SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Ventricular bypass (assist) device (21CFR 870.3545)

Device Trade Name: Thoratec HeartMate® II Left Ventricular Assist System (LVAS)

Applicants Name and Address: Thoratec Corporation
6035 Stoneridge Drive
Pleasanton, CA 94588

Date of Panel Recommendation: N/A

Premarket Approval Application (PMA) Number: P060040/S005

Date of Notice of Approval to Applicant: January 20, 2010

The HeartMate II LVAS is currently indicated as a bridge to transplantation in cardiac transplant candidates at risk of imminent death from non-reversible left ventricular failure. The PMA for this device for that indication was approved on April 21, 2008. Thoratec Corporation submitted a PMA supplement to expand the Indications for Use of the HeartMate II LVAS to include patients who are not candidates for cardiac transplantation. This expanded indication for permanent support is called destination therapy (DT).

The preclinical test results that apply to this device were presented in the original PMA application and are not repeated here. For information on the data that were used to support the original Indications for Use, the summary of safety and effectiveness data (SSED) from the previous application should be referenced. Written requests for copies can be obtained from the Dockets Management Branch (HFZ-305), Food and Drug Administration, 12420 Parklawn Drive, Rm. 1-23, Rockville, MD 20857, under Dockets 94M-0404 and 99M-1520, or via the Internet at http://www.fda.gov/cdrh/pmapage.html.

II. INDICATIONS FOR USE

The HeartMate II LVAS is intended for use as a bridge to transplantation in cardiac transplant candidates at risk of imminent death from non-reversible left ventricular failure. The HeartMate II LVAS is also indicated for use in patients with New York Heart Association (NYHA) Class IIIB or IV end-stage left ventricular failure who have received optimal medical therapy for at least 45 of the last 60 days, and who are not candidates for cardiac transplantation. The HeartMate II LVAS is intended for use both inside and outside the hospital, or for transportation of Ventricular Assist Device (VAD) patients via ground ambulance, fixed-wing aircraft, or helicopter.

III. CONTRAINDICATIONS

The HeartMate II LVAS is contraindicated for patients who cannot tolerate anticoagulation therapy.

IV. WARNINGS AND PRECAUTIONS

See Warnings and Precautions in the final labeling (Instructions for Use)

V. DEVICE DESCRIPTION

The HeartMate II Left Ventricular Assist System (LVAS) consists of an implanted axial flow blood pump and external components as shown in Figure 1. The HeartMate II is smaller than the HeartMate XVE LVAS which is also approved for the DT indication. Because of its size, the HeartMate II LVAS can be used in the treatment of smaller sized non-cardiac transplant patients. These smaller sized patients include mostly women and men of small stature. It can also be used in patients with anatomic features that preclude use of the larger HeartMate XVE device.

The HeartMate II LVAS is powered through the System Controller, a microprocessor-based unit that initiates motor actuation, monitors and reports on system function, and serves as the primary interface with the system. Electrical power is provided by either a pair of wearable, rechargeable batteries (Figure 1), or through connection to a dedicated power supply (Power Module) as shown in Figure 2. The electrical power to the implanted blood pump is delivered through a percutaneous lead that connects the blood pump to the external System Controller.

Figure 1 – HeartMate II LVAS, Implantable and External Components (Battery-powered Configuration)

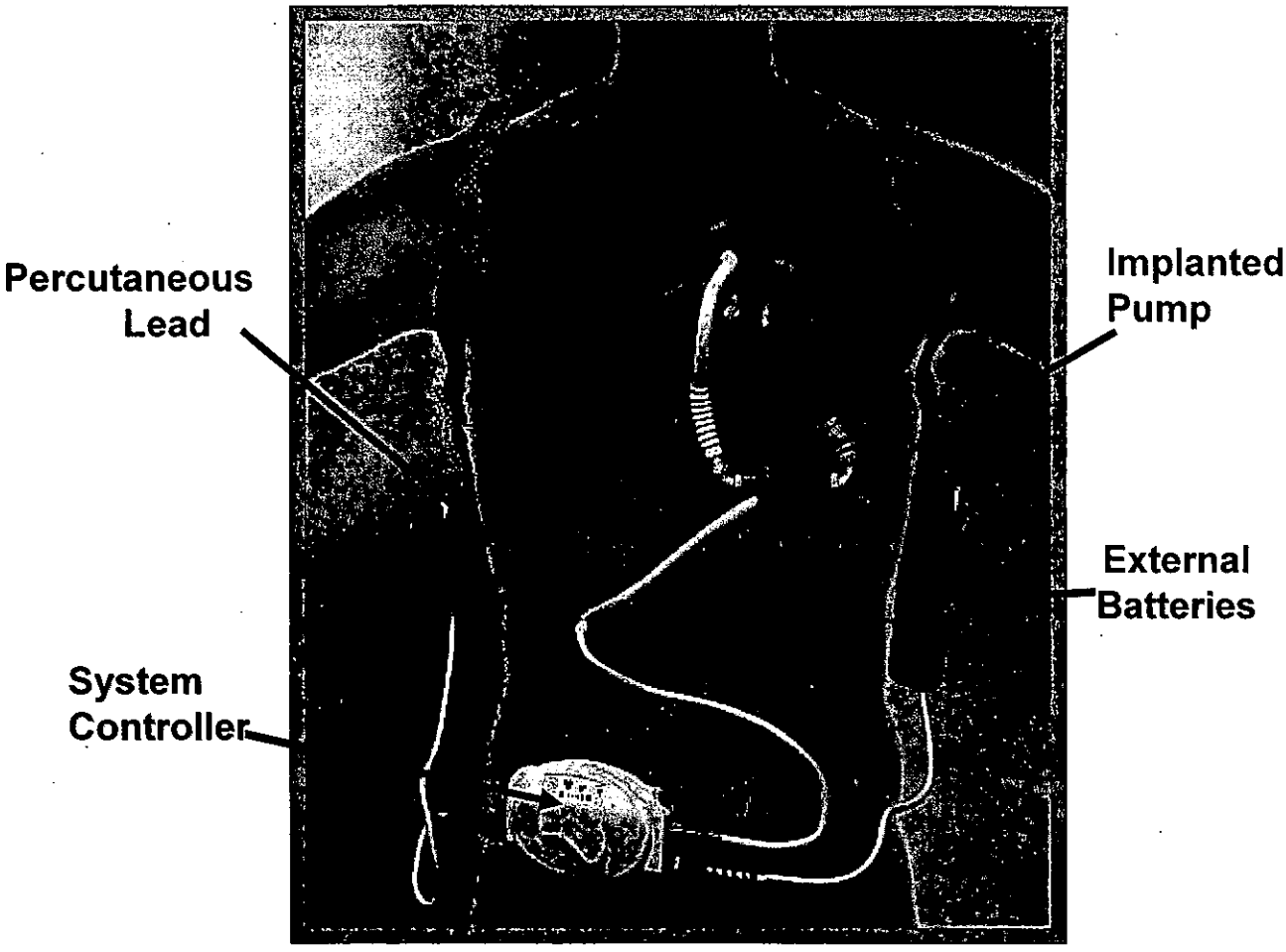
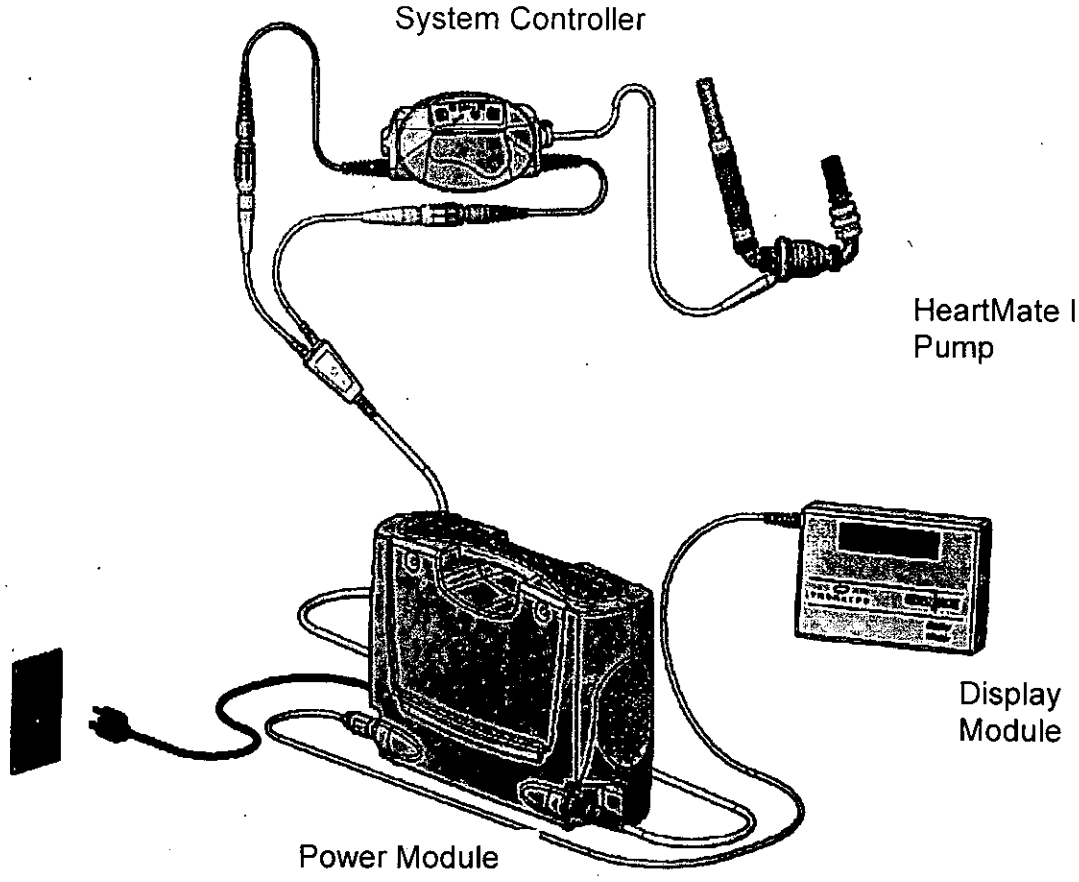


Figure 2 – HeartMate II LVAS Configuration with Power Module and System Monitor



VI. ALTERNATIVE PRACTICES OR PROCEDURES

The current standard of care for patients in end-stage heart failure includes three treatment modalities: pharmacologic therapy (including digoxin, ACE inhibitors/Angiotensin II receptor blockers, beta blockers, diuretics and inotropes), cardiac transplantation, and mechanical circulatory support devices.

