SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Ventricular assist device

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: November 30, 2007

Premarket Approval Application (PMA) Number: P060040

Date of Notice of Approval to Applicant: April 21, 2008

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 nonreversible left ventricular failure. The HeartMate II LVAS is intended for use both inside and outside the hospital, or for transportation of ventricular assist device 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.

Electrical power to the implanted blood pump is delivered through a percutaneous lead that connects to an external System Controller. The System Controller is powered by a Power Base Unit (PBU) that connects to AC mains power, or by two batteries that the patient carries or wears in shoulder holsters. These two power configurations are shown in Figures 2 and 3. The PBU, System Monitor and batteries are identical to the components approved for use with the HeartMate XVE LVAS (ref. PMA P920014).

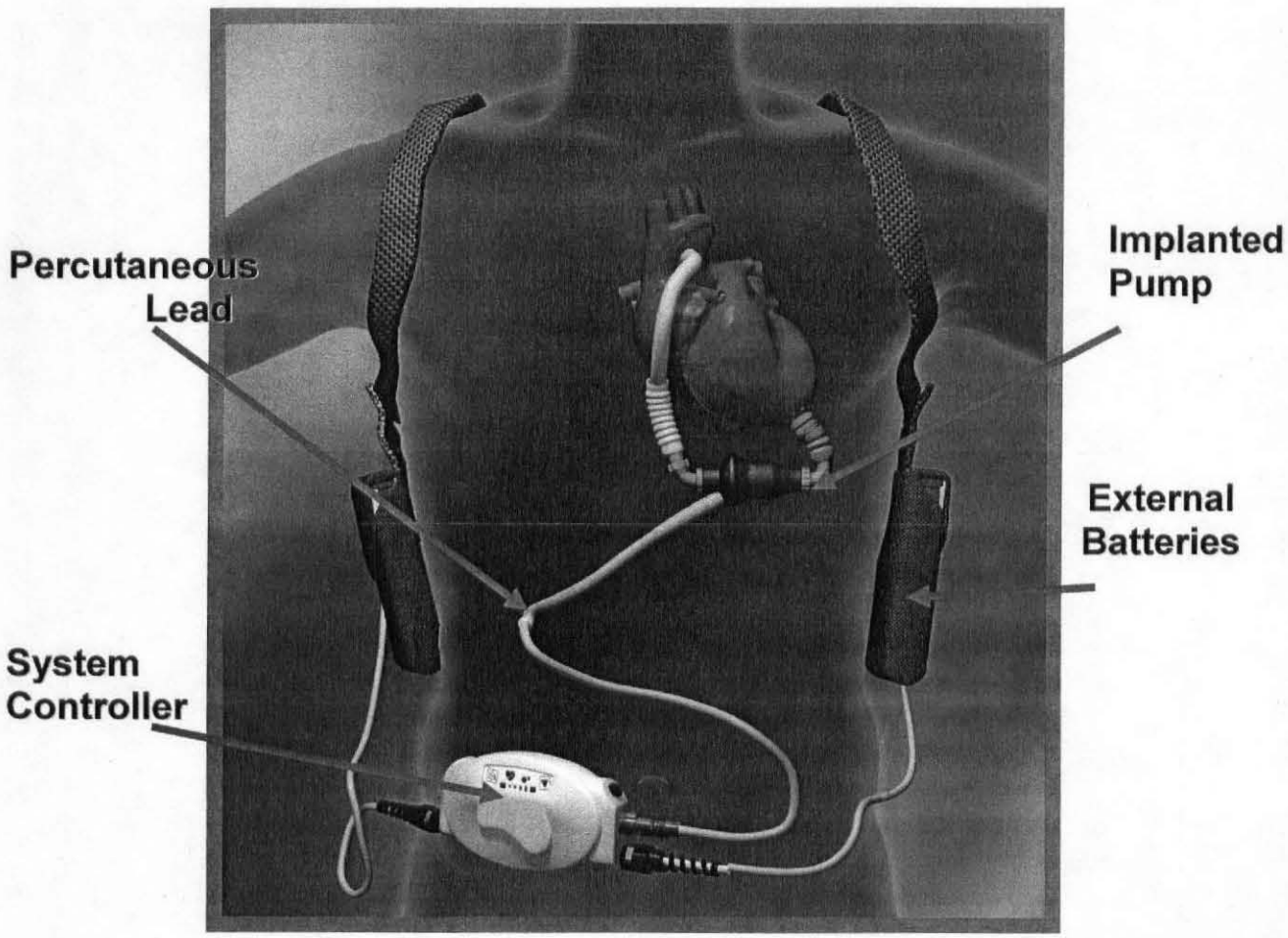


Figure 1 HeartMate II LVAS, Implantable and External Components

11

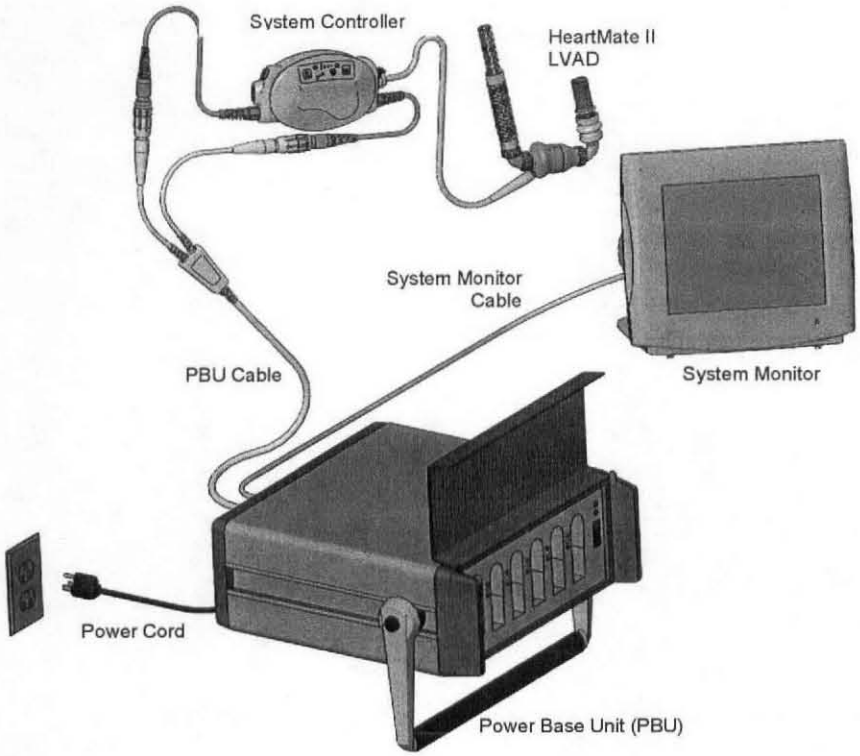


Figure 2 HeartMate II LVAS Configuration with Power Base Unit and System Monitor

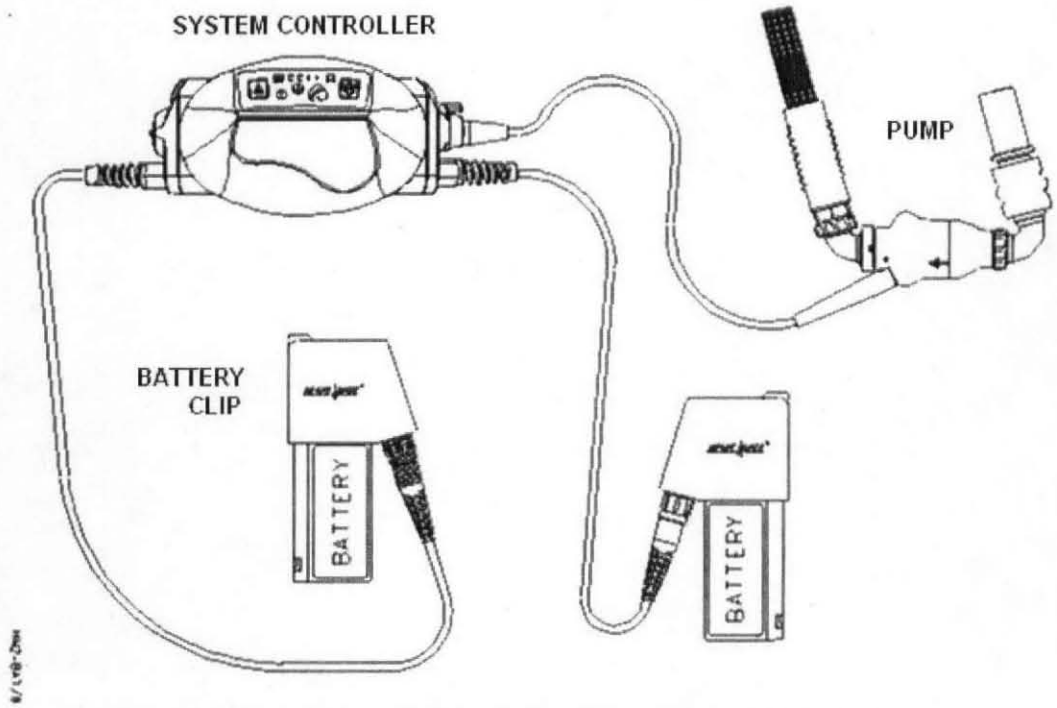


Figure 3 HeartMate II LVAS Configuration with Batteries

12

VI. ALTERNATIVE PRACTICES OR PROCEDURES

Several left ventricular assist device (LVAD) systems are currently approved by FDA for use as a bridge to cardiac transplantation. However, the electrically driven implantable systems are large and contraindicated for patients having a body surface area (BSA) of less than 1.5 m^2.

