

FDA EXECUTIVE SUMMARY MEMORANDUM

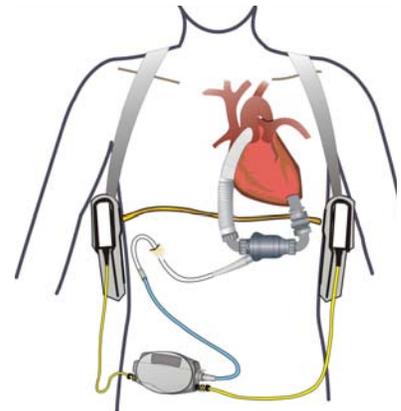
Prepared for the November 30, 2007, meeting of the
Circulatory System Devices Panel

PMA P060040
Thoratec® Corporation
HeartMate® II Left Ventricular Assist System (LVAS)

PROPOSED INDICATIONS FOR USE

The HeartMate II Left Ventricular Assist System (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 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.

The HeartMate II LVAS is contraindicated for patients whose body surface area is less than 1.3 m².

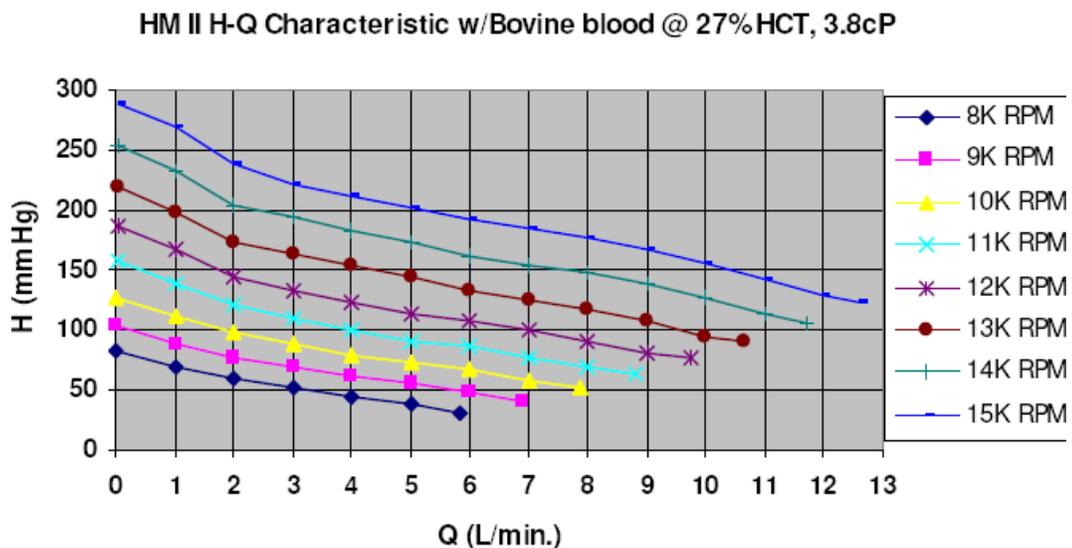


DEVICE DESCRIPTION

The HeartMate II LVAS consists of an implanted continuous axial flow blood pump and external components as shown in the figure to the right. The blood pump has one moving part, the rotor assembly that spins on bearings located at either end of the assembly. Electrical power to the blood pump is delivered through a percutaneous cable that is connected from the blood pump to the external system controller. The system controller is powered by two batteries or a Power Base Unit (PBU) that connects to the AC main power. The primary functions of the system controller include motor speed control and performance evaluation. Two batteries are used in conjunction when operating in battery mode, but the system can operate on one battery with an audible alarm sounding. An emergency power pack is provided to a patient and is a single-use battery pack that can operate the system for approximately 12 hours. The system controller connects directly to the emergency power pack. The system also contains a display module that provides read-only display of the performance parameters of the system and is typically used at the patient's home. The HeartMate II has accessories that facilitate various patient activities while on support: shower kit, battery holster, pocket pak, and stabilization belt.

The HeartMate II blood pump has an operating speed range of 8000 to 15000 RPM. The blood pump's inlet cannula is placed in the apex of the left ventricle while the outlet cannula is connected to the ascending aorta. A textured surface composed of titanium microspheres is incorporated into the inflow and outflow conduits to promote the formation of a neointimal layer.

The volume of blood flow generated by the HeartMate II is determined by the speed of rotation of the rotor and the pressure differential that exists across the pump. Since the HeartMate II is designed to function clinically at a fixed, patient-specific speed, flow varies inversely with pressure (i.e., increasing pump pressure differential decreases flow rate). The pressure-flow (H-Q) curve characteristics of the HeartMate II are fundamental to understanding the interaction between the pump and the physiological circulatory system as shown below. During any point in the cardiac cycle, the differential pressure across the pump is equal to the aortic pressure minus left ventricular pressure, plus the combined pressure loss across the inlet and outlet cannula. In nominal operating conditions with a patient's aortic pressure at a nominal value, the net cannula pressure drop is at some value set by the flow rate (e.g., 10 mmHg at 6 L/min). Thus, the dynamic parameter that determines pump differential pressure is left ventricular pressure, which is dependent upon the contractile state of the ventricle. Rhythmic contraction of the left ventricle creates a pressure pulse that in turn affects the flow rate.