VII. MARKETING HISTORY

The HeartMate II LVAS has met the conformity requirements of the European Union Active Implantable Medical Device Directive, as indicated by the CE Mark. Since November 7, 2005, the HeartMate II has been commercially distributed in the European Union, Switzerland, Iceland, Canada, Israel, Singapore, the Bahamas and South Africa.

The HeartMate II LVAS was initially approved for marketing in the United States for the bridge to transplant indication on April 21, 2008.

The HeartMate II LVAS has not been withdrawn from the market in any country.

VIII. POTENTIAL ADVERSE EVENTS

Adverse events that may be associated with the use of the HeartMate II LVAS are listed below. Other than death, adverse events are listed in decreasing order of frequency observed in the clinical study. For additional information on adverse events that occurred in the destination therapy clinical study, please see Section X below.

- Death
- Bleeding, perioperative or late
- Cardiac arrhythmia
- Local infection
- Respiratory failure
- Device malfunction
- Sepsis
- Right heart failure
- Driveline or pocket infection
- Renal failure
- Stroke
- Neurologic dysfunction
- Psychiatric episode
- Thromboembolic event, peripheral
- Hemolysis
- Hepatic dysfunction
- Device thrombosis
- Myocardial infarction

IX. SUMMARY OF PRE-CLINICAL STUDIES

Thoratec conducted testing on the components and sub-systems of the HeartMate II LVAS. *In vitro* and *in vivo* system performance and characterization studies and long-term reliability studies demonstrated reasonable system safety of the HeartMate II LVAS. Pre-clinical testing demonstrated compliance with internationally recognized standards for electrical safety, electromagnetic compatibility, and biocompatibility. Packaging and sterilization processes were validated according to internationally recognized standards.

Pre-clinical laboratory studies that were summarized in the Summary of Safety and Effectiveness for the original PMA (P060040) are equally applicable to the expanded Indications for Use.

X. SUMMARY OF CLINICAL STUDIES

Study Overview

The objective of the study was to determine the safety and effectiveness of the HeartMate II LVAS as a destination therapy (DT) device in end-stage heart failure patients who were not candidates for cardiac transplantation. Effectiveness of the device was compared to the HeartMate XVE by evaluating a composite endpoint that included survival at two years free of stroke resulting in a Modified Rankin Score > 3 or reoperation to repair or replace the device. The safety of the HeartMate II was documented by the incidence of adverse events as well as device malfunctions and failures during LVAS support compared to the HeartMate XVE results.

In addition, a number of secondary objectives were evaluated during the study, including separate evaluations of each component of the composite endpoint (2 year survival, stroke rates, and device reliability), functional status (6-minute walk, patient activity score, and NYHA classification), health status including quality of life (Minnesota Living with Heart Failure and Kansas City Cardiomyopathy Questionnaire), assessment of all adverse events, re-operations, re-hospitalizations, and neurocognitive assessments (memory, language, visual/spatial perception, processing speed and abstract/executive function).

Study Design

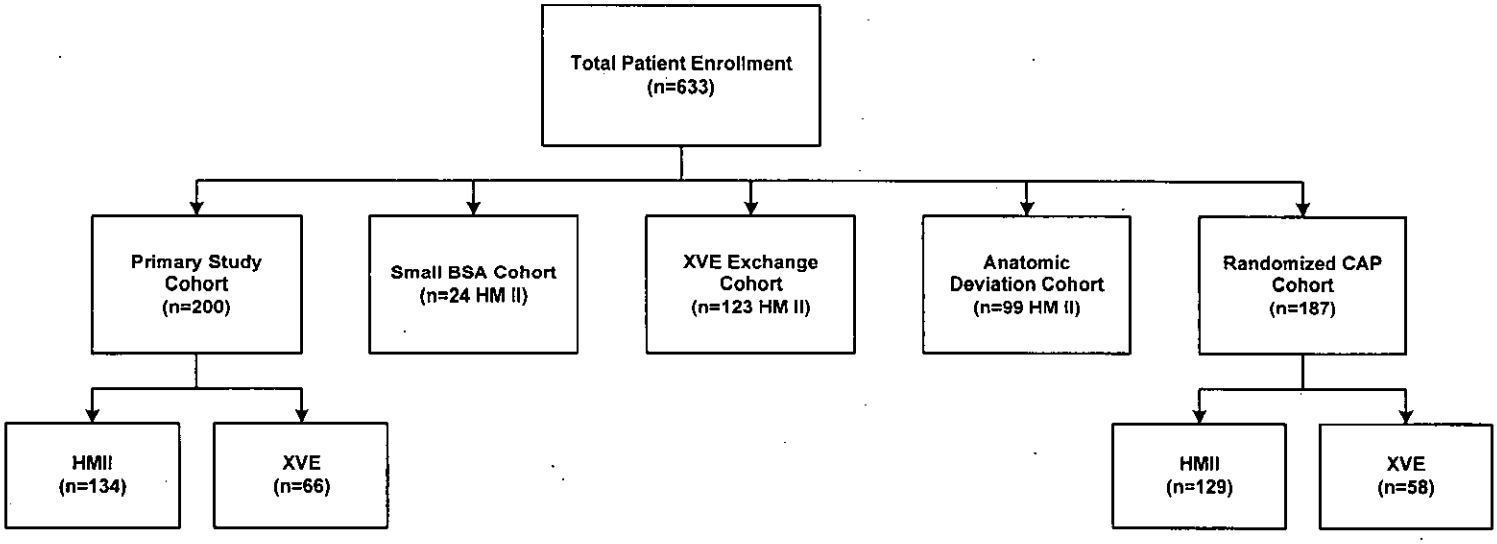
The Destination Therapy (DT) pivotal study was a prospective, randomized, unblinded, non-inferiority evaluation of the HeartMate II LVAS in end-stage left ventricular failure patients who were not candidates for cardiac transplantation and were refractory to optimal medical therapy. The statistical analysis plan in the study protocol specified testing for superiority once non-inferiority was established. Patients were randomly assigned to treatment with the HeartMate XVE (control group) or to treatment with the HeartMate II. Two patients were randomized to the HeartMate II for every one patient randomized to the HeartMate XVE. The randomization was stratified by study center

and blocked to maintain the 2:1 ratio over time. Block sizes of 3, 6, or 9 patients were randomly selected to prevent manipulation of the treatment assignment. Two hundred patients were enrolled into the Primary Study Cohort (134 HeartMate II and 66 HeartMate XVE) at 38 investigational sites from March 2005 to May 2007. All 200 patients enrolled into the Primary Study Cohort were followed for at least two years.

This study also enrolled patients into four additional study cohorts. Refer to Figure 3 for a summary of the cohorts and number of patients enrolled.

- *Small BSA Cohort:* Patients who had a BSA of less than $1.5m^2$ and therefore, could not be randomized to the HeartMate XVE due to its size.
- *XVE Exchange Cohort:* Destination Therapy patients who received the HeartMate II as a replacement for a failed HeartMate XVE originally implanted under commercial use.
- *Randomized Continued Access Protocol (CAP) Cohort:* Upon completing enrollment in the Primary Study Cohort, patient enrollment continued under CAP, using the same study protocol as the Primary Study Cohort.
- *Anatomic Deviation Cohort:* This cohort included patients that had a BSA > $1.5m^2$ but could not be randomized to the HeartMate XVE due to their body habitus or other anatomic considerations.

Figure 3 – Total Number of Patients Enrolled in Each Cohort (as of December 15, 2008)



The study had two oversight committees: a Clinical Events Committee (CEC), which adjudicated all adverse events and deaths, and a Data and Safety Monitoring Board (DSMB), which reviewed the study data periodically to ensure that the study was safe to continue. The members of these committees were independent of Thoratec Corporation, the investigational sites, and the principal investigators.

The primary endpoint of the study was a composite endpoint: two year survival free of stroke resulting in a Modified Rankin score > 3 or reoperation to repair or replace the device. Patients were considered a success if they achieved the composite endpoint and a failure if they did not. Patients who were urgently transplanted due to device failure were considered a failure. Patients who were electively transplanted after reversal of a pre-enrollment co-morbidity were followed and considered a success if they achieved two years of survival from the day of their VAD implant without experiencing a stroke resulting in a Modified Rankin score > 3. The HeartMate II was judged a success if the proportion of HeartMate II patients who achieved the composite endpoint was equal to or better than the HeartMate XVE comparison group.

Primary Study Cohort Patient Population

The HeartMate II was implanted as Destination Therapy in patients who were not candidates for cardiac transplantation. Patients were ineligible for transplant primarily due to age (28%), recent history of cancer (9%), obesity (7%), and substance abuse or insufficient social support (7%). The patients' ages ranged from 26 to 81 years, with a median of 64 years. The majority of patients were Caucasian males with ischemic heart disease. No significant differences were seen in age, BSA, body mass index (BMI), etiology or ethnicity between the HeartMate II and HeartMate XVE groups. Despite randomization, the HeartMate II arm included a significantly larger number of females than the HeartMate XVE arm. A gender analysis was performed and it was determined that there was no influence on the treatment effect (refer to the Gender Analysis Section at the end of this document). Patient demographics are presented in Table 1.

Table 1 – Primary Study Cohort: Baseline Demographics

	HeartMate II (n=134)	HeartMate XVE (n=66)	P*
Age (years)**	64 (26-79)	65 (29-81)	0.8125
Etiology	66% Ischemic	68% Ischemic	0.7526
Gender	81% Male 19% Female	92% Male 8% Female	0.0369
BSA (m2)**	2.0 (1.6-2.8)	2.0 (1.6-2.8)	0.5438
BMI (kg/m2)**	27.4 (18.0-43.4)	27.9 (18.2-40.1)	0.9913

* Unpaired t-test or Fisher's exact test, as appropriate

**Median and range

The baseline laboratory assessments, hemodynamic values and cardiovascular history did not reveal any statistically significant differences between the HeartMate II and HeartMate XVE group. Of note in the cardiovascular history is that 83% of the patients entered the study with implantable cardioverter defibrillators (ICD) and 16% of the patients had a history of stroke (refer to Table 2). Overall, 79% of the patients were on inotropes at baseline, 23% on intra-aortic balloon pump (IABP) and 8% on mechanical ventilation, thus indicating an end-stage heart failure patient population. The similarity in baseline characteristics indicates that the two treatment arms are comparable.