VII. MARKETING HISTORY

Thoratec Corporation was authorized to apply the European Active Implantable Medical Device Directive CE Mark on November 7, 2005. Since that authorization, HeartMate II has been commercially distributed in the following European countries: Germany, France, United Kingdom, Greece, Italy, Netherlands, Denmark, Slovakia, Switzerland, Iceland, Bulgaria, Belgium, Czech Republic and Sweden. The HeartMate II LVAS is also approved for commercial distribution in Israel, the Bahamas and South Africa. 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 the adverse events that occurred in the clinical study, please see Section X below.

- Death
- Bleeding, perioperative or late
- Cardiac arrhythmia
- Local infection
- Respiratory failure
- Device malfunction
- Sepsis
- Right heart failure
- Percutaneous 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. The following information provides brief descriptions of the verification and validation tests conducted on the HeartMate II LVAS.

In Vitro Testing

Pump characterization testing was performed under dynamic conditions in a mock circulatory loop with an active mock ventricle to demonstrate stable operation under simulated use conditions. The test acceptance criteria were met and the pump demonstrated stable, predictable operation in the presence of simulated physiological disturbances.

Electrical Safety and Electromagnetic Compatibility

The HeartMate II LVAS was tested for compliance with the FDA recognized standards for electrical safety, IEC 60601-1:1988/A1:1991/A2:1995 and IEC 60601-1-2:2001. The HeartMate II LVAS also met the requirements for immunity to the effects of external defibrillation per Clause 20.2 of the European standard, EN 45502-1:1997 (Active implantable medical devices - Part 1: General requirements for safety, marking and information to be provided by the manufacturer).

Other Environmental Testing

The HeartMate II LVAS has also been successfully tested, during simulated patient support, for compliance with standards for air transportation in both fixed wing aircraft and helicopters. Under FAA guidelines (FAA Advisory Circular 91.21.1A, 10/2/200, *Use of Portable Electronic Devices Aboard Aircraft* and RTCA DO-160D, *Environmental Conditions and Test Procedures for Airborne Equipment*), the HeartMate II LVAS falls under category M for portable electronic devices, for which the requirements are limited to EMC testing. The HeartMate II LVAS met the FAA requirements, indicating that the device should not affect the electronics on the aircraft, and the aircraft should not affect the device.

Software Validation

The HeartMate II System Controller and the System Monitor are software-driven components of the LVAS. The software development process complies with the requirements of IEC 60601-1-4:1996.

Hazard Analysis

Potential hazards associated with the device, in both normal operation and potential abnormal conditions, were identified and analyzed for their short-term and long-term effects. This information was fed into the hazard analysis process. Based on this analysis, measures were taken to minimize the occurrence of the hazards and the remaining risk was determined to be acceptable.

In Vitro Long Term Device Reliability

Long-term reliability of the HeartMate II LVAS blood pump, based on *in vitro* tests evaluating 16 pumps, is summarized in Table 1. As of January 2, 2008, sixteen HeartMate II blood pumps have each run for an average of 1308 days (3.6 years, ranging from 1.2 to 6.1 years) without failure on mock circulatory loops. Based on these data, the estimate *in vitro* reliability for various intervals is provided in Table 1 below.

Table 1: Estimated *In vitro* HeartMate II LVAD Reliability

	Lower, One-Sided 80% Confidence Limit on Reliability R(t)
Months	***In vitro****
6	0.986
12	0.972
24	0.945

*assuming 12,000 rpm pump speed

Biocompatibility Testing

The primary material of construction in the HeartMate II blood pump is a titanium alloy, Ti6Al4V; a material that has a history of use in implantable medical devices, including the PMA approved HeartMate IP, VE and XVE LVAS configurations. The inflow and outflow grafts are similar to the HeartMate LVAS configurations, being constructed of polyester vascular graft prostheses. Due to the use of small amounts of materials not used in the previous HeartMate LVAS pumps, such as the ceramic bearings, extracts of the complete pump assembly were tested for biocompatibility in accordance with the requirements of ISO 10993-1:2003 and met all test acceptance criteria.

Table 2: Biocompatibility Testing

Biocompatibility Test	Test Method
Cytotoxicity	MEM elution cytotoxicity assay
Sensitization	Magnusson-Kligman Guinea pig maximization test
Irritation/ Intracutaneous Toxicity	Intracutaneous Reactivity Test, USP <88> Biological Reactivity – *in vivo* method
Systemic toxicity (acute)	Systemic Injection Test, USP <88> Biological Reactivity – *in vivo* method
Hemocompatibiltiy	ASTM F 756 Hemolysis test
	Complement Activation Test (C3a)
	Direct contact prothrombin time (PT)
	Direct contact activated partial thromboplastin time (PTT)
Pyrogenicity	USP <151> Pyrogen Test
Chronic toxicity	USP <88> Biological Reactivity Test – *in vivo* (180 days)

Testing for sub-chronic toxicity, implantation, genotoxicity, carcinogenicity and biodegradation that was conducted on the previous PMA-approved HeartMate LVAS configurations (ref. PMA P920014) was deemed to be also applicable to the HeartMate II blood pump.

Sterilization Information

The following HeartMate II system components are provided sterile: HeartMate II blood pump, inflow and outflow cannulae, outflow bend relief, coring knife, apical sewing ring, thread protector, coring punch and the system controller. The sterilization method is 100% ethylene oxide (EO) and the sterilization process is validated to provide a sterility assurance level (SAL) of 10^{-6} in accordance with international standards for sterilization processes for medical devices, ANSI/AAMI/ISO 11135:1994, ANSI/AAMI/ISO 14937:2000, and EN 550:1994. A validated post-sterilization aeration process assures that residual levels of EO and ECH (ethylene chlorohydrin) are within acceptable limits specified by ANSI/AAMI/ISO 10993-7:1995. Two implant accessories, a tunneler and sizer, are re-usable tools that are sterilized by the user.

Animal Studies

A total of 65 calf implants were performed with the HeartMate II LVAS during its development history from 1994 – 2003 to evaluate various design iterations, including bearing design, conduit configurations, stator surface finish and control modes. Five calves were implanted with the same pump configuration that was used in the clinical study. Three of the calves were evaluated per a 30-day, and two were evaluated per a 90-day, *in vivo* bovine protocol to evaluate the thrombogenicity and hemolysis characteristics of HeartMate II blood pump and to demonstrate overall hemodynamic performance of the system. The test results show that the current configuration of the device met the intended requirements.

Acceptance criteria included maintenance of acceptable hemolysis levels and that post device explant examinations found no thrombus formations beyond the acceptable low levels specified in the protocol.

Shelf Life

Based on accelerated shelf-life testing, the packaged HeartMate II LVAS was validated to bear a three-year expiration date.

X. SUMMARY OF CLINICAL STUDIES

Study Overview

One hundred twenty-six (126) patients were enrolled in the HeartMate II (HMII) Bridge to Transplantation (BTT) Primary Study Cohort between March 2005 and March 2007 at 26 investigational sites across the United States as the pivotal study sample size. The primary objective of the study was to determine the safety and effectiveness of the HeartMate II LVAS as a BTT device in end-stage heart failure patients who are listed for cardiac transplant and at imminent risk of death. Effectiveness of the device was assessed on the basis of the percentage of patients surviving either to cardiac transplantation or 180 days of LVAS support while being listed UNOS 1A/1B. Safety of the HeartMate II LVAS was assessed by the incidence of adverse events during LVAS support.

