvement in 6MWT was also observed in both arms, as shown in Figure 13. Baseline 6MWT data were unavailable for approximately half of the subjects in both arms and were imputed as being 0. Similar proportions of subjects completed 6MWT evaluations at scheduled post-implantation follow-ups.

Figure 13: Six-Minute Walk Test over Time
(least-squared means, linear mixed model)



Quality of Life

Quality of life was assessed by the EQ-5D-5L and the KCCQ questionnaires, as summarized in Figures 14-17. Subjects 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 14: Total EQ-5D-5L Score over Time (AT Population)

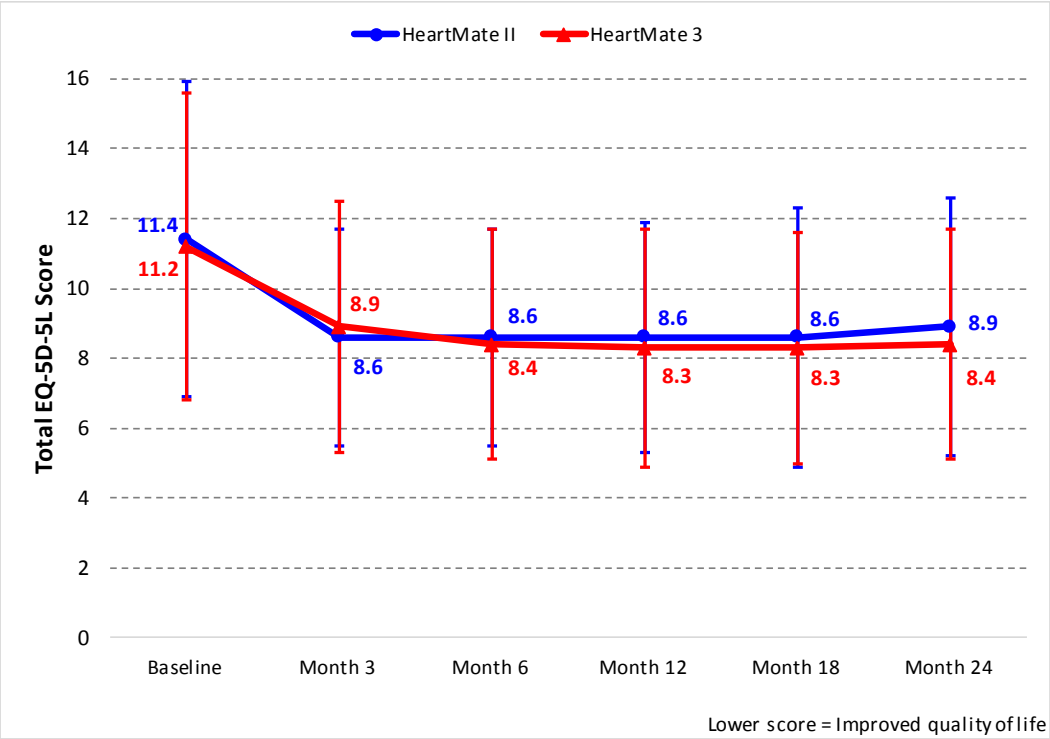


Figure 15: EQ-5D-5L Visual Analog Score over Time (AT Population)