Table 2 – Primary Study Cohort: Baseline Cardiovascular History

	HeartMate II (n=134)		HeartMate XVE (n=66)		
Cardiovascular	**# Pts**	**% Pts**	**# Pts**	**% Pts**	**P***
Arrhythmias	115	86%	55	83%	0.6762
Ventricular Arrhythmias	65	49%	38	58%	0.2337
Congenital Heart Disease	1	1%	1	2%	0.5522
Coronary Artery Disease	90	67%	48	73%	0.5159
Hypertension	87	65%	34	52%	0.0903
Ischemic	88	66%	46	68%	0.7526
Implantable Cardiac Defibrillator (ICD)	111	83%	52	79%	0.5619
LV Aneurysm / Repair	4	3%	4	6%	0.4433
Myocardial Infarction	70	52%	38	58%	0.5468
Revascularization	71	53%	32	48%	0.6550
Stroke	21	16%	11	17%	0.8403
Valve Replacement / Repair	14	10%	7	11%	1.0000
Valve Insufficiency	103	77%	46	70%	0.3026
Ventricular Pacing	105	78%	45	68%	0.1225
Biventricular Pacing	85	63%	39	59%	0.6423

*Fisher's exact test

Primary Study Endpoint:

The primary endpoint of this study was a composite endpoint: two year survival, free of stroke resulting in a Modified Rankin Score > 3 and free of reoperation to repair or replace the device. Of note, this endpoint combines the primary safety and effectiveness assessments for the device. Based on past experience with ventricular assist devices in this patient population, this type of endpoint does reflect the intended use of the device and represent a clinically meaningful outcome for patients, which are two critical factors in determining an appropriate primary endpoint.

Complete follow-up was obtained for all 200 Primary Study Cohort patients. The results of the analysis demonstrated statistical superiority of the HeartMate II ($p<0.0001$). Forty-six percent (62/134) of the patients randomized into the HeartMate II cohort successfully achieved the composite endpoint, while only 11% (7/66) of patients randomized into the HeartMate XVE cohort achieved the composite endpoint. This analysis is displayed in Table 3.

Table 3 – Primary Study Cohort (Intent To Treat): Final Analysis Results

Endpoint Analysis	HeartMate II (n=134) No. Pts (%) [95% CI]	HeartMate XVE (n=66) No. Pts (%) [95% CI]	P Value[1]
Primary Composite Endpoint[2]	62 (46%) [38-55%]	7 (11%) [3-18%]	**0.000000246**
Components of Primary Composite Endpoint[3]			
1) Stroke w/ Rankin score >3	15 (11%) [6-17%)]	8 (12%) [4-20%]	
2) Reoperation to repair or replace pump	13 (10%) [5-15%]	24 (36%) [25-48%]	
3) Death < 2 years	44 (33%) [25-41%]	27 (41%) [29-53%]	
Total of Composite Events	72 (54%) [45-62%]	59 (89%) [82-97%]	

[1] Fisher exact test

[2] Two-year survival free of stroke resulting in a Modified Rankin score > 3 or reoperation to repair or replace the device

[3] Only the first event was counted (i.e., if a patient had a stroke then subsequently died, only the stroke would be counted)

Composite Endpoint Component: Overall Survival (As Initially Treated)

Subsequent to randomization, eight patients were not implanted and four patients were implanted with the alternate device. Therefore, 133 patients were initially implanted with the HeartMate II and fifty-nine (59) patients were initially implanted with the HeartMate XVE. Patients were followed to death or two years, whichever occurred first, regardless of whether they were transplanted, explanted, or had their device exchanged.

Table 4 shows the survival at two years with a breakdown of the type of device present at two years if the device needed replacing. The protocol specified that the HeartMate XVE patients could have the HeartMate II implanted if their device needed replacing at the preference of the investigator. The HeartMate II patients could also crossover to the HeartMate XVE, but none did.

Table 4 – Survival Status at 2 Years

Survival Status at 2 Years	Original Implanted Device	
	HeartMate II (n=133)	HeartMate XVE (n=59)
Ongoing on original implanted device	50 (38%)	0 (0%)
Ongoing with replacement of original device with same type	12 (9%)	2 (3%)
Ongoing with replacement of original device with alternate type	0 (0%)	14* (24%)
Transplanted	13 (10%)	8 (19%)
Explanted for recovery	1 (1%)	1 (2%)
Total:	76 (57%)	25 (42%)

* Includes one patient who crossed-over to HeartMate II and was subsequently transplanted

Figure 4 and Table 5 below present overall survival in an As Initially Treated Kaplan-Meier analysis, with no censoring of device cross-overs or transplants. As seen in Figure 4, the overall survival including device cross-overs and transplants favors the HeartMate II group when compared to the HeartMate XVE group. Competing outcomes (ongoing, transplant, death, etc.) over time for each of the two devices are shown in Figure 5 and Figure 6. Table 5 provides the details of the analysis, including the number of patients at each interval. Causes of death while on LVAS support are listed in Table 6.

Figure 4 – Primary Study Cohort (As Initially Treated): Kaplan-Meier Survival Including Device Cross-overs and Transplants

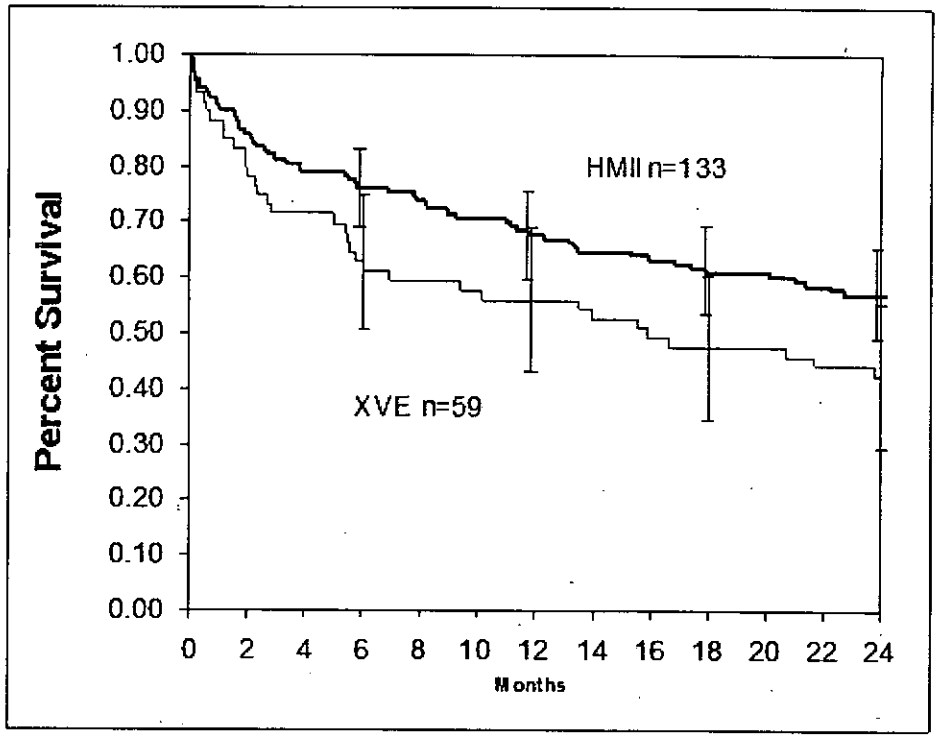


Table 5 – Primary Study Cohort (As Initially Treated): Kaplan-Meier Survival Including Device Cross-overs and Transplants

HeartMate II							
	Time Interval (Months)						
	0 - 1	1 - 3	3 - 6	6 – 9	9 - 12	12 - 18	18 – 24
Number of patients starting interval	133	121	108	101	95	90	81
Number of patients who died this interval	12	13	7	6	5	9	5
Number of cumulative patient deaths	12	25	32	38	43	52	57
Number of patients censored in interval	0	0	0	0	0	0	0
Number of cumulative censored patients	0	0	0	0	0	0	0
Probability of surviving interval	0.910	0.812	0.759	0.714	0.677	0.609	0.571
+/- 95% Confidence Limit at end of interval	0.05	0.07	0.07	0.08	0.08	0.08	0.08
HeartMate XVE							
	Time Interval (Months)						
	0 - 1	1 - 3	3 - 6	6 - 9	9 - 12	12 - 18	18 - 24
Number of patients starting interval	59	52	42	37	35	33	28
Number of patients who died this interval	7	10	5	2	2	5	3
Number of cumulative patient deaths	7	17	22	24	26	31	34
Number of patients censored in interval	0	0	0	0	0	0	0
Number of cumulative censored patients	0	0	0	0	0	0	0
Probability of surviving interval	0.881	0.712	0.627	0.593	0.559	0.475	0.424
+/- 95% Confidence Limit at end of interval	0.08	0.12	0.12	0.13	0.13	0.13	0.13

Figure 5 – Competing Outcomes for HeartMate II LVAS (As Treated)

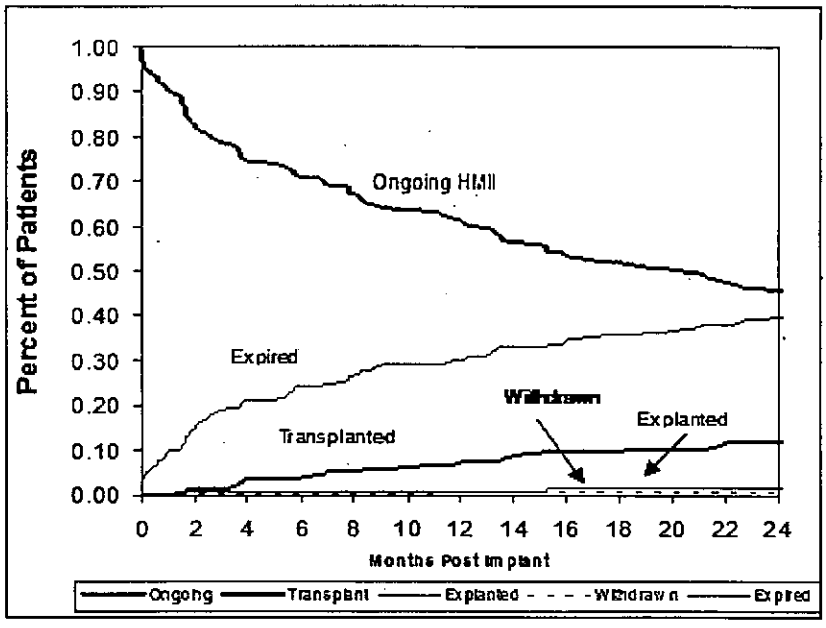


Figure 6 – Competing Outcomes for HeartMate XVE LVAS (As Treated)