A number of secondary objectives were also evaluated during the study, including clinical reliability (malfunctions/failures), functional status (6-minute walk and patient activity score), quality of life (Minnesota Living with Heart Failure and Kansas City Cardiomyopathy Questionnaire), re-operations, neuro-cognitive assessment (memory, language, visual/spatial perception, processing speed and abstract/executive function), and 30-day and 180-day post-transplant survival.

After completion of enrollment in the Primary Study Cohort, enrollment continued under a Continued Access Protocol (CAP), which was identical to the Primary Study Cohort protocol. Patients who were originally enrolled into these two study cohorts but who had a body surface area (BSA) less than $1.5m^2$ were separated out into a Small BSA Patient cohort for analysis.

Study Design

The study was a multi-center, non-blinded, non-randomized, prospective study. The study had two oversight committees, a Clinical Events Committee which adjudicated all adverse events and deaths and a Data and Safety Monitoring Board which reviewed the study data periodically to ensure that continuation of the study did not present any unacceptable risk. The members of these committees were independent of Thoratec, the investigational sites and the principal investigators.

The primary study outcomes were defined as death, cardiac transplantation, device explantation due to myocardial recovery, or survival to 180 days on LVAS support while remaining listed UNOS 1A/1B. After reaching the 180 day assessment point, patients continued to be followed until transplantation, explantation or death.

Patient Population

The patients enrolled into the HeartMate II study were patients listed for cardiac transplant in end-stage heart failure who demonstrated no evidence of severe end-organ damage that would make HeartMate II LVAS implantation futile. The BTT inclusion and exclusion criteria were based on study criteria used in previously approved LVAD BTT studies. The criteria included patients in New York Heart Association (NYHA) class IV heart failure, on inotropic support, and without contraindication to listing for cardiac transplantation as UNOS Status 1A or 1B. If the patient was 1B, they also needed to meet hemodynamic criteria to qualify, including pulmonary capillary wedge pressure (PCWP) or pulmonary artery diastolic pressure (PAD) > 20 mmHg and either a cardiac index < 2.2 L/min/m^2 or systolic blood pressure < 90 mmHg. The exclusion criteria excluded patients with moderately severe end-organ damage, as evidenced by elevated total bilirubin, elevated creatinine values, or low platelet counts, and also excluded patients that may not be able to tolerate the management of the HeartMate II LVAS due to intolerance to anticoagulation or compliance issues.

Two hundred and seventy-nine (279) patients were enrolled at 33 study sites between March 2005 and March 2007. Twenty-six (26) sites enrolled patients into both the Primary Study Cohort and the Continued Access Protocol Cohort (CAP). Seven additional sites enrolled patients only under the Continued Access Protocol. Of the 279 patients enrolled into the three cohorts of the HeartMate II study (Primary Study, Continued Access, and Small BSA), 194 patients have been followed to a study outcome point, and if ongoing on HeartMate II LVAS support, for at least one year as of September 14, 2007, and are presented in the following clinical summary. As shown in Figure 4, the 194 patients are divided among three cohorts; 126 patients in the Primary Study cohort and 58 patients in the Continued Access Protocol cohort. An additional 10 patients were originally enrolled in these two cohorts but were separated out for analysis in the Small BSA Patient cohort (1.2 $m^2 \leq$ BSA < 1.5 m^2). Data are presented for each cohort separately and also in the aggregate for all 194 patients.

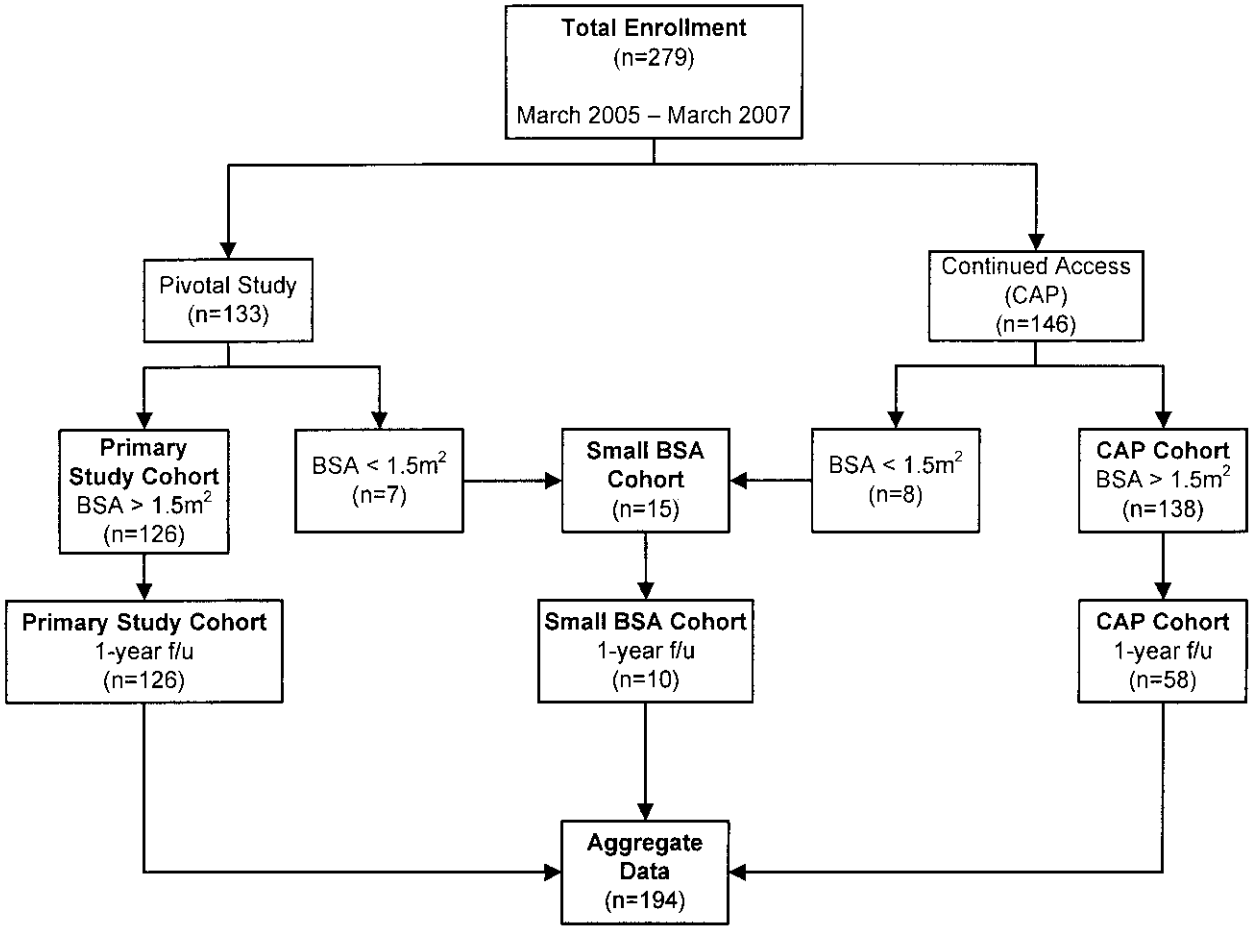


Figure 4: HeartMate II Study Enrollment

The overall mean age in the HeartMate II LVAS study was 51 years (range 16-69 years). The smallest patient implanted had a BSA of 1.33 m^2 and the largest patient, a BSA of 2.62 m^2, with a mean BSA of 1.99 m^2. The mean body mass index (BMI) was 27 kg/m^2 (range 15.6 – 44.0 kg/m^2). The most prevalent etiology was idiopathic cardiomyopathy (48%) followed by ischemic cardiomyopathy (41%). Of note in the cardiovascular history is that 78% of the patients had pre-existing arrhythmias and 76% of the patients entered the study with implantable cardiac defibrillators (ICD). Patient demographics and cardiovascular history for each of the three study cohorts and the aggregate data are shown in Tables 3 and 4.