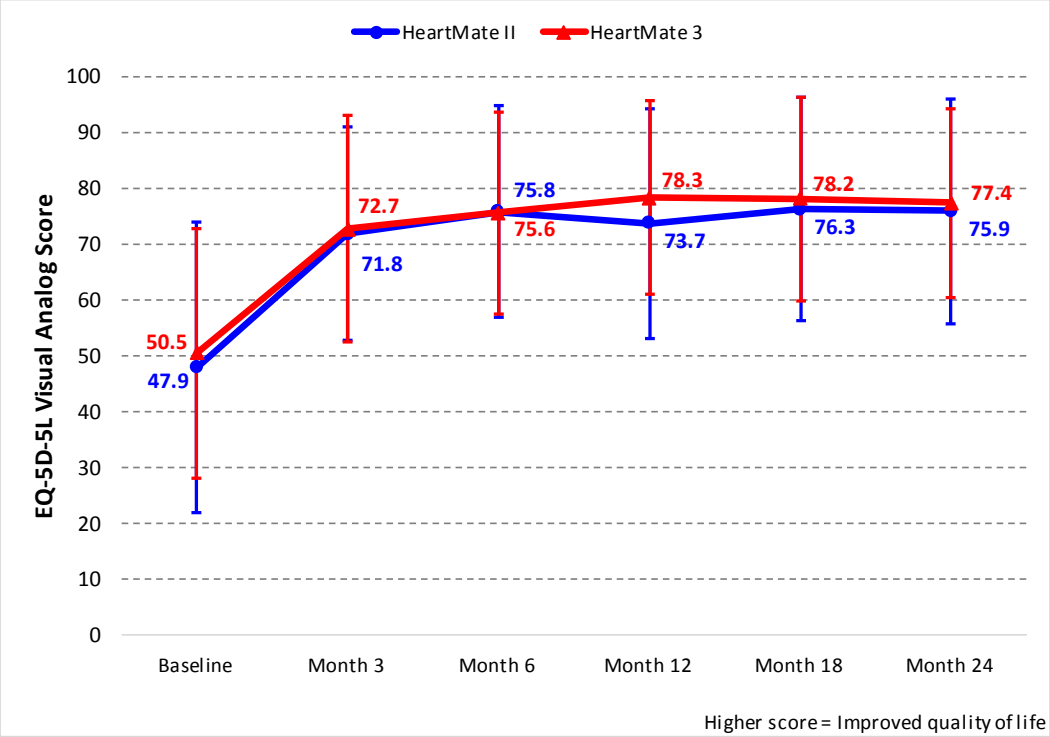


Figure 16: KCCQ Overall Summary Score over Time (AT Population)