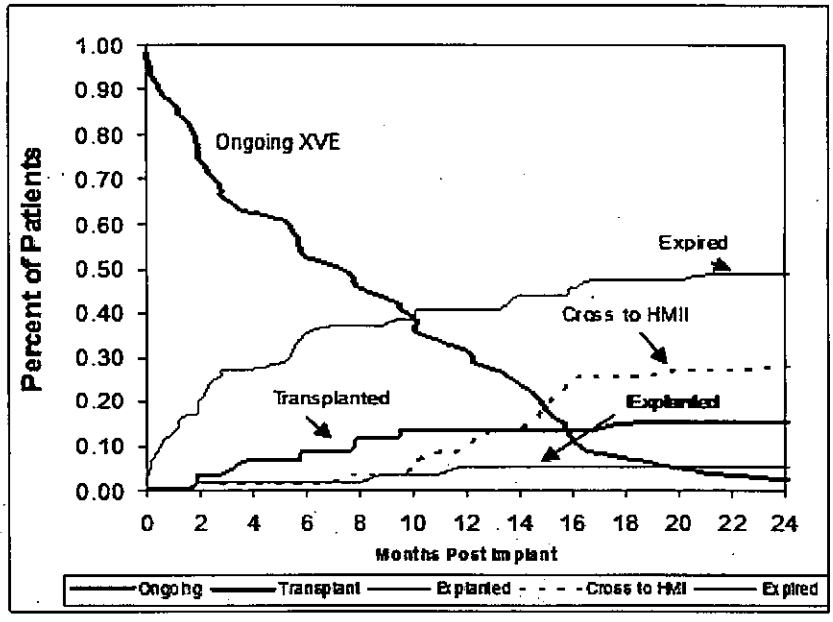


Table 6 – Primary Study Cohort (As Treated): Causes of Death During LVAS Support

	HeartMate II (n=133)		HeartMate XVE (n=59)	
	# Pts	% Pts	# Pts	% Pts
Bleeding	4	3%	1	2%
Brain related:				
Air Embolism	1	1%	0	0%
Anoxic Brain Injury	0	0%	1	2%
Stroke	13	10%	11	19%
Traumatic Brain Injury	2	2%	1	2%
Cardiopulmonary:				
Cardiac Arrest	4	3%	1	2%
Heart Failure	1	1%	1	2%
Respiratory Failure	4	3%	2	3%
Myocardial Infarction	1	1%	0	0%
Right Heart Failure	8	6%	5	8%
Device Malfunctions/Failure:				
Loss of Power	5	4%	0	0%
Device Thrombosis	2	2%	0	0%
Inflow Obstruction	0	0%	1	2%
VAD Dysfunction/fail	3	2%	2	3%
Infection	5	4%	6	10%
Miscellaneous:				
Amyloidosis	1	1%	0	0%
Cancer	2	2%	0	0%
Ischemic Bowel	0	0%	1	2%
Unknown	5	4%	0	0%
Withdrawal of Support	2	2%	1	2%
Multi-system Organ Failure	3	2%	4	7%

Composite Endpoint Component: Stroke with Modified Rankin Score >3 (As Initially Treated Analysis)

Figure 7 and Table 7 provide an As Initially Treated Kaplan-Meier analysis of survival free of stroke (Modified Rankin score > 3), with no censoring of patients at the time of any device cross-overs or transplants. Patients were followed to death or stroke, whichever occurred first, regardless of whether they were transplanted, explanted, or had their device exchanged. As can be seen in Figure 7, the overall stroke-free survival results favor the HeartMate II group when compared to the HeartMate XVE group. Patients initially treated with the HeartMate II have a two-year predicted survival free of stroke (Modified Rankin > 3) of 56% compared to 41% for the patients initially treated with the HeartMate XVE. Table 7 provides the details of the analysis including the number of patients at each time interval.

Figure 7 – Primary Study Cohort (As Initially Treated): Kaplan-Meier Survival Free of Stroke with Modified Rankin Score>3

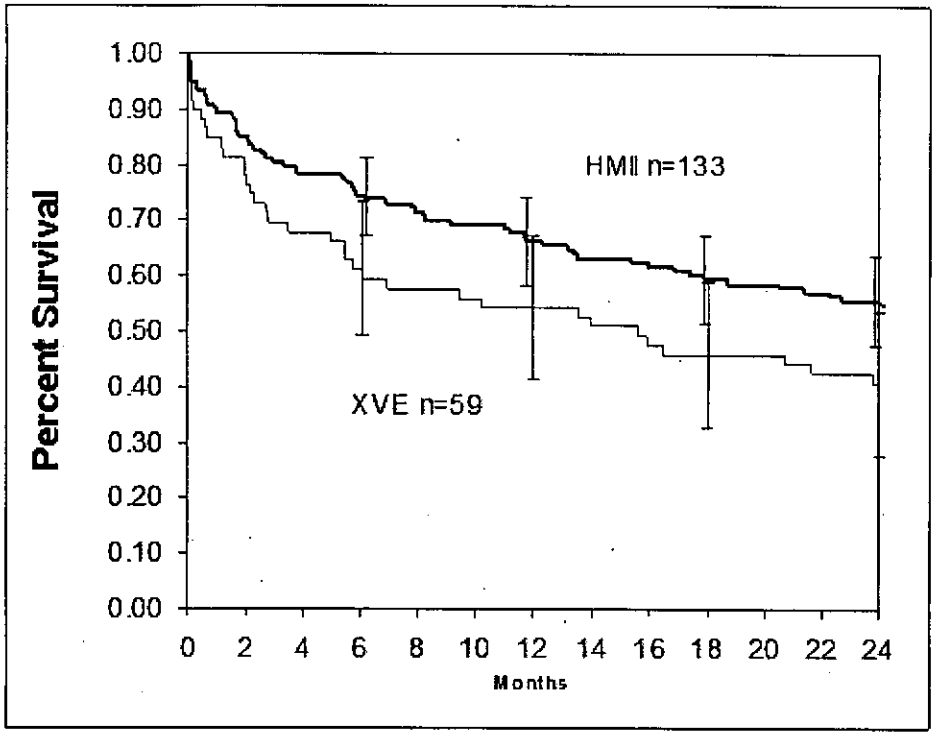


Table 7 – Primary Study Cohort (As Initially Treated): Kaplan-Meier Survival Free of Stroke with Modified Rankin Score>3

HeartMate II							
	Time Interval (Months)						
	0 - 1	1 - 3	3 - 6	6 - 9	9 - 12	12 - 18	18 – 24
Number of patients starting interval	133	119	107	99	93	88	78
Number of patients who had event this interval	14	12	8	6	5	10	4
Number of cumulative patient events	14	26	34	40	45	55	59
Number of patients censored in interval	0	0	0	0	0	0	0
Number of cumulative censored patients	0	0	0	0	0	0	0
Probability of surviving interval	0.895	0.805	0.744	0.699	0.662	0.587	0.556
+/- 95% Confidence Limit at end of interval	0.05	0.07	0.07	0.08	0.08	0.08	0.08
HeartMate XVE							
	Time Interval (Months)						
	0 - 1	1 - 3	3 - 6	6 - 9	9 - 12	12 - 18	18 - 24
Number of patients starting interval	59	50	41	36	34	32	27
Number of patients who had event this interval	9	9	5	2	2	5	3
Number of cumulative patient events	9	18	23	25	27	32	35
Number of patients censored in interval	0	0	0	0	0	0	0
Number of cumulative censored patients	0	0	0	0	0	0	0
Probability of surviving interval	0.848	0.695	0.610	0.576	0.542	0.458	0.407
+/- 95% Confidence Limit at end of interval	0.09	0.12	0.12	0.13	0.13	0.13	0.13

Composite Endpoint Component: Reoperation to Repair or Replace Pump (As Initially Treated Analysis)

Figure 8 and Table 8 provide an As Initially Treated Kaplan-Meier analysis of survival free of reoperation to replace or repair the pump, with no censoring of patients at the time of any transplant. Patients were followed to death or pump replacement or repair, whichever occurred first, regardless of whether they were transplanted or explanted. As can be seen in Figure 8, the overall results for survival free of reoperation to repair or replace the pump favor the HeartMate II group when compared to the HeartMate XVE group. Patients initially treated with the HeartMate II have a two-year predicted survival free of pump replacement or repair of 49% compared to 15% for the patients initially treated with the HeartMate XVE. Table 8 provides the details of the analysis including the number of patients at each time interval.

Figure 8 – Primary Study Cohort (As Initially Treated): Kaplan-Meier Survival Free of Reoperation to Repair or Replace the Device

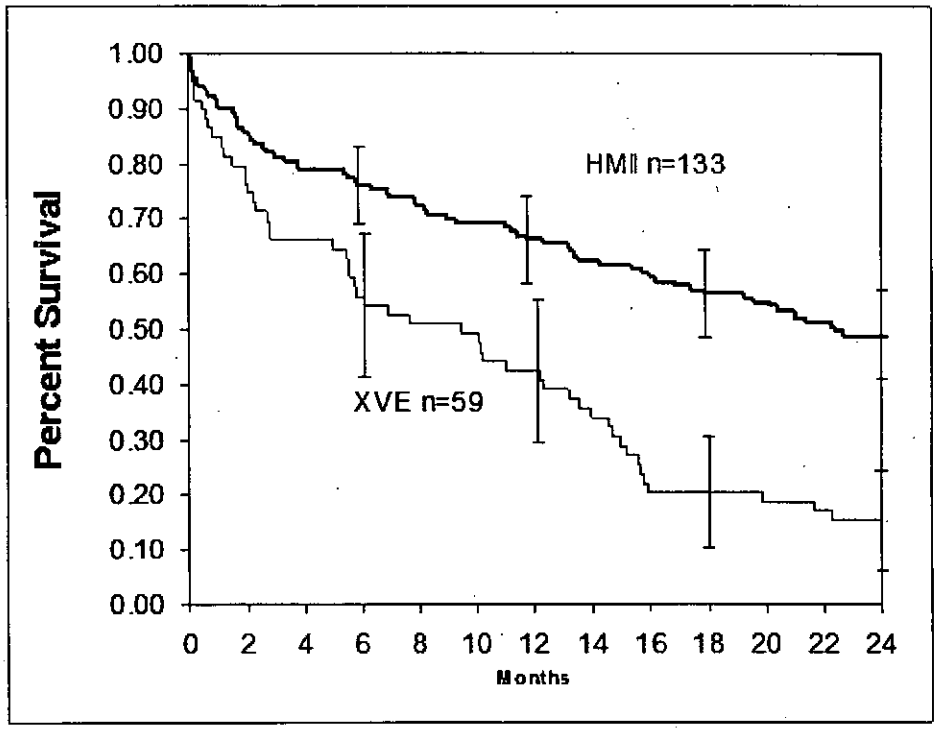


Table 8 – Primary Study Cohort (As Initially Treated): Kaplan-Meier Survival Free of Reoperation to Repair or Replace the Device