REGULATORY HISTORY OF HEARTMATE II LVAS

Thoratec's clinical investigation for the HeartMate II LVAS was formally proposed to FDA under IDE G010230 dated August 30, 2001 as a feasibility study. This feasibility study incorporated a prospective, non-randomized study design and enrolled 24 subjects in 9 investigational sites.

The HeartMate II bridge to cardiac transplantation (BTT) multi-center pivotal study was conditionally approved on February 18, 2005 for 133 subjects and was fully approved for 40 sites on December 14, 2005.

The complete Premarket Approval (PMA) application was received on December 22, 2006. A meeting was held between Thoratec and the FDA on May 1, 2007 to review the status of the PMA application. At the meeting, FDA recommended that Thoratec analyze the data according to the prospectively agreed upon data analysis plan in which the 7 small body surface area (BSA) patients would be analyzed separately from the primary cohort patients since the most recent clinical protocol (HeartMate II Pivotal Study Protocol, Rev. 18 03/31/05) indicated that the small BSA patients would be analyzed separately from the primary cohort because of the inclusion criteria for the primary cohort required that patients have a $BSA \geq 1.5 \text{ m}^2$. No pre-specified analysis plan existed for the small BSA patients; rather, it was expected that the data would be summarized and presented to FDA in the marketing application to determine if labeling could be extended to this cohort. In addition, the primary analysis would be conducted using the pre-specified definition of the endpoint (survival to transplant or survival to 180 days while transplant listed 1A or 1B). Per the discussions on May 1, 2007, Thoratec submitted an amendment to the PMA on July 23, 2007 with an updated dataset as of March 16, 2007.

PRECLINICAL INFORMATION

Thoratec conducted component and sub-system testing, *in vitro* and *in vivo* system performance and characterization studies, and long-term reliability studies with the HeartMate II. Test results demonstrated that the device is compliant with FDA and internationally recognized standards for electrical safety, electromagnetic compatibility, and biocompatibility. Packaging and sterilization processes were validated according to FDA and internationally recognized standards as well. Some minor engineering questions remain open, and FDA is working interactively with the sponsor to resolve these issues. FDA does not believe that these open issues require consideration by the Circulatory Systems Devices Panel. All other issues have been resolved.

REGULATORY HISTORY OF APPROVED BTT DEVICES

No randomized, prospective studies have been performed comparing mechanical circulatory assist devices to optimum medical therapy for the BTT patient population. There are currently six devices approved for the BTT indication through the Premarket Approval process. The HeartMate IP, HeartMate VE/XVE and Novacor are approved as left ventricular assist devices; the Thoratec PVAD and Thoratec IVAD are approved as a left-, right-, or biventricular assist devices; and the Syncardia TAH-t is approved as a temporary artificial heart.

In 2002, the FDA developed a Performance Goal using prospectively identified criteria to define success for bridging to cardiac transplantation in order to facilitate single-arm clinical trials for BTT devices. Publications reporting on approved BTT devices were used to support development of a Performance Goal for the rate of survival to cardiac transplantation. After an extensive literature review, six publications⁽¹⁻⁶⁾ were used as the basis for this Performance Goal.

It should be noted that for the majority of approved BTT devices, there exists a lower BSA limit of 1.5 m^2 . Thus, the performance goal was only extended to patients with a $\text{BSA} \geq 1.5 \text{ m}^2$. This also explains why the sponsor was asked to create a small BSA cohort to evaluate the device in smaller patients.

These papers supported a 65%-70% survival to cardiac transplantation rate as the Performance Goal for approved BTT devices. No assessment of goals for adverse events were identified because of the lack of common definitions for adverse events, and since the rates for adverse events differed among devices over time. FDA's development of this Performance Goal has served as the basis for FDA's current thinking of bridge to cardiac transplantation studies for left ventricular assist devices.

It is important to note that the Performance Goal only considered survival to cardiac transplantation and did not include evaluation of transplant status at 180 days. Thoratec requested a 180-day time point in order to capture an endpoint on all patients in a discrete time period. The 180-day time point did not stop data collection for patients who remained on the device past the 180-day time point. FDA and Thoratec agreed that the primary endpoint would be "survival to transplant or transplant listed 1A or 1B at 180 days." The FDA did not approve a more qualitative endpoint of "transplant eligible" since doing so would have made data interpretation difficult. The primary endpoint of "survival to transplant or transplant listed 1A or 1B" allowed all patients transplanted after 180 days to be counted as a success even if they had not been transplant listed 1A or 1B at 180 days. Patients from whom the device was removed due to permanent cardiac "recovery," as well as patients who expired on the