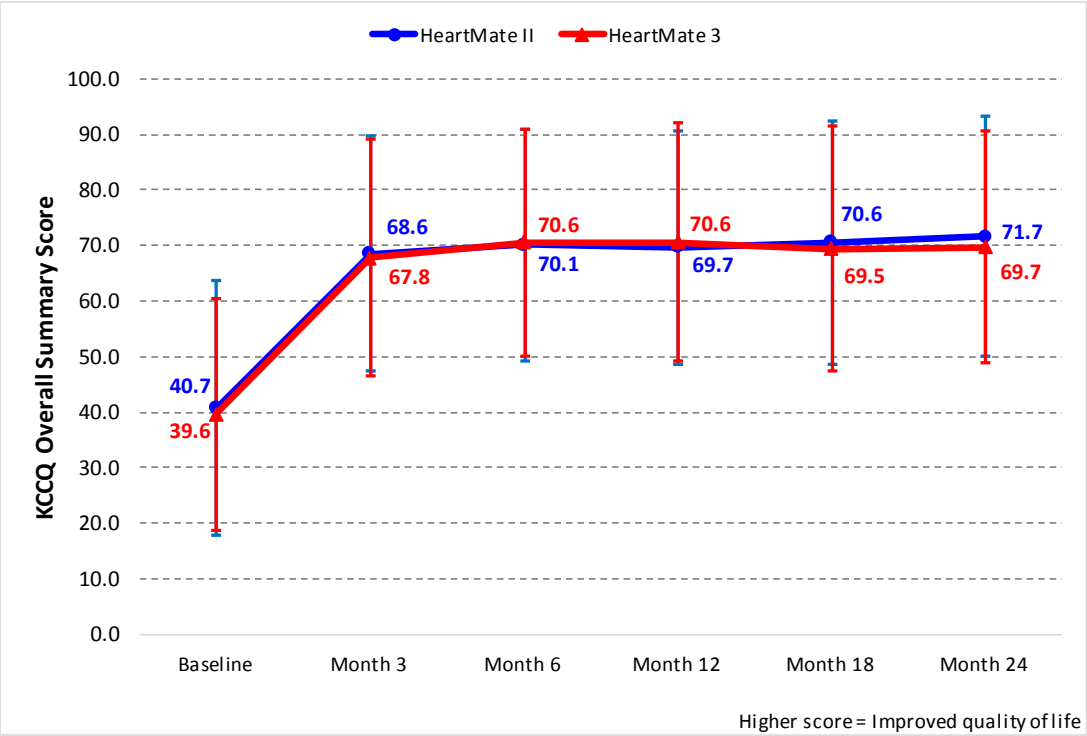
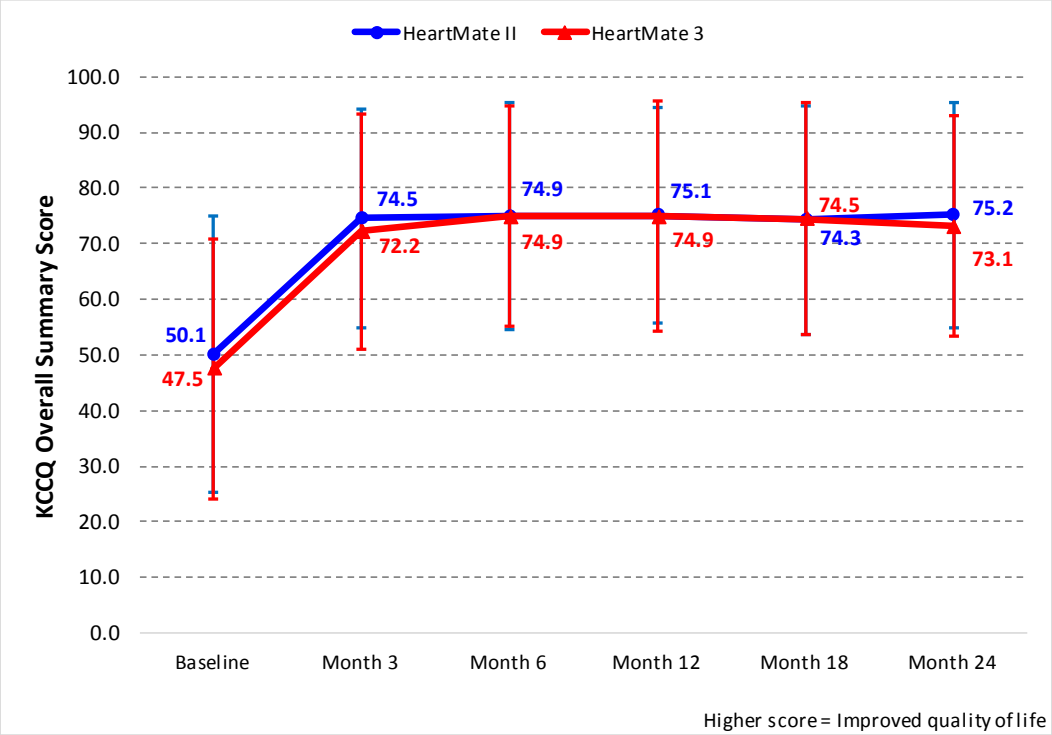


Figure 17: KCCQ Clinical Summary Score over Time (AT Population)



Competing Outcomes Analysis

Plots of the competing outcomes (ongoing on LVAS support, expiration, transplantation, exchanged to non-study device) are provided in Figures 18 and 19 for HeartMate II and HeartMate 3, respectively.