HeartMate II							
	Time Interval (Months)						
	0 - 1	1 - 3	3 - 6	6 - 9	9 - 12	12 - 18	18 - 24
Number of patients starting interval	133	121	108	101	93	88	75
Number of patients with events this interval	12	13	7	8	5	13	10
Number of cumulative patient events	12	25	32	40	45	58	68
Number of patients censored in interval	0	0	0	0	0	0	0
Number of cumulative censored patients	0	0	0	0	0	0	0
Probability of surviving interval	0.910	0.812	0.759	0.699	0.662	0.564	0.489
+/- 95% Confidence Limit at end of interval	0.05	0.07	0.07	0.08	0.08	0.08	0.08
HeartMate XVE							
	Time Interval (Months)						
	0 - 1	1 - 3	3 - 6	6 - 9	9 - 12	12 - 18	18 - 24
Number of patients starting interval	59	50	39	33	30	25	12
Number of patients with events this interval	9	11	6	3	5	13	3
Number of cumulative patient events	9	20	26	29	34	47	50
Number of patients censored in interval	0	0	0	0	0	0	0
Number of cumulative censored patients	0	0	0	0	0	0	0
Probability of surviving interval	0.848	0.661	0.559	0.509	0.424	0.203	0.153
+/- 95% Confidence Limit at end of interval	0.09	0.12	0.13	0.13	0.13	0.10	0.09

Safety: Adverse events

The incidence of serious adverse events is presented in Table 9. Serious adverse events were defined as those that resulted in death, were life-threatening, resulted in permanent disability, required hospitalization, or prolonged a hospital stay. The study was not powered for a specific analysis of the adverse events. To take into account differences in patient support durations, adverse events were normalized to events per patient-year and analyzed using Poisson regression to obtain risk ratios with 95% confidence intervals. Table 12 presents the results of this As Treated analysis for serious adverse events. The rates of serious adverse events (as treated) over various time intervals are presented below.

Table 9 - Primary Study Cohort (As Treated): Serious Adverse Events

	HeartMate II (n=133)			HeartMate XVE (n=59		
	# Pts	% Patients [95% Confidence interval]	# Events	# Pts	% Patients [95% Confidence interval]	# Events
Bleeding	102	77% [70 – 84%]	278	41	69% [58 – 81%]	70
Bleeding requiring surgery	40	30% [22 – 38%]	50	9	15% [6 – 24%]	12
Stroke	24	18% [12 – 25%]	27	8	14% [5 – 22%]	9
Peri-operative (≤POD2)	3	2% [0 – 5%]	3	1	2% [0 – 5%]	1
Post-operative (>POD2)	21	16% [10 – 22%]	24	7	12% [4 – 20%]	8
Peripheral TE	14	11% [5 – 16%]	21	6	10% [2 – 18%]	6
Other Neurological*	27	20% [13 – 27%]	32	9	15% [6 – 24%]	11
Psychological	4	3% [0 – 6%]	4	0	0% [0 – 0%]	0
Local Infection	40	30% [22 – 38%]	60	19	32% [20 – 44%]	30
Drive Line Infection	39	29% [22 – 37%]	75	14	24% [13 – 35%]	22
Pocket Infection	12	9% [4 – 14%]	19	8	14% [5 – 22%]	10
Sepsis	48	36% [28 – 44%]	80	26	44% [31 – 57%]	45
Pump Housing	1	1% [0 – 2%]	1	2	3% [0 – 8%]	2
Right Heart Failure	31	23% [16 – 30%]	34	19	32% [20 – 44%]	22
Inotropes Only	27	20% [13 – 27%]	29	16	27% [16 – 38%]	19
RVAD	5	4% [1 – 7%]	5	3	5% [0 – 11%]	3
Renal Failure	21	16% [10 – 22%]	21	14	24% [13 – 35%]	14
Hepatic Dysfunction	3	2% [0 – 5%]	3	0	0% [0 – 0%]	0
Respiratory Failure	47	35% [27 – 43%]	61	24	41% [28 – 53%]	33
Cardiac Arrhythmias	62	47% [38 – 55%]	110	21	36% [23 – 48%]	30
Myocardial Infarction	0	0% [0 – 0%]	0	1	2% [0 – 5%]	1

*Includes transient ischemic attacks (TIA) and non-stroke neurological events

Safety: Device Complications

This section discusses three selected device complications that are inherent to mechanical circulatory support devices. These complications were device malfunctions, device thrombosis, and hemolysis.

Ninety-three percent (93%, 25/27) of the HeartMate XVE malfunctions that resulted in adverse clinical effects were related to the implanted pump, primarily the result of wear-out of either the bearings or valve conduit (Table 16). In contrast, only 53% of the HeartMate II malfunctions with adverse clinical effects were related to the implanted pump. The balance of the malfunctions was primarily associated with the System Controller, an external component of the system that is designed for easy and rapid exchange in the event of a malfunction.

The malfunctions of the HeartMate II pump were primarily related to the percutaneous lead that connects the implanted pump with the external System Controller. Repair procedures were developed that can extend the useful life of the external portion of the percutaneous lead; however, failures of the internal portion of the percutaneous lead require immediate pump replacement.

The serious complications of device thrombosis and hemolysis each occurred in 4% (5 patients) of the HeartMate II patients. The HeartMate XVE patients did not experience any of these events. Table 10 lists serious adverse events that occurred because of the device while Table 11 illustrates the relative risk of those events. Three of the five (60%) hemolysis events were associated with device thrombosis. The other two hemolysis events resolved over time with no intervention.

Table 10 - Primary Study Cohort (As Treated): Device Related Serious Adverse Events

	HeartMate II (n=133)			HeartMate XVE (n=59		
	# Pts	% Patients [95% Confidence interval]	# Events	# Pts	% Patients [95% Confidence interval]	#. Events
Device Thrombosis	5	4% [1 – 7%]	5	0	0% [0 – 0%]	0
Hemolysis	5	4% [1 – 7%]	5	0	0% [0 – 0%]	0
Confirmed Malfunctions	30	23% [15 – 30%]	39	12	20% [10 – 31%]	13

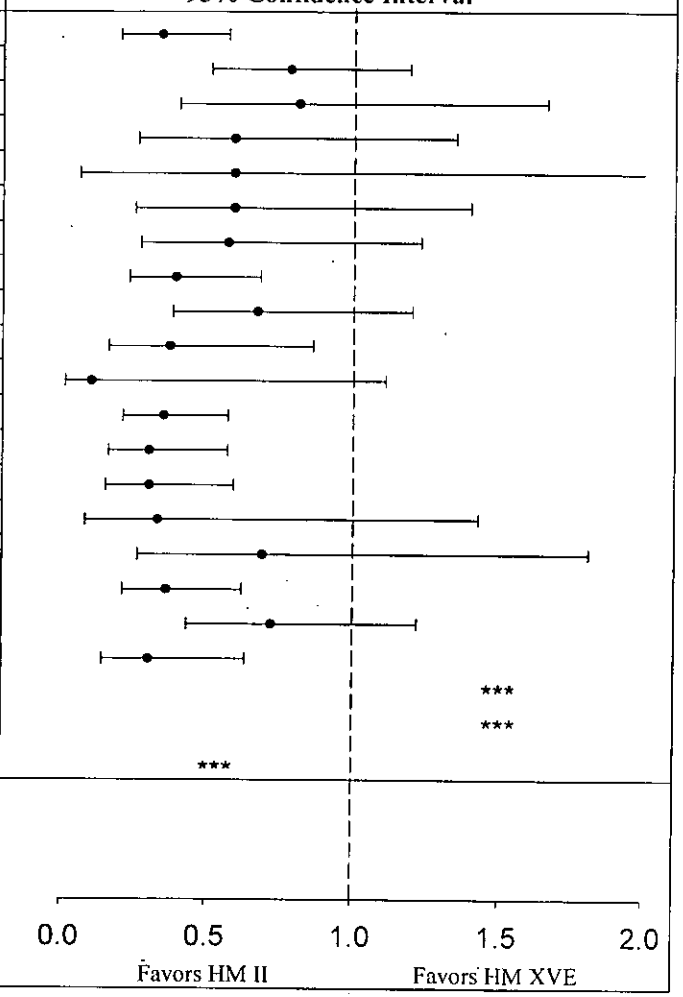
Table 11 – Primary Study Cohort (As Treated): Device Related Serious Adverse Events

	HeartMate II (n=133) 210 pt-years	HeartMate XVE (n=59) 41 pt-years	
Event	**Events/pt-yr**	**Events/pt-yr**	**Risk Ratio**
Device Thrombosis	0.02	0.00	***
Hemolysis	0.02	0.00	***
Confirmed Malfunctions	0.19	0.31	0.59

*** Unable to calculate relative risk because of no occurrences in one group

Table 12 – Primary Study Cohort (As Treated): All Serious Adverse Events

	HM II (n=133) 210 pt-years	HM XVE (n=59) 41 pt-years		
Event	**Events/pt-yr**	**Events/pt-yr**	**Risk Ratio**	**95% Confidence Interval****
Death	0.31	0.92	0.34	
Bleeding	1.32	1.69	0.78	
Bleeding requiring surgery	0.24	0.29	0.81	
Stroke	0.13	0.22	0.59	
Peri-operative (≤POD2)	0.01	0.02	0.59	
Post-operative (>POD2)	0.11	0.19	0.59	
Other Neurological*	0.16	0.27	0.57	
Local Infection	0.29	0.73	0.39	
Drive Line Infection	0.36	0.53	0.67	
Pocket Infection	0.09	0.24	0.37	
Pump Housing	0.00	0.05	0.10	
Sepsis	0.38	1.09	0.35	
Right Heart Failure	0.16	0.53	0.30	
Inotropes Only	0.14	0.46	0.30	
RVAD	0.02	0.07	0.33	
Peripheral TE	0.10	0.15	0.69	
Respiratory Failure	0.29	0.80	0.36	
Cardiac Arrhythmias	0.52	0.73	0.72	
Renal Failure	0.10	0.34	0.30	
Hepatic Dysfunction	0.01	0.00	---	***
Psychological	0.02	0.00	---	***
Myocardial Infarction	0.00	0.02	---	***



* Includes transient ischemic attacks (TIA) and non-stroke neurological events
** No adjustments made for multiplicity; no conclusions may be drawn regarding statistical significance
*** Unable to calculate risk ratio because of no occurrence in one group

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Table 13 - Primary Study Cohort: Serious Adverse Event Rate per Patient-year by Time Interval (As Treated)