Table 3: Patient Demographics

	Primary Cohort (n = 126)	CAP Cohort (n= 58)	Small BSA Cohort (n = 10)	Aggregate Data (n = 194)
Age (years)*	55 (17 – 68)	56 (16 – 69)	47 (20 – 69)	55 (16 – 69.1)
Etiology	39% Ischemic	50% Ischemic	10% Ischemic	41% Ischemic
Gender	83% Male 17% Female	78% Male 22% Female	0% Male 100% Female	77% Male 23% Female
BMI (kg/m^2)*	26.5 (10 – 40)	27.6 (18 – 44)	17.0 (15.6 – 20.8)	26.6 (15.6 – 44.0)
BSA (m^2)*	1.99 (1.5 – 2.6)	2.00 (1.52 – 2.57)	1.40 (1.33 – 1.47)	1.99 (1.33 – 2.62)

*Median and range

Table 4: Cardiovascular History

	Primary Cohort (n = 126)	CAP Cohort (n = 58)	Small BSA Cohort (n = 10)	Aggregate Data (n = 194)
Arrhythmias	101 (80%)	46 (79%)	5 (50%)	152 (78%)
Ventricular Arrhythmias	71 (56%)	34 (59%)	0 (0%)	109 (56%)
Ventricular Pacing	77 (61%)	35 (60%)	5 (50%)	117 (60%)
Biventricular Pacing	61 (48%)	30 (52%)	0 (0%)	95 (49%)
Implantable Cardioverter / Defibrillator	96 (76%)	45 (78%)	6 (60%)	147 (76%)
Stroke	12 (10%)	6 (10%)	1 (10%)	19 (10%)

PRIMARY OBJECTIVE: TRANSPLANT OR SURVIVAL TO 180 DAYS WHILE LISTED UNOS 1A/1B

Overall patient outcomes:

After reaching the 180 day assessment point, patients continued to be followed until transplantation, explantation or death. Patient outcomes for each study cohort (Primary, CAP, Small BSA and Aggregate Data) as of September 14, 2007 are presented in Tables 5 and 6 below.

The pre-specified primary endpoint for the Primary Study Cohort of HeartMate II LVAS BTT pivotal study was "patient survival to cardiac transplantation or 180 days of LVAS support while remaining listed status 1A or 1B." The HeartMate II pivotal study was to be prospectively determined successful if the one-sided 95% lower confidence limit of the true success rate exceeded 65%, the Performance Goal.

The results show that the lower confidence limit (LCL) of success was 64.0% in the Primary Study Cohort, thereby not quite meeting the pre-specified agreed-upon LCL endpoint, > 65%. Although outcomes were similar in the CAP and Small BSA cohorts, the LCLs are lower due to the smaller sample sizes.

Table 5: Primary Study Outcomes (as of September 14, 2007)

	Primary Cohort (n=126)	**CAP Cohort (n=58)**	**Small BSA Cohort (n=10)**	**Aggregate Data (n=194)**
Cardiac Transplantation[1]	72 (57%)	33 (57%)	7 (70%)	112 (58%)
Myocardial Recovery[1]	4 (3%)	2 (3%)	0 (0%)	6 (3%)
Supported ≥ 180 days and:				
Listed UNOS Status 1A or 1B[1]	13 (10%)	5 (9%)	0 (0%)	18 (9%)
Not listed Status 1A or 1B[2,3]	9 (7%)	7 (12%)	3 (30%)	19 (10%)
Expired < 180 days on LVAD[2]	25 (20%)	11 (19%)	0 (0%)	36 (19%)
Treatment failure; received other VAD[2]	3 (2%)	0 (0%)	0 (0%)	3 (2%)
Pre-specified Lower 95% Confidence Limit of True Success Rate	65.0%			
Observed Lower 95% Confidence Limit of Study Success Rate	64.0%	59.0%	46.2%	64.7%

[1] Classified as success per pre-specified study criteria
[2] Classified as failure per pre-specified study criteria
[3] Reasons for not listing included medical ineligibility, elective withdrawal from transplant list, substance abuse and non-compliance with medical therapy

Table 6: Additional Study Results (as of September 14, 2007)

	Primary Cohort (n=126)	CAP Cohort (n=58)	Small BSA Cohort (n=10)	Aggregate Data (n=194)
30 day (peri-operative) mortality	12 (10%)	7 (12%)	0 (0%)	19 (10%)
Patient survival to hospital discharge/transplant	105 (83%)	48 (83%)	10 (100%)	163 (84%)
Median time to transplant (days)	102.5	152	194	117
Median duration of device support (days)	117	163.5	374	131.5
Cumulative support duration (patient–years)	71	29	9	109

Plots of the competing outcomes (transplantation, weaning due to myocardial recovery, expiration, ongoing LVAS support and study withdrawal) are provided in Figures 5 and 6 for the Primary Study Cohort and the Aggregate Data, respectively.

Figure 5 – Competing Outcome Plot of HeartMate II Bridge to Transplant Primary Study Cohort (n=126) as of September 14, 2007

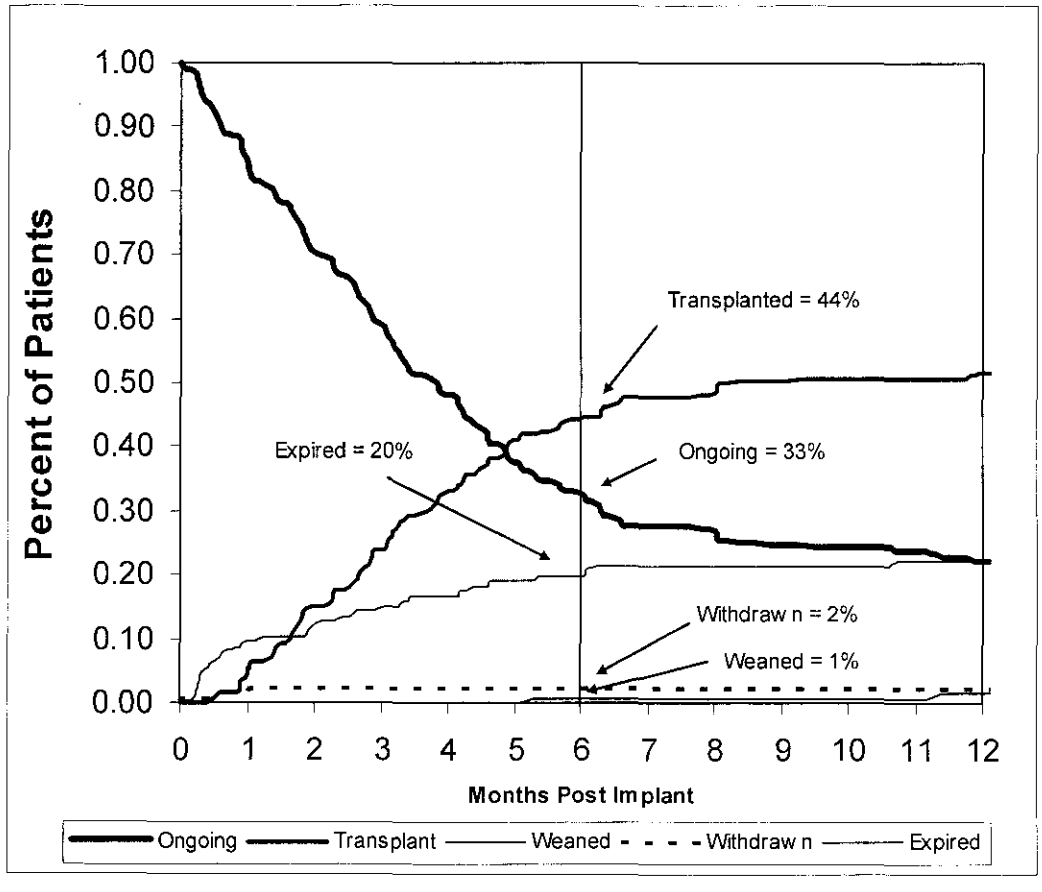
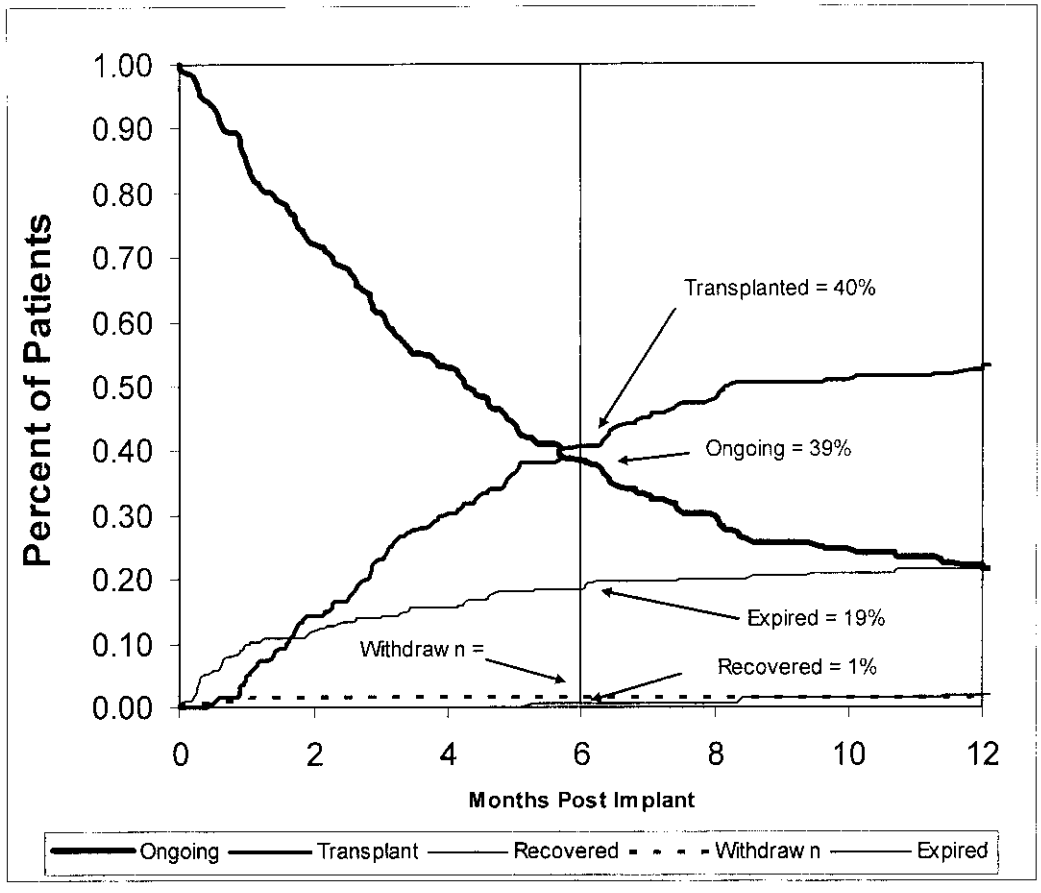