Figure 18: Competing Outcomes of HeartMate II Patients at 24 Months

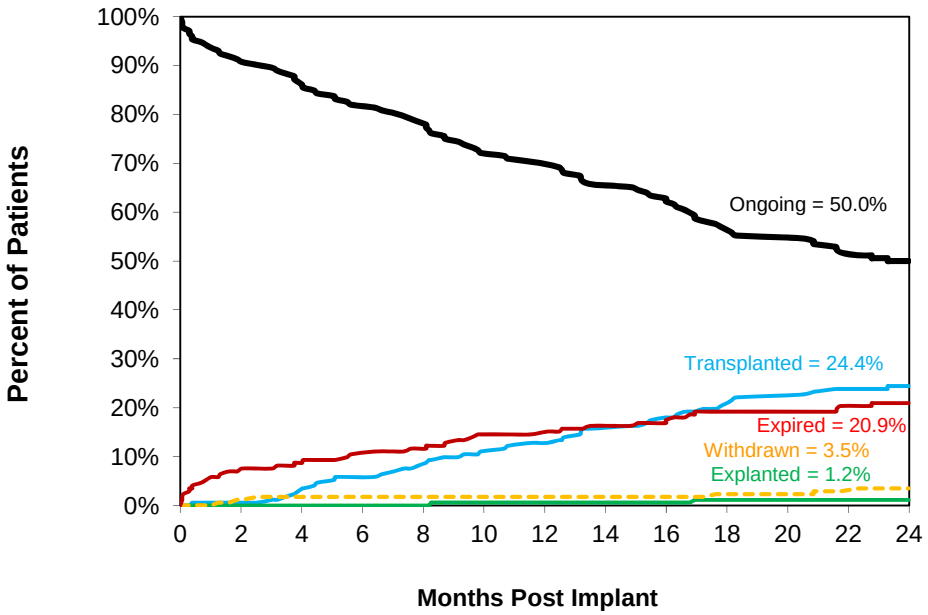
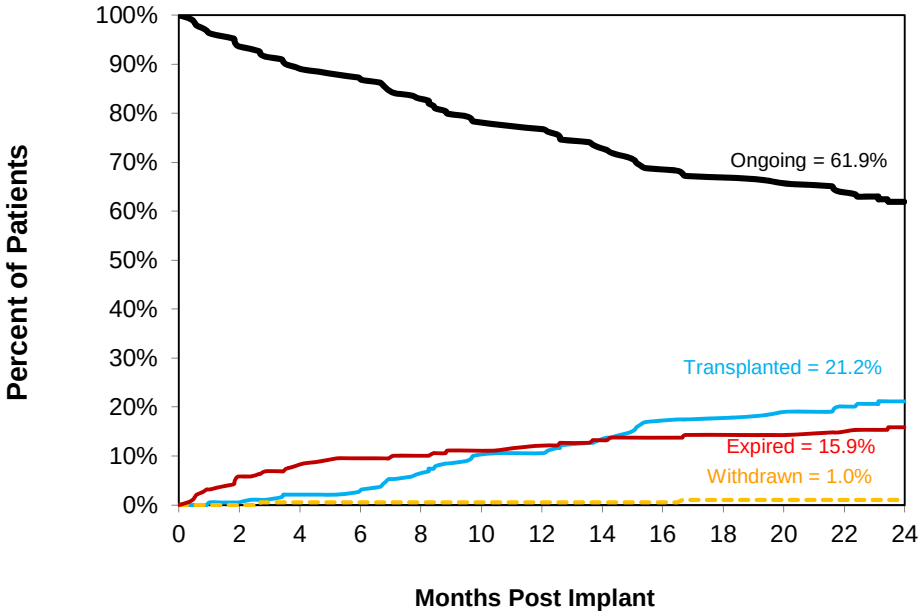


Figure 19: Competing Outcomes of HeartMate 3 LVAS Patients at 24 Months



3. Subgroup Analyses

Subgroup analysis of the primary endpoint was pre-specified for age, gender, race, intended use, and INTERMACS profile. The results for the ITT and AT populations are shown in Tables 16 and 17, respectively.

Table 16: Subgroup Analysis of the Primary Endpoint (ITT Population)

Variable	Subgroup	Primary Endpoint Success*	
		HeartMate II (n=176)	HeartMate 3 (n=190)
Age	18 - 59	52/84 (62%)	59/70 (84%)
	60 - 69	34/53 (64%)	62/75 (83%)
	70+	20/39 (51%)	30/45 (67%)
Gender	Male	89/143 (62%)	119/150 (79%)
	Female	17/33 (52%)	32/40 (80%)
Race	Caucasian	81/131 (62%)	96/127 (76%)
	Non-Caucasian	25/45 (56%)	55/63 (87%)
Intended Use	BTT/BTC	47/70 (67%)	65/79 (82%)
	DT	59/106 (56%)	86/111 (77%)
INTERMACS Profile†	INTERMACS 2 or 3	89/142 (63%)	132/162 (81%)
	INTERMACS 4 or 5	16/30 (53%)	18/26 (69%)

*No. of patients counted as a study endpoint success/no. of patients in subgroup (%).
†One (1) HeartMate 3 subject and two (2) HeartMate II subjects were INTERMACS I.