	Group	0 – 30 days	31 – 180 days	181-365 days	366-730 Days
Cumulative years support	HeartMate II	10.30	43.10	44.4	70.0
	HeartMate XVE	4.40	16.60	12.8	7.1
Adverse Event					
Bleeding[1]	HeartMate II	12.33	0.86	1.01	0.81
	HeartMate XVE	10.91	1.08	0.16	0.28
Stroke[2]	HeartMate II	0.49	0.09	0.16	0.13
	HeartMate XVE	0.91	0.18	0.00	0.28
Other Neurological[3]	HeartMate II	0.78	0.23	0.00	0.16
	HeartMate XVE	0.45	0.24	0.23	0.14
Local Infection	HeartMate II	2.14	0.32	0.14	0.21
	HeartMate XVE	3.18	0.66	0.23	0.28
Drive Line Infection	HeartMate II	0.00	0.37	0.65	0.30
	HeartMate XVE	0.23	0.60	0.63	0.42
Pocket Infection	HeartMate II	0.39	0.14	0.09	0.06
	HeartMate XVE	0.45	0.30	0.16	0.14
Pump Housing Infection	HeartMate II	0.00	0.00	0.00	0.01
	HeartMate XVE	0.00	0.12	0.00	0.00
Sepsis	HeartMate II	1.65	0.37	0.29	0.40
	HeartMate XVE	2.95	1.08	0.94	0.28
Right Heart Failure	HeartMate II	2.33	0.07	0.02	0.04
	HeartMate XVE	3.86	0.18	0.08	0.14
Peripheral TE	HeartMate II	0.87	0.14	0.14	0.00
	HeartMate XVE	0.91	0.00	0.16	0.00
Respiratory Failure	HeartMate II	3.50	0.21	0.11	0.10
	HeartMate XVE	1.82	0.48	0.23	0.00
Cardiac Arrhythmias	HeartMate II	3.98	0.51	0.32	0.39
	HeartMate XVE	4.09	0.48	0.16	0.14
Renal Failure	HeartMate II	1.36	0.07	0.02	0.03
	HeartMate XVE	2.27	0.18	0.08	0.00
Hepatic Dysfunction	HeartMate II	0.19	0.00	0.00	0.00
	HeartMate XVE	0.00	0.00	0.00	0.00
Device Thrombosis	HeartMate II	0.10	0.02	0.02	0.03
	HeartMate XVE	0.00	0.00	0.00	0.00
Hemolysis	HeartMate II	0.19	0.00	0.02	0.03
	HeartMate XVE	0.00	0.00	0.00	0.00
Psychological	HeartMate II	0.19	0.02	0.00	0.01
	HeartMate XVE	0.00	0.00	0.00	0.00
Myocardial Infarction	HeartMate II	0.00	0.00	0.00	0.00
	HeartMate XVE	0.23	0.00	0.00	0.00

[1] HeartMate II: 80.52 events/pt-yr over 0-1 days; 6.78 events/pt-yr over 2-30 days
HeartMate XVE: 100.00 events/pt-yr over 0-1 days; 3.92 events/pt-yr over 2-30 days
[2] HeartMate II: 2.75 events/pt-yr over 0-1 days; 0.31 events/pt-yr over 2-30 days
HeartMate XVE: 3.13 events/pt-yr over 0-1 days; 0.76 events/pt-yr over 2-30 days
[3] Includes transient ischemic attacks (TIA) and non-stroke neurological events

Secondary Objectives:

Secondary objectives were also assessed in this study, including the following: re-operations, clinical reliability, functional status, health status including quality of life, neurocognitive evaluation and post-explant follow-up.

Reoperations

Reoperations included any return to the operating room for any reason following implant. Reoperations were device or patient related, such as driveline debridement or bleeding, and included routine operations, such as appendectomy and orthopedic procedures. As reflected in Table 14, the incidence of reoperations was similar between the groups. There was a higher percentage of patients in the HeartMate II group requiring reoperation. However, when normalized to events per patient-year, there is a lower rate of reoperations per patient-year in the HeartMate II group (risk ratio 0.53). As expected, the rate of reoperations is greatest during the first 30 days after LVAS implantation.

Table 14 – Primary Study Cohort (As Treated): Reoperations

	# pts	# pts with reoperations	% pts with reoperations	# events	Reops/ pt-yr	Risk Ratio
HeartMate II	133	106	80%	325	1.55	0.53
HeartMate XVE	59	43	73%	120	2.91	

Thirty-six (36) of the reoperations that occurred in the Primary Study Cohort were due to the need for pump replacements (21 HeartMate XVE and 15 HeartMate II). Of the 59 patients implanted with the HeartMate XVE, 20 patients received 21 pump exchanges. Of the 133 patients implanted with the HeartMate II, 14 patients received 15 pump exchanges.

Clinical Reliability

Clinical reliability was evaluated by taking into account all HeartMate II study experience through January 20, 2009, regardless of study cohort. One hundred and one (101) reports of suspected malfunctions related to the implanted components of the HeartMate II LVAS were received from the 509 HeartMate II patients enrolled into the Destination Therapy clinical study. Eighty-five percent of those reports were related to the percutaneous lead. There were 28 reports of malfunctions that resulted in hemodynamic compromise, reoperations for pump replacement, pump explantation, or death, 27 of which were related to the percutaneous lead. As shown in Table 15, reliability of the current configuration of the percutaneous lead is improved compared to the overall reliability, as a result of design modifications to the external strain relief intended to reduce the most frequent failure modes.

Table 15 – HeartMate II Percutaneous Lead Reliability (All Cohorts)

Percutaneous Lead Configuration	Type of Malfunction	Reliability[1] at:		
		1 yr	2 yr	3 yr
All configurations[2]	All malfunctions	85%	62%	39%
	Reoperation/Death	96%	87%	75%
Current Configuration[3]	All malfunctions	95%	91%	87%
	Reoperation/Death	97%	95%	92%

[1] Reliability estimates based on Weibull analysis
[2] Both original external strain relief and current external strain relief design
[3] External strain relief design at time of PMA approval

The mean time to failure (defined as malfunctions resulting in hemodynamic compromise, reoperations for pump replacement, pump explantation, or death) was 1677 days (at the 80% confidence level). The 28 individual failures described above occurred between 36 and 1277 days of VAD support. The observed clinical reliability is less than the original reliability estimates based on *in vitro* testing because the *in vitro* test environment did not reflect all of the factors associated with the LVAD user environment.

Twenty-five (25) clinical failures (defined as malfunctions or damage resulting in pump replacement, urgent transplant or death) occurred in the 59 HeartMate XVE patients in the Primary Study Cohort and 58 HeartMate XVE patients in the Randomized Continuous Access Protocol (CAP) cohort. In contrast to the HeartMate II in which failures were predominately related to one component, the percutaneous lead, there were several failure modes of the HeartMate XVE, as shown in Table 16 below.

Table 16 – HeartMate XVE Failure Modes

Failure Mode	**No. of Failures**
Valve and/or conduit wear	8
Bearing wear	7
Low flow and/or pump stopped	5
Other	5
Total:	25

These 25 failures occurred over a range of 0 to 676 days. A Weibull analysis of the clinical reliability of the HeartMate XVE observed in this study is provided in Table 17.

Table 17 – HeartMate XVE Clinical Reliability Calculations

Time (months)	Clinical Reliability* at 80% Confidence Level
6	84%
12	69%
18	55%

*Weibull analysis parameters: beta=1.1515, eta=1023.9663, rho=0.9023

Of the patients that were originally implanted with the HeartMate XVE, 18 were exchanged to the HeartMate II and three (3) patients were exchanged to another HeartMate XVE. Sixteen (16) of the 21 pump exchanges were due to: inflow or outflow valve malfunction (4), bearing wear (11), and infection (1). In the other 5 cases, pumps were exchanged in patients with clinical symptoms and diagnostic indicators (e.g. waveforms, vent filter analysis) suggestive of end of pump life or fluid ingress. Pumps were functional during explant analysis but fluid ingress was noted in three (3) of the five (5) and bearing wear was noted in the other two (2).

All of the patients originally implanted with the HeartMate II that needed pump replacements were exchanged to another HeartMate II pump. The reasons for exchange included: suspected pump thrombus (2), suspected percutaneous lead wire breakage in external portion of driveline (7), percutaneous lead breakage at pump end (5), and outflow elbow disconnect (1).

Functional Status, Quality of Life and Neurocognitive Measures

The secondary objectives that were studied included functional evaluations based on NYHA class, six-minute walk, and Metabolic Equivalents scores (METs). Health Status including quality of life (QoL) was measured via the Minnesota Living with Heart Failure Questionnaire (MLWHF) and Kansas City Cardiomyopathy Questionnaire (KCCQ). A battery of neurocognitive evaluations was also performed. In summary, significant improvement was seen in both device groups in quality of life scores and in functional status over baseline and over time through 12 months, as can be seen in Figure 9 through Figure 13 below. After 12 months, there were too few HeartMate XVE patients to analyze. No significant difference in QoL was seen between the HeartMate II and HeartMate XVE groups. An additional measure of QoL was time spent out of hospital. Once implanted, HeartMate II patients spent 87% of their support time out of hospital compared to 69% for patients implanted with the HeartMate XVE (As Treated analysis). No decline in neurocognitive function was observed, and trends toward improvement over time were observed for some neurocognitive measures with both devices.

The number of patients able to perform these tests of functional status and quality of life decreases at each time interval as patients expire, are transplanted, are weaned off the device, or are crossed over to the alternate device. Besides outcome-related reasons why testing could not be performed, reasons included: patient issue (e.g., patient too sick to perform the testing), management issue (e.g., scheduling or site staff oversight and testing not performed), patient refusal, or in some cases a reason was not provided. The tables following the graphs (Table 18 through Table 21) indicate the number and percentage of patients performing each test.

In Figure 9 through Figure 13 the numbers of patients analyzed at each interval is shown above each bar. Error bars extending beyond the data bars in the Figures denote 95% confidence intervals or standard deviation, as noted in each Figure.