Figure 6 – Competing Outcome Plot of HeartMate II Bridge to Transplant Aggregate Data (n=194) as of September 14, 2007



Safety: Adverse events

The incidence of all adverse events observed during the HeartMate II LVAS study, regardless of severity, is provided in Table 7 for each data cohort. Adverse events were defined as events that occurred while on HeartMate II LVAS support that may have a deleterious effect on the patient. The incidence of adverse events defined as serious are presented in Table 8. Adverse Events were classified as serious if they resulted in death or permanent disability, were life threatening, required hospitalization or prolonged hospitalization. Adverse event rates during various time intervals are presented in Table 9, which shows that the majority of adverse events occurred during the first 30 days after implantation of the device.

Table 7 – All Adverse Events as of September 14, 2007

	Primary Cohort (n=126)	CAP Cohort (n=58)	Small BSA Cohort (n=10)	Aggregate Data (n=194)
	# Pts (% Pts)	# Pts (% Pts)	# Pts (% Pts)	# Pts (% Pts)
Bleeding (all requiring PRBC ≥2)*	89 (71%)	35 (60%)	9 (90%)	133 (69%)
Bleeding requiring surgery	37 (29%)	15 (26%)	4 (40%)	56 (29%)
Stroke	12 (10%)	3 (5%)	2 (20%)	17 (9%)
Peri-operative (≤POD2)	5 (4%)	0 (0%)	0 (0%)	5 (3%)
Post-operative (>POD2)	7 (6%)	3 (5%)	2 (20%)	12 (6%)
Other Neurological**	12 (10%)	3 (5%)	2 (20%)	17 (9%)
Local Infection	36 (29%)	21 (36%)	3 (30%)	60 (31%)
Drive Line Infection	20 (16%)	4 (7%)	2 (20%)	26 (13%)
Pocket Infection	2 (2%)	2 (3%)	0 (0%)	4 (2%)
Sepsis	27 (21%)	7 (12%)	2 (20%)	36 (19%)
Right Heart Failure	22 (17%)	11 (19%)	3 (30%)	36 (19%)
Peripheral TE	10 (8%)	1 (2%)	0 (0%)	11 (6%)
Respiratory Failure	33 (26%)	17 (29%)	3 (30%)	53 (27%)
Cardiac Arrhythmias	77 (61%)	28 (48%)	6 (60%)	111 (57%)
Renal Failure	17 (13%)	6 (10%)	2 (20%)	25 (13%)
Hepatic Dysfunction	3 (2%)	0 (0%)	0 (0%)	3 (2%)
Device Thrombosis	2 (2%)	1 (2%)	0 (0%)	3 (2%)
Hemolysis	3 (2%)	2 (3%)	3 (30%)	8 (4%)
Psychological	8 (6%)	3 (5%)	2 (20%)	13 (7%)
Myocardial Infarction	1 (1%)	(0%)	1 (10%)	2 (1%)
Confirmed Malfunctions	36 (29%)	11 (19%)	6 (60%)	53 (27%)

*Bleeding requiring PRBC ≥ 2 units or surgery.

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

Table 8 - Serious Adverse Events as of September 14, 2007

	Primary Cohort (n=126)	CAP Cohort (n=58)	Small BSA Cohort (n=10)	Aggregate Data (n=194)
	# Pts (% Pts)	# Pts (% Pts)	# Pts (% Pts)	# Pts (% Pts)
Bleeding (all requiring PRBC ≥2)*	75 (60%)	34 (59%)	8 (80%)	117 (60%)
Bleeding requiring surgery	38 (30%)	15 (26%)	4 (40%)	56 (29%)
Stroke	12 (10%)	3 (5%)	2 (20%)	17 (9%)
Peri-operative (≤POD2)	5 (4%)	0 (0%)	0 (0%)	5 (3%)
Post-operative (>POD2)	7 (6%)	3 (5%)	2 (20%)	12 (6%)
Other Neurological**	11 (9%)	3 (5%)	1 (10%)	15 (8%)
Local Infection	27 (21%)	16 (28%)	2 (20%)	45 (23%)
Drive Line Infection	12 (10%)	3 (5%)	1 (10%)	16 (8%)
Pocket Infection	2 (2%)	2 (3%)	0 (0%)	4 (2%)
Sepsis	26 (21%)	7 (12%)	2 (20%)	35 (18%)
Right Heart Failure	22 (17%)	11 (19%)	3 (30%)	36 (19%)
Peripheral TE	9 (7%)	1 (2%)	0 (0%)	10 (5%)
Respiratory Failure	33 (26%)	17 (29%)	3 (30%)	53 (27%)
Cardiac Arrhythmias	56 (44%)	21 (36%)	5 (50%)	82 (42%)
Renal Failure	17 (13%)	6 (10%)	2 (20%)	25 (13%)
Hepatic Dysfunction	3 (2%)	0 (0%)	0 (0%)	3 (2%)
Device Thrombosis	2 (2%)	1 (2%)	0 (0%)	3 (2%)
Hemolysis	3 (2%)	2 (3%)	1 (10%)	6 (3%)
Psychological	2 (2%)	1 (2%)	0 (0%)	3 (2%)
Myocardial Infarction	1 (1%)	0 (0%)	1 (10%)	2 (1%)
Confirmed Malfunctions	10 (8%)	4 (7%)	3 (30%)	17 (9%)

*Bleeding requiring PRBC ≥ 2 units or surgery.