Table 17: Subgroup Analysis of the Primary Endpoint (AT Population)

Variable	Subgroup	Primary Endpoint Success*	
		HeartMate II (n=172)	HeartMate 3 (n=189)
Age	18 - 59	52/83 (63%)	59/69 (86%)
	60 - 69	34/50 (68%)	62/75 (83%)
	70+	20/39 (51%)	30/45 (67%)
Gender	Male	89/140 (64%)	119/149 (80%)
	Female	17/32 (53%)	32/40 (80%)
Race	Caucasian	81/129 (63%)	96/126 (76%)
	Non-Caucasian	25/43 (58%)	55/63 (87%)
Intended Use	BTT/BTC	47/66 (71%)	65/78 (83%)
	DT	59/106 (56%)	86/111 (77%)
INTERMACS Profile†	INTERMACS 2 or 3	89/141 (63%)	132/162 (81%)
	INTERMACS 4 or 5	16/29 (55%)	18/26 (69%)

*No. of patients counted as a study endpoint success/no. of patients in subgroup (%).
†One (1) HeartMate 3 subject and two (2) HeartMate II subjects were INTERMACS I.

Subgroup analyses of the adverse events were also pre-specified for age, gender, race, intended use, and INTERMACS profile. The results for debilitating stroke and gastrointestinal bleeding are summarized in Table 18 and 19, respectively.

Table 18: Subgroup Analysis of Debilitating Strokes (AT Population)

Variable	Subgroup	Debilitating Strokes*	
		HeartMate II (n=172)	HeartMate 3 (n=189)
Age	18 - 59	4/83 (5%)	0/69 (0%)
	60 - 69	2/50 (4%)	8/75 (10%)
	70+	3/39 (8%)	5/45 (11%)
Gender	Male	7/140 (5%)	9/149 (6%)
	Female	2/32 (6%)	4/40 (10%)
Race	Caucasian	6/129 (5%)	10/126 (8%)
	Non-Caucasian	3/43 (7%)	3/63 (5%)
Intended Use	BTT/BTC	1/66 (2%)	5/78 (6%)
	DT	8/106 (8%)	8/111 (7%)
INTERMACS Profile†	INTERMACS 2 or 3	8/141 (6%)	11/162 (7%)
	INTERMACS 4 or 5	1/29 (3%)	2/26 (8%)

*No. of patients with debilitating strokes/no. of patients in subgroup (%).
†One (1) HeartMate 3 subject and two (2) HeartMate II subjects were INTERMACS I.

Table 19: Subgroup Analysis of Gastrointestinal Bleeding (AT Population)

Variable	Subgroup	Gastrointestinal Bleeding*	
		HeartMate II (n=172)	HeartMate 3 (n=189)
Age	18 - 59	21/83 (25%)	11/69 (15%)
	60 - 69	19/50 (38%)	26/75 (34%)
	70+	7/39 (17%)	14/45 (31%)
Gender	Male	40/140 (28%)	36/149 (24%)
	Female	7/32 (21%)	15/40 (37%)
Race	Caucasian	35/129 (27%)	34/126 (27%)
	Non-Caucasian	12/43 (27%)	17/63 (27%)
Intended Use	BTT/BTC	14/66 (21%)	15/78 (19%)
	DT	33/106 (31%)	36/111 (32%)
INTERMACS Profile†	INTERMACS 2 or 3	41/141 (29%)	43/162 (26%)
	INTERMACS 4 or 5	6/29 (20%)	8/26 (30%)

*No. of patients with GI bleeding/no. of patients in subgroup (%).
†One (1) HeartMate 3 subject and two (2) HeartMate II subjects were INTERMACS I.

4. 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 trial included 71 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 24 months post implantation, 79% of subjects in the HeartMate 3 arm achieved success in the composite primary endpoint as compared to 60% of subjects in the HeartMate II arm, thus demonstrating non-inferiority of the HeartMate 3 LVAS to the HeartMate II LVAS (ITT: lower 95% CI of risk difference = 9.1%, less that the prespecified non-inferiority margin of 10%; $p<0.0001$). The HeartMate 3 LVAS also demonstrated superiority to the HeartMate II LVAS through a superiority analysis of the ITT population, which was corroborated in the AT population. The difference in the primary endpoint outcome between the two arms was mainly driven by a clinically significantly higher number of pump exchanges and urgent transplants in the HeartMate II arm (17.6%) as compared to the HeartMate 3 arm (2.0%).