Figure 10 – Primary Study Cohort (As Treated): NYHA Class I or II over Time

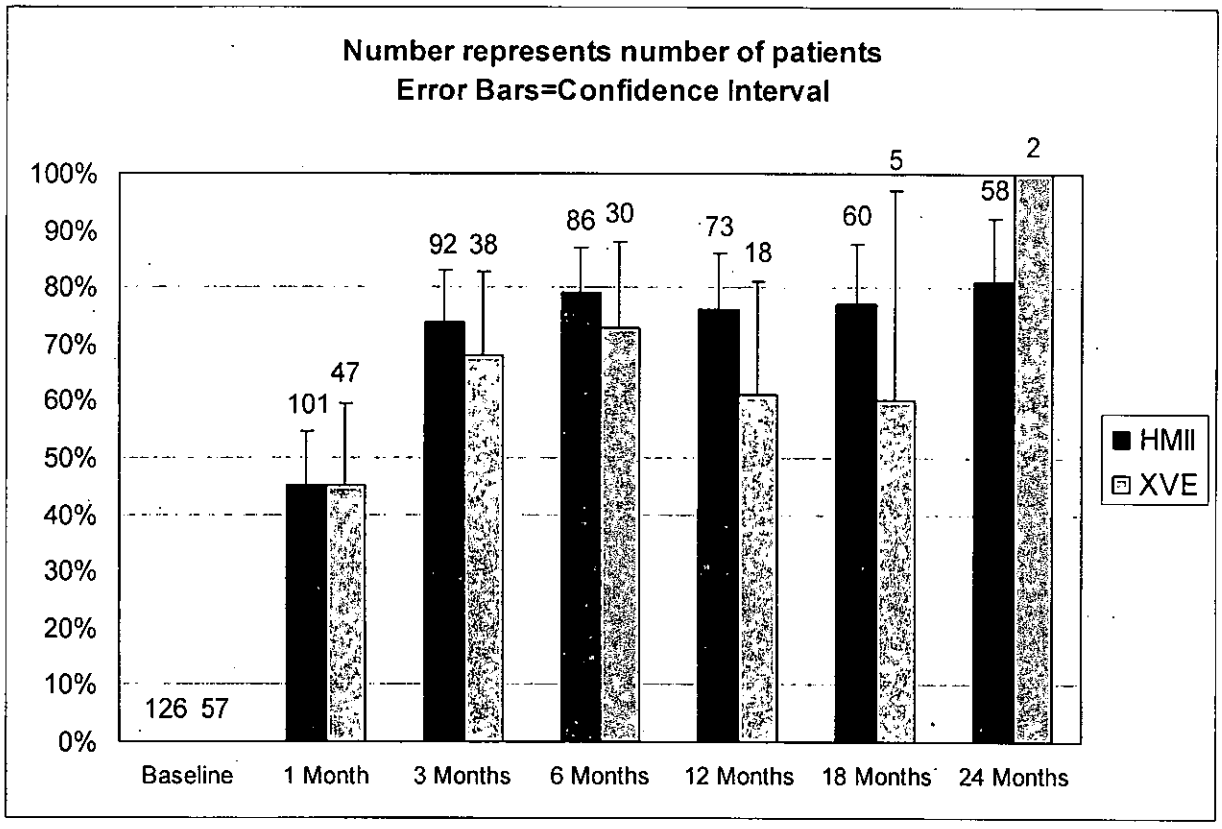

Table 18 - Primary Study Cohort (As Treated): NYHA Class I or II Compliance

		Base-line	Month 1	Month 3	Month 6	Month 12	Month 18	Month 24
# pts at interval	HeartMate II	133	121	105	95	82	70	59
	HeartMate XVE	59	52	39	32	19	5	2
# pts performing test	HeartMate II	126	101	92	86	73	60	58
	HeartMate XVE	57	47	38	30	18	5	2
% pt performing test	HeartMate II	95%	83%	88%	91%	89%	86%	98%
	HeartMate XVE	97%	90%	97%	94%	95%	100%	100%

Figure 11 – Primary Study Cohort (As Treated): Six Minute Walk – Meters Walked over Time

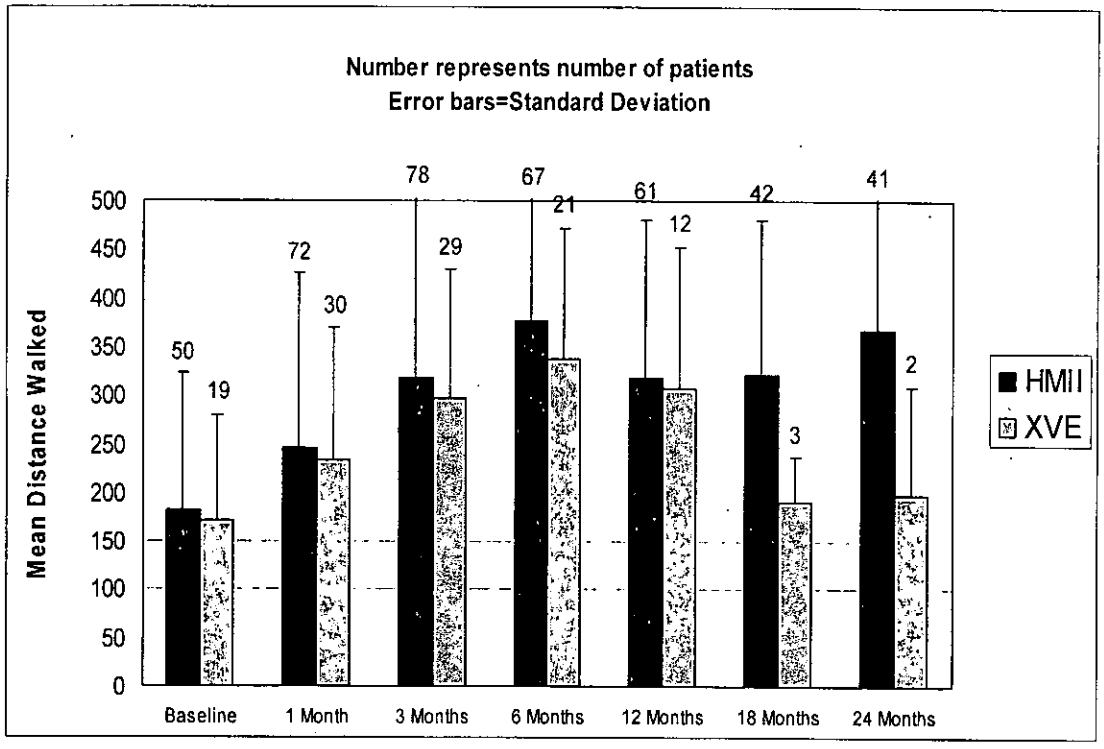

Table 19 - Primary Study Cohort (As Treated): Six Minute Walk Test Compliance

		Base-line	Month 1	Month 3	Month 6	Month 12	Month 18	Month 24
# pts at interval	HeartMate II	133	121	105	95	82	70	59
	HeartMate XVE	59	52	39	32	19	5	2
# pts performing test	HeartMate II	50	72	78	67	61	42	41
	HeartMate XVE	19	30	29	21	12	3	2
% pt performing test	HeartMate II	38%	60%	74%	71%	74%	60%	69%
	HeartMate XVE	32%	59%	74%	66%	63%	60%	100%

Figure 12 – Primary Study Cohort (As Treated): MLWHF Scores over Time

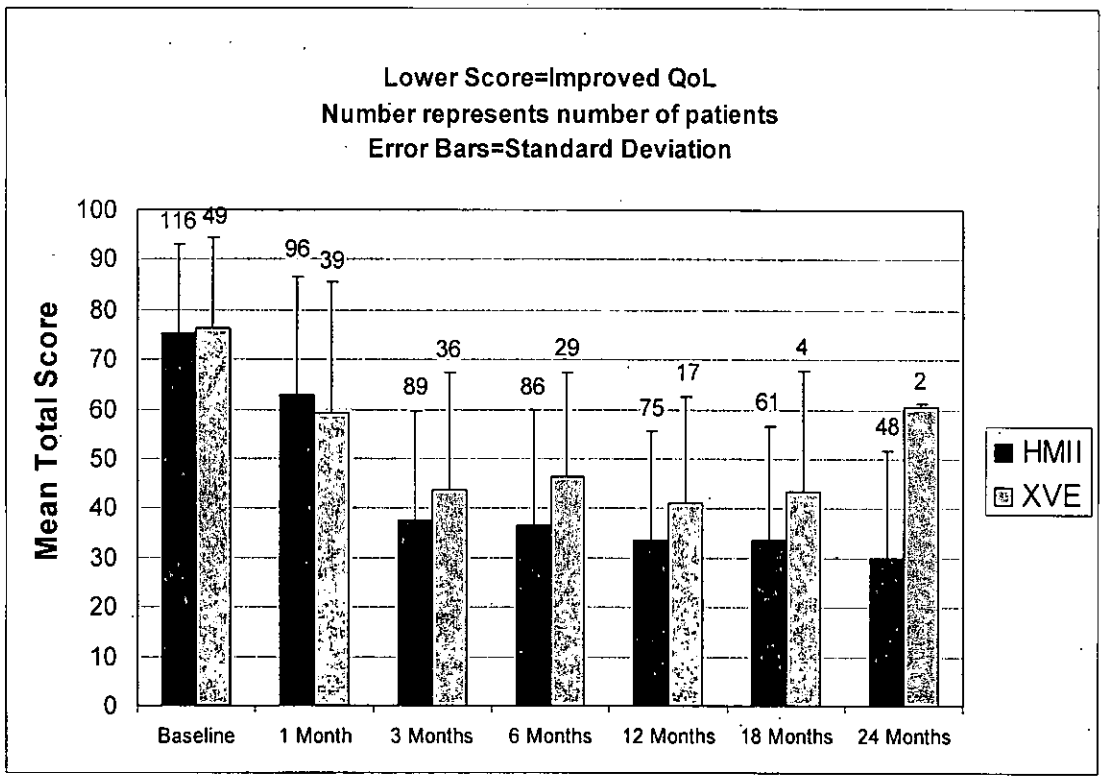

Table 20 - Primary Study Cohort (As Treated): MLWHF Testing Compliance

		Base-line	Month 1	Month 3	Month 6	Month 12	Month 18	Month 24
# pts at interval	HeartMate II	133	121	105	95	82	70	59
	HeartMate XVE	59	52	41	34	20	5	2
# pts performing test	HeartMate II	116	96	89	86	75	61	48
	HeartMate XVE	49	39	36	29	17	4	2
% pt performing test	HeartMate II	87%	79%	85%	91%	91%	87%	81%
	HeartMate XVE	83%	75%	87%	85%	85%	80%	100%

Figure 13 – Primary Study Cohort (As Treated):
KCCQ Overall Summary Score over Time

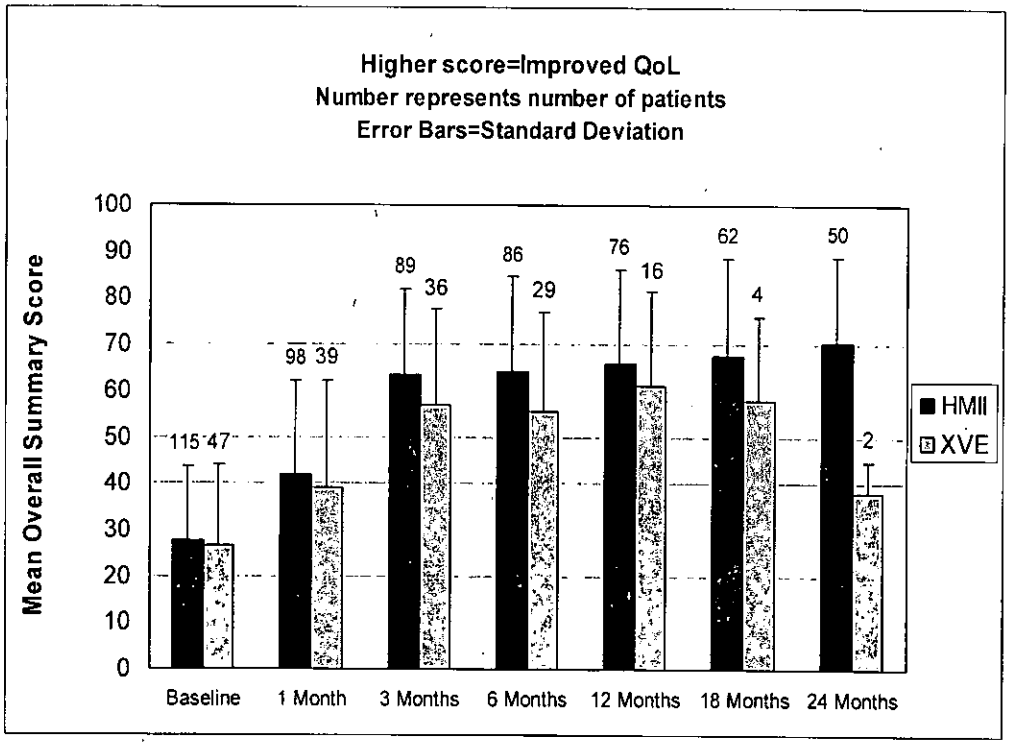

Figure 14 – Primary Study Cohort (As Treated):
KCCQ Clinical Summary Score over Time

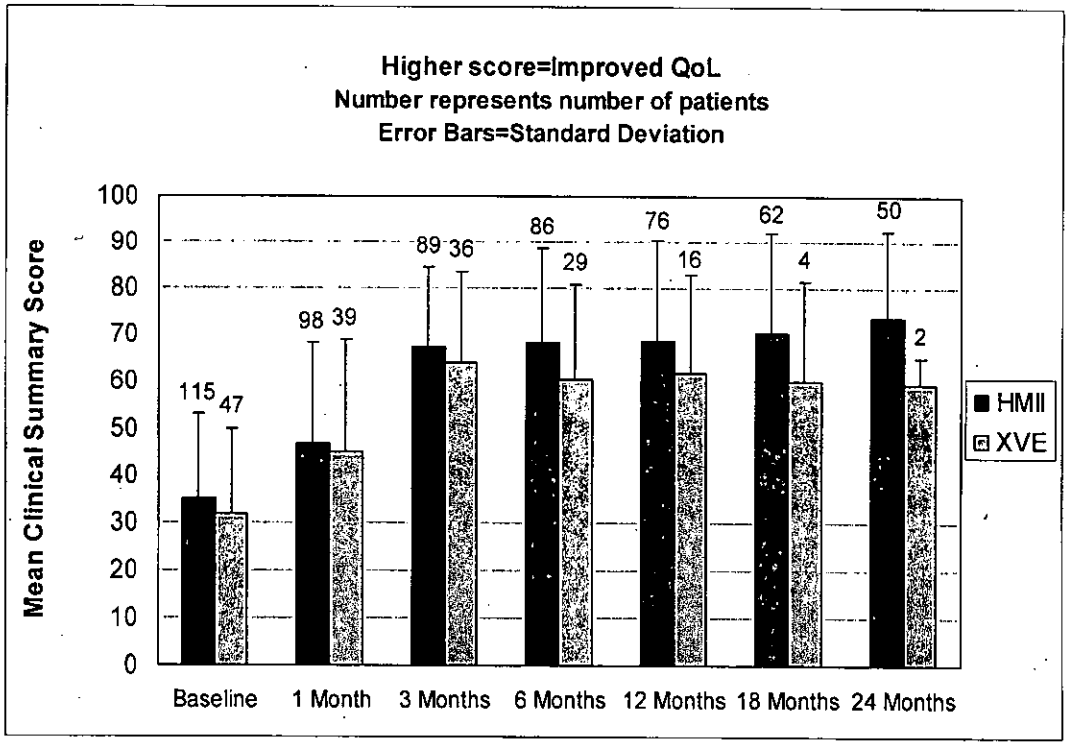

Table 21 - Primary Study Cohort (As Treated):
KCCQ Testing Completion by Follow-up Intervals

		Base-line	Month 1	Month 3	Month 6	Month 12	Month 18	Month 24
# pts at interval	HeartMate II	133	121	105	95	82	70	59
	HeartMate XVE	59	52	40	33	19	5	2
# pts performing test	HeartMate II	115	98	89	86	76	62	50
	HeartMate XVE	47	39	36	29	16	4	2
% pt performing test	HeartMate II	86%	81%	85%	91%	84%	89%	85%
	HeartMate XVE	80%	75%	90%	88%	90%	80%	100%

Gender Analysis

An analysis was performed to determine if the treatment effect observed in the trial was influenced by the gender differences between treatment groups. In addition, Kaplan-Meier analyses were performed by gender to determine if the superior results obtained by patients supported with the HeartMate II were experienced by both males and females.

In the Primary Study Cohort, despite randomizing patients into treatment arms, 16% of patients randomized into the HeartMate II cohort were female compared to 8% in the HeartMate XVE cohort. This difference in gender was statistically significant (P=0.0369). Logistic regression was used to determine that this gender difference did not influence the treatment effect seen in the trial. A Kaplan-Meier analysis of the study's primary composite endpoint, stratified by gender, was limited due to the small number of females enrolled in the trial.

A *post hoc* analysis was conducted which included patients from other cohorts. Patients enrolled in the Primary Study Cohort were combined with patients randomized into the Continued Access Protocol (CAP) for the trial. This pooled cohort will be referred to as the Randomized Cohort. Sixteen percent (16%) of patients randomized into the HeartMate II group were female, compared to 10% in the HeartMate XVE Cohort. The difference in gender enrollment was no longer significant (P=0.2094). The Randomized Cohort provided 54 female patients to evaluate. An analysis of baseline demographics and etiology demonstrated that the groups remained comparable.

A Kaplan-Meier analysis comparison of the Randomized Cohort males (222 HeartMate II vs. 111 HeartMate XVE) and females (41 HeartMate II vs. 13 HeartMate XVE), for the study's primary composite endpoint resulted in a significant survival advantage ($p<0.0001$) for HeartMate II patients irrespective of gender. This analysis provides evidence that gender differences have not influenced the outcome results observed in the trial and that the superior results of the HeartMate II are shared by both males and females.

Adverse event rates between females who received a HeartMate II compared to females who received the HeartMate XVE were similar to overall study results for the Primary

Study Cohort, with differences in adverse event rates favoring the females implanted with the HeartMate II. The same result was also true for males implanted with the HeartMate II.

A second *post hoc* analysis was performed to provide additional females by combining patients enrolled into the Small BSA Cohort (patients with BSA < $1.5m^2$) and the HeartMate II Anatomical Deviation Cohort (patients with BSA ≥ $1.5m^2$, but who could not receive an HeartMate XVE due to body habitus or surgical issues) with the HeartMate II patients from the Randomized Cohort described above. This combined cohort included 286 males and 100 females, all supported with the HeartMate II. A Kaplan-Meier analysis of survival free of stroke (Rankin > 3) or reoperation to repair or replace the device resulted in no significant difference between males supported with the HeartMate II compared to females supported with the HeartMate II (p=0.2650).

One noted observation is that males supported with the HeartMate II had better adverse event rates for local infection and peripheral thrombo-embolic events when compared to females supported with the HeartMate II (Table 22). However, the thrombo-embolic event rate was influenced by one female who had eight thrombo-embolic events in her lower extremities.

In conclusion, the gender analysis shows that the benefits and risks of the HeartMate II are similar for males and females and that the observed treatment effect was not influenced by gender.

Table 22 – Adverse Event Differences (As Treated), Males vs. Females (events/pt-year)

Adverse Event	Males (n=279)	Females (n=102)
Local infection	0.62	0.95
Peripheral thrombo-embolic events	0.08	0.12

XI. PANEL MEETING RECOMMENDATION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices 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 THE CLINICAL STUDY

The sponsor conducted a multi-center randomized pivotal study comparing the safety and effectiveness of the HeartMate II LVAS to the HeartMate XVE for the destination therapy indication. The device is already approved as a bridge to transplant. The primary endpoint of the study was a composite of 2 year survival with freedom from debilitating stroke (Modified Rankin > 3) or reoperation to repair or replace the device. The composite endpoint analysis showed the HeartMate II to be superior to the control HeartMate XVE device. In addition, both intent to treat and per protocol analyses demonstrated a Kaplan Meier survival advantage with the HeartMate II compared to control. No safety or engineering problems were detected that suggested that the increased benefit seen with the HeartMate II device was accompanied by significantly increased risk compared to the HeartMate XVE control. Hence, a favorable risk-benefit profile has been established for the HeartMate II device. Approval is recommended with careful follow-up through a post-approval study.

XIII. CDRH DECISION

CDRH issued an approval order on January 20, 2010. The final conditions of approval cited in the approval order are described below.

You have agreed to implement a post-approval study that will enroll consecutive HeartMate II patients who give their consent for inclusion in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registry with an indication of Destination Therapy. The patients will be followed in the post-approval study until study outcome or 2 years, whichever occurs first. A detailed protocol, including but not limited to, patient characteristics at the time of implantation, incidence of adverse events (including definitions) while being supported by the device system, patient outcome(s), standardized anticoagulation protocol, quality of life assessment tools, functional status instruments, and the proposed reporting interval (e.g., 6 months) will be implemented. The study protocol will also collect data regarding sex, age, and race/ethnicity to determine if differences exist in the safety and effectiveness of the device in these populations as well as data regarding the relationship between bleeding, thrombosis, and anticoagulation in all patients. Furthermore, you have agreed to perform a second post-approval study to collect data regarding the relationship between bleeding, thrombosis, von Willebrand syndrome, and anticoagulation in LVAD patients. The post-approval study enrollment will begin immediately upon FDA approval of the HeartMate II® LVAS as a destination therapy device. Please note that FDA requests that you work

interactively with us to resolve the issues related to this second post-approval study as we believe some deficiencies from our approvable letter dated November 20, 2009 remain outstanding.

The applicant's manufacturing facility was 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 (Instructions for Use)

Hazards to Health from Use of the Device: See *Indications, Contraindications, Warnings and Precautions,* and *Adverse Events* in the labeling

Post-approval Requirements and Restrictions: See Approval Order