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

Table 9: Adverse Event Rate per Patient-Year by Time Interval

Adverse Events	Cohort	0 – 7 days	8 – 30 days	31 – 90 days	91 – 180 days	> 180 days
Bleeding	Primary (n=126)	36.25	5.25	1.60	0.58	0.60
	CAP (n=58)	30.91	4.41	1.45	0.91	0.39
	Small BSA (n=10)	60.00	4.84	2.00	2.48	0.96
	Aggregate (n=194)	3.53	4.99	1.59	0.85	0.60
Stroke	Primary (n=126)	2.08	0.28	0.00	0.22	0.09
	CAP (n=58)	0.00	0.29	0.14	0.26	0.00
	Small BSA (n=10)	0.00	0.00	1.33	0.00	0.00
	Aggregate (n=194)	1.36	0.27	0.13	0.21	0.06
Other Neurological	Primary (n=126)	0.42	0.41	0.27	0.15	0.09
	CAP (n=58)	0.91	0.29	0.14	0.00	0.00
	Small BSA (n=10)	0.00	1.61	0.67	0.99	0.00
	Aggregate (n=194)	0.54	0.45	0.26	0.17	0.06
Local Infection	Primary (n=126)	8.33	2.62	1.67	0.36	0.18
	CAP (n=58)	10.00	2.65	1.45	0.39	0.00
	Small BSA (n=10)	0.00	1.61	0.67	0.50	1.34
	Aggregate (n=194)	8.42	2.58	1.55	0.38	0.27
Drive Line Infection	Primary (n=126)	0.00	0.00	0.27	0.58	0.48
	CAP (n=58)	0.00	0.00	0.29	0.26	0.00
	Small BSA (n=10)	0.00	0.00	0.00	0.99	0.38
	Aggregate (n=194)	0.00	0.00	0.26	0.51	0.37
Pocket Infection	Primary (n=126)	0.00	0.14	0.00	0.00	0.03
	CAP (n=58)	0.00	0.00	0.00	0.13	0.10
	Small BSA (n=10)	0.00	0.00	0.00	0.00	0.00
	Aggregate (n=194)	0.00	0.09	0.00	0.04	0.04
Sepsis	Primary (n=126)	1.67	1.80	0.47	0.36	0.24
	CAP (n=58)	1.82	0.59	0.00	0.26	0.10
	Small BSA (n=10)	0.00	1.61	0.00	0.00	0.57
	Aggregate (n=194)	1.63	1.42	0.30	0.30	0.25
Right Heart Failure	Primary (n=126)	1.67	1.80	0.33	0.00	0.03
	CAP (n=58)	3.64	2.06	0.00	0.00	0.00
	Small BSA (n=10)	5.00	1.61	0.00	0.00	0.19
	Aggregate (n=194)	2.45	1.87	0.21	0.00	0.04
Peripheral TE	Primary (n=126)	1.25	0.83	0.13	0.00	0.00
	CAP (n=58)	0.91	0.00	0.00	0.00	0.00
	Small BSA (n=10)	0.00	0.00	0.00	0.00	0.00
	Aggregate (n=194)	1.09	0.53	0.09	0.00	0.00
Respiratory Failure	Primary (n=126)	7.92	1.66	0.47	0.22	0.03
	CAP (n=58)	10.91	1.76	0.14	0.26	0.00
	Small BSA (n=10)	10.00	1.61	0.67	0.00	0.00
	Aggregate (n=194)	8.97	1.69	0.39	0.21	0.02
Cardiac Arrhythmias	Primary (n=126)	25.00	4.01	1.47	1.09	0.48
	CAP (n=58)	14.55	5.59	0.72	0.52	0.39
	Small BSA (n=10)	20.00	4.84	0.67	1.49	0.57
	Aggregate (n=194)	21.74	4.54	1.20	0.94	0.47

Table 9: Adverse Event Rate per Patient-Year by Time Interval

Adverse Events	Cohort	0 – 7 days	8 – 30 days	31 – 90 days	91 – 180 days	> 180 days
Renal Failure	Primary (n=126)	3.75	0.69	0.13	0.15	0.00
	CAP (n=58)	2.73	0.59	0.00	0.13	0.00
	Small BSA (n=10)	10.00	0.00	0.00	0.00	0.00
	Aggregate (n=194)	3.80	0.62	0.09	0.13	0.00
Hepatic Dysfunction	Primary (n=126)	0.42	0.14	0.07	0.00	0.00
	CAP (n=58)	0.00	0.00	0.00	0.00	0.00
	Small BSA (n=10)	0.00	0.00	0.00	0.00	0.00
	Aggregate (n=194)	0.27	0.09	0.04	0.00	0.00
Device Thrombosis	Primary (n=126)	0.42	0.00	0.07	0.00	0.00
	CAP (n=58)	0.91	0.00	0.00	0.00	0.00
	Small BSA (n=10)	0.00	0.00	0.00	0.00	0.00
	Aggregate (n=194)	0.54	0.00	0.04	0.00	0.00
Hemolysis	Primary (n=126)	0.83	0.00	0.00	0.00	0.03
	CAP (n=58)	0.00	0.00	0.00	0.13	0.10
	Small BSA (n=10)	10.00	0.00	0.00	0.50	0.00
	Aggregate (n=194)	1.09	0.00	0.00	0.09	0.04
Psychological	Primary (n=126)	1.67	0.14	0.07	0.29	0.00
	CAP (n=58)	1.82	0.29	0.00	0.00	0.00
	Small BSA (n=10)	5.00	1.61	0.00	0.00	0.00
	Aggregate (n=194)	1.90	0.27	0.04	0.17	0.00
Myocardial Infarction	Primary (n=126)	0.00	0.00	0.07	0.00	0.00
	CAP (n=58)	0.00	0.00	0.00	0.00	0.00
	Small BSA (n=10)	0.00	0.00	0.00	0.50	0.00
	Aggregate (n=194)	0.00	0.00	0.04	0.04	0.00

No new adverse events were observed in the HeartMate II LVAS study that have not been seen in previous studies of ventricular assist devices. The study was not powered for a specific analysis of the adverse events.

Secondary Objectives

Secondary objectives were collected which included the following: re-operations, clinical reliability, functional status, quality of life, neurocognitive evaluation and post-explant follow-up.

Re-operations:

Re-operations that were performed for any reason were captured as a secondary objective. In the Primary Study Cohort, 63% (79/126) of the patients had a re-operation. The majority (56%) of these events took place within 30 days of implant and was due to

bleeding or delayed chest closure. Three patients received HMII pump replacements within 30 days of implant. Twenty-one (21%) percent of the re-operation events took place after 30 days post implant. Abdominal incision and drainage, RVAD placement or removal, dialysis catheter placement and driveline/pocket revision accounted for the majority of these events. Three patients received HMII pump replacements after 30 days post implant. As shown in Table 10, the incidence of reoperations was similar in both the CAP and Small BSA cohorts. The major reasons requiring reoperations were also similar to those observed in the Primary Study Cohort.

Table 10. Incidence and Timing of Reoperations

	Primary Study Cohort (n=126)	CAP Cohort (n=58	Small BSA Cohort (n=10)	Aggregate Data Cohort (n=194)
Patients having reoperations	79 (63%)	36 (58%)	7 (70%)	122 (63%)
Reoperations within 30 days of implant	56%	55%	60%	56%

Clinical Reliability:

During the clinical study there were 78 reports of confirmed malfunctions in 194 patients having a median support duration of 131 days. Forty-four percent (44%, 34/78) involved implanted system components (i.e., pump and cannulae) and 56% (44/78) involved external system components (i.e., controllers, monitors, batteries, etc). Some suspected malfunctions were determined to not be malfunctions or failures of the device. These events included technical errors, system management errors, and uncertainty regarding system alarms and displays. However, eleven of the malfunctions of the implanted system components were classified as serious adverse events (i.e., resulted in death or permanent disability, or required prolonged hospitalization). These eleven reports included percutaneous lead separation (4), pump thrombosis (3), inflow cannula twists (2) and outflow conduit leakage (2). Twelve malfunctions of the external system components were also classified as serious adverse events, including damaged printed circuit boards in the system controller (10), power base unit cable breakdown (1) and inadequate battery capacity (1).

During the course of normal HeartMate II support, daily exposure to external environments can sometimes damage the system controller because patients wear the system controller on their belt or carry it in a backpack. Since the system controller manages pump function, patients are required to always carry a backup controller in case a system controller exchange is necessary. Several improvements were made to the system controller based on malfunctions reported during the clinical trial. These improvements include enhancement to the belt clip, strengthening the robustness of the strain relief connector to the system controller and redesigning the lead lock to prevent accidental disconnection of the lead. All of these enhancements were reviewed and approved by FDA. These design improvements were implemented to mitigate reports of component malfunctions.

Estimated clinical reliability of the HeartMate II LVAS blood pump is summarized in Table 11. Clinical reliability is estimated based on a Weibull analysis of the 10 malfunctions reported above (please note that 4 of these 10 events involved system components, which were not evaluated in the *in vitro* reliability test: percutaneous lead separation (3), and outflow conduit leakage (1).

Table 11: Estimated Clinical HeartMate II LVAD Reliability

Lower, One-Sided 80% Confidence Limit on Reliability R(t)	
Months	**Reliability**
6	0.932
12	0.896
24	0.833

Functional Status:

Functional status was evaluated based on NYHA class assessments and 6-minute walk tests as summarized in Figures 7 and 8, below. These measures were obtained at baseline, 1 month, 3 months and 6 months (study outcome). Despite major heart surgery and adverse events, HeartMate II patients appeared to have improved functional capacity.

Figure 7: NYHA Class Over Time
(error bars = standard deviation)

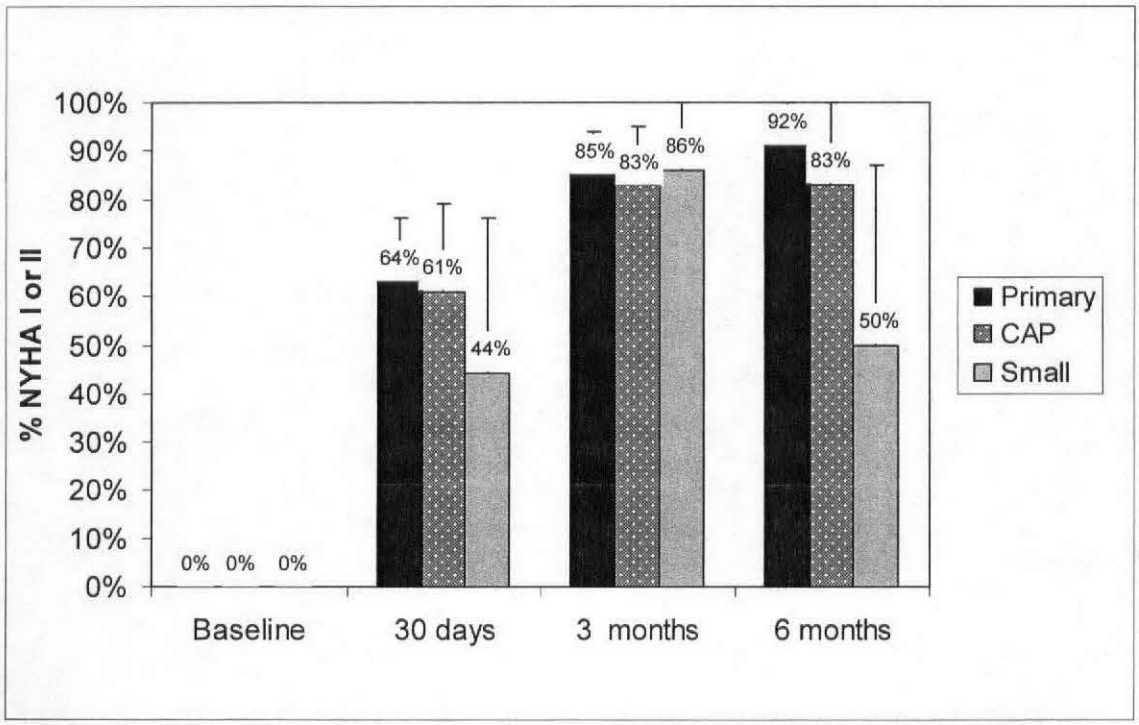
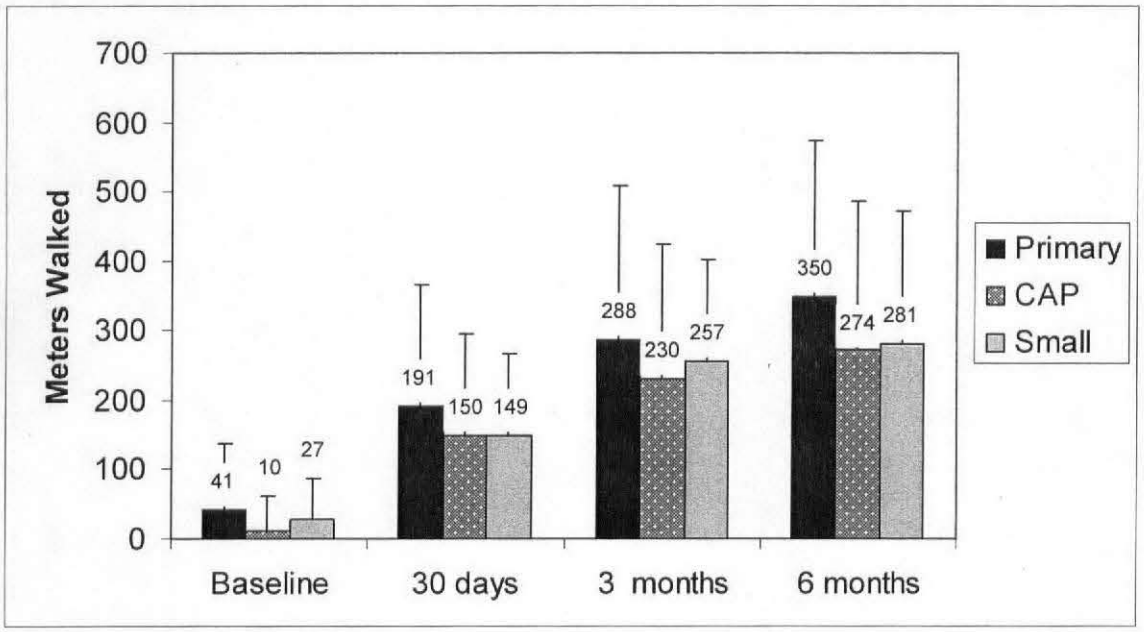


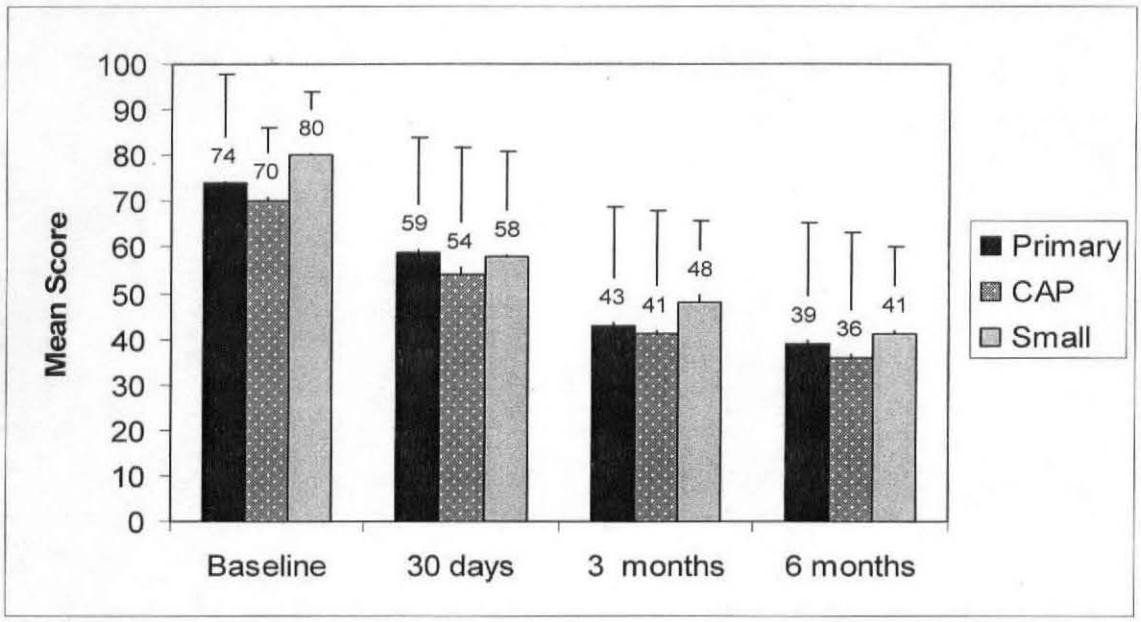
Figure 8: Summary of Six Minute Walk over Time
(error bars = standard deviation)



Quality of Life:

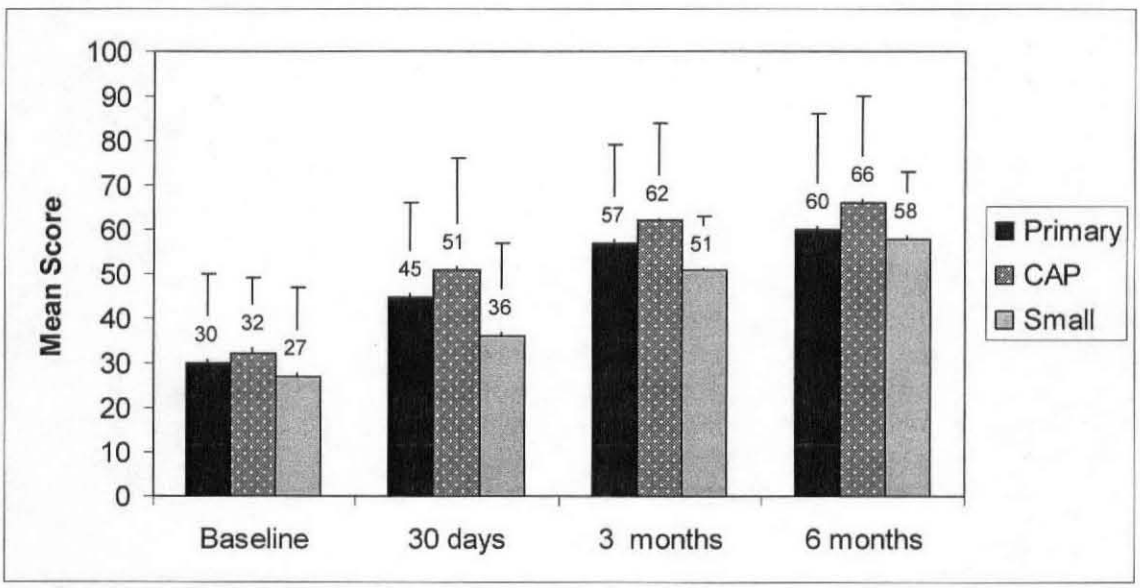
Quality of life was measured via the Minnesota Living with Heart Failure Questionnaire (MLHF) and Kansas City Cardiomyopathy Questionnaire (KCCQ) as summarized in the Figures 9 and 10, below. These measures were obtained at baseline, 1 month, 3 months and 6 months (study outcome). Despite major heart surgery and adverse events, HeartMate II patients appeared to have improved quality of life.

Figure 9: Minnesota Living with Heart Failure Questionnaire (MLHF)
(error bars = standard deviation)



Note: A lower score indicates better quality of life.

Figure 10: Kansas City Cardiomyopathy Questionnaire (KCCQ)
(error bars = standard deviation)



Note: A higher score indicates better quality of life.

Neurocognitive Evaluations:

Neurocognitive evaluations were performed in 11 of the 33 study sites. Eight standard neurocognitive measures with ten procedures were administered at baseline (1 month post-implant), 3 and 6 months post-implant. The tests surveyed cognitive domains involving memory, language, abstract/executive functions, visual/special perception and processing speed. Because of the small sample size (n=86), it is difficult to draw conclusions; however, important trends were seen. There was no significant cognitive decline in patients assessed between baseline and the 3 month or 6 month interval. There were significant improvements in cognitive test performance at 3 and 6 months over baseline for auditory memory, visual memory delay and processing speed. The majority of the cognitive test performance improvement was observed in the first 3 months post implant, with less change seen over extended follow-up intervals. As expected, most of the neurocognitive adverse events occurred at baseline and are likely due to cognitive instability shortly after implant. Over time, as the patients stabilized, neurocognitive functions improved and the incidence of adverse events declined.

Post-Explant Followup:

Table 12: 30 Day Post Explant Survival as of September 14, 2007

Cohort	# Pts Transplanted (or recovered)	# Alive at 30 days post explant	% Alive at 30 days post explant
Primary	72 (3)	73	97%
CAP	33 (2)	35	100%
Small	7	5	71%
Aggregate Data	112 (5)	113	97%

Table 13: 1-Year Post Explant Survival as of September 14, 2007

Cohort	# Pts Transplanted (or recovered)	# Alive at 1 Year post explant	% Alive at 1 year post explant
Primary	58 (2)	51 (2)	88%
CAP	7	7	100%
Small	4	2	50%
Aggregate Data	69 (2)	60 (2)	87%

Gender Analysis

A *post hoc* analysis of the aggregate data for variations associated with gender was performed. Of the 194 patients who were followed to a study outcome or, if ongoing on HeartMate II LVAS support, for at least a year, the majority were male (77% males vs. 23% females). Some statistically significant differences were observed in some baseline

hemodynamic and biochemistry parameters, but they are not considered to be clinically significant. Women were observed to have a higher incidence of strokes (18% vs. 6%), but the strokes did not have a significant effect on their overall survival compared with men. Trends toward a higher incidence of bleeding and infection events were observed in females than males. Nonetheless, the sample size of men compared to women (150 vs. 44) makes it difficult to draw any conclusions regarding differences in safety profile of the device between men and women. The results show that there do not appear to be differences with primary study outcome, NYHA Classification, 6 minute walk, MLWHF, and KCCQ assessments.

XI. PANEL RECOMMENDATION

At an advisory meeting held on November 30, 2007, the Circulatory System Devices Panel recommended that Thoratec's PMA for the HeartMate II LVAS be approved subject to submission to and approval by, the Center for Devices and Radiological Health (CDRH) of the following conditions:

1. A post-approval study to include adequate collection of data regarding both gender and body surface area to determine if differences exist in safety and effectiveness of the device.

2. The post-approval study must have a concurrent comparator.

3. Labeling changes to reflect separate presentation of the Primary Study Cohort, the Continued Access Protocol and the Small BSA Cohort Data.

4. A contraindications statement to state that no patient shall receive this device if they cannot be on anticoagulation medications.

5. The post-approval study should capture bleeding and anticoagulation data in their post-approval study.

6. A statement is to be placed in the warnings section of the label to show that this device has minimal data for patients with a body surface area $< 1.3m^2$.

7. Adequate neurological/neurocognitive evaluation was necessary in the post-approval study.

XII. CDRH DECISION

The clinical study results showed that the lower confidence limit (LCL) for the success rate of the pre-specified primary endpoint was 64.0% for the HeartMate II LVAS and, therefore, did not meet the pre-established success criterion of the LCL greater than 65%. The Circulatory System Devices Panel recommended that the PMA application was approvable on November 30, 2007, because the clinical evidence provided a reasonable assurance of safety and effectiveness for the device.

FDA reviewed the data supporting the PMA application and determined that even though the true success rate established from the clinical study results was slightly lower than the pre-specified primary endpoint, there was sufficient clinical evidence to demonstrate a reasonable assurance of effectiveness for the device in the intended patient population. The clinical study results demonstrated that the HeartMate II LVAS had comparable bridge to transplant success rates as currently approved devices. Similarly, patients appeared to have improved their quality of life and functional capacity while supported with the device as shown by the improvement in secondary endpoint scores.

The incidence of adverse events occurring in patients implanted with the HeartMate II indicated a reasonable assurance of safety. The adverse events experienced were comparable to those seen in previous bridge to transplant trials and reported in the literature. Bleeding and infection continue to be a concern with blood contacting implantable devices; but nonetheless, no problematic concerns were identified with the adverse event rates.

FDA reviewed the data supporting the use of the HeartMate II in patients with a smaller body habitus. The clinical study results showed that the survival to transplant of smaller sized patients was 70%, but this success rate was based on a sample size of 10 patients. Similarly, the incidence of adverse events appeared to be similar to that seen with the primary study cohort. Therefore, the Circulatory System Devices Advisory Panel and FDA determined that the sponsor include in their labeling that limited clinical data was available supporting the safety and effectiveness of the device in patients with a body surface area less than 1.5 m^2 and the clinical decision to implant the device in smaller sized patients should be based on the individual assessment of body habitus and device fit by the clinician.

FDA concurs with the Circulatory System Devices Panel, that the data contained in PMA P060040 for the Thoratec HeartMate II Left Ventricular Assist System for the intended for use as a bridge to transplantation in cardiac transplant candidates at risk of imminent death from non-reversible left ventricular failure has demonstrated a reasonable assurance of safety and effectiveness and should be approved.

A post-approval study for the HeartMate II LVAS was deemed necessary to assess use of the device outside the clinical trial environment. The post-approval study will also collect data on the use of the device in smaller size patients, gender-specific outcomes, and peri- and post-operative management of hemorrhagic and thrombotic events. The study will have a concurrent comparator group consisting of the other commercially available devices that are approved for the same indication for use. FDA has determined that because the sponsor

provided additional neurocognitive data a full battery of neurocognitive assessment testing is not necessary for in the post-approval study. However, if the incidence of neurological adverse events is problematic, neurocognitive assessment could be initiated. A total of 338 patients will be enrolled and will include the first consecutive 169 HeartMate II patients. The patients will be followed until study outcome of cardiac transplant, death, or explant for recovery. The post-approval study will also track the incidence of adverse events, clinical reliability of the device, quality of life, and 1 year post-explant survival. Thoratec proposed using the Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) as the vehicle to collect their post-approval study data which, as of March 13, 2008, was comprised of 610 patients from 89 centers that voluntarily joined the registry.

INTERMACS is a partnership between the National Heart Lung, and Blood Institute (NHLBI), the FDA, Centers for Medicare and Medicaid Services (CMS), participating hospitals and the device industry. It is a national registry that collects data on patients who are receiving mechanical circulatory support device therapy to treat advanced heart failure. Patients must give their consent to have their data collected by INTERMACS.

FDA issued an approval order on April 21, 2008. The applicant's manufacturing facilities were inspected and found to be in compliance with the Quality System Regulation (21 CFR 820).

XIII. APPROVAL SPECIFICATIONS

Directions for Use: See Final Draft 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