Subjects in both arms showed comparable improvement in functional status at 24 months relative to baseline. The percentage of subjects who were in NYHA Class IV decreased from 94% at baseline to 4% at 24 months in the HeartMate 3 arm and from 98% at baseline to 5% at

24 months in the HeartMate II arm. The average 6MWT distance increased from 155 m at baseline to 292 m at 24 months in the HeartMate 3 arm as compared to 133 m at baseline and 323 m at 24 months in the HeartMate II arm. Patients in both arms also showed comparable improvement in quality of life from baseline to 24 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 presented in the original PMA as well as data collected in the clinical study conducted to support approval of the expanded indication for use as described above. The serious adverse events that occurred in more than 5% of the subjects in the clinical trial included: death (HeartMate 3: 15.9% vs. HeartMate II: 20.9%), major infection (50% vs. 50%), bleeding (41% vs. 51%), right heart failure (32% vs. 28%), cardiac arrhythmias (33% vs. 37%), respiratory failure (24% vs. 23%), renal dysfunction (13% vs. 11%), stroke (10% vs. 19%; debilitating stroke: 7% vs. 5%), and other neurological events (12% vs. 9%). Device malfunctions occurred more frequently in HeartMate 3 than HeartMate II. However, among the total number of suspected device malfunctions at 24 months, suspected malfunctions of the implanted components were more frequent in HeartMate II (27%) than in HeartMate 3 (8%). There were 2 (1%) suspected pump thrombosis events in the HeartMate 3 arm at 24 months post implantation, while 16% of the subjects in the HeartMate II arm experienced suspected pump thrombosis. Gastrointestinal bleeding occurred at a clinically significant rate (27%) in both arms of the study; 37% of female HeartMate 3 recipients and 21% female HeartMate II recipients developed gastrointestinal bleeding.

C. Benefit-Risk Determination

The probable benefits of the HeartMate 3 LVAS for patients with advanced refractory left ventricular heart failure include a 79% chance of survival free from debilitating stroke and without the need for a reoperation to replace the pump at 24 months. As compared to the HeartMate II LVAS, the HeartMate 3 LVAS was associated with a lower risk of pump thrombosis.

The probable risks of the HeartMate 3 LVAS include serious adverse events such as death, stroke and other neurological events, major infection, bleeding, right heart failure, cardiac arrhythmias, respiratory failure, and renal dysfunction.

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 long-term mechanical circulatory support in patients with advanced refractory left ventricular heart failure.

XIII. CDRH DECISION

CDRH issued an approval order on October 18, 2018. The final condition of approval cited in the approval order is described below.

The applicant must conduct the following post-approval studies:

1. **Continued Follow-up of the Premarket Pivotal Cohort**: The study will consist of all living subjects (both HeartMate 3 and HeartMate II) who were enrolled in the premarket pivotal cohort. The objective of this study is to characterize the clinical outcomes through 5 years post implantation. The safety and effectiveness endpoints include the composite endpoint of survival to transplant or recovery, or on left ventricular assist device (LVAD) support free of debilitating stroke (Modified Rankin Score > 3) or reoperation to replace the pump; mortality; bleeding; major infection; hemolysis; device thrombosis; neurological dysfunction; and any other serious adverse events; as well as New York Heart Association (NYHA) classification and 6-minute walk distance (6MWD).

2. **Continued Follow-up of the Continued Access Cohort**: The study will consist of all living subjects who were enrolled in the Continued Access Protocol (CAP) investigation. The objective of this study is to characterize the clinical outcomes through 2 years post implantation. The safety and effectiveness endpoints include the composite endpoint of survival to transplant or recovery, or on LVAD support free of debilitating stroke (Modified Rankin Score > 3) or reoperation to replace the pump; mortality; bleeding; major infection; hemolysis; device thrombosis; neurological dysfunction; and any other serious adverse events; as well as NYHA classification and 6MWD.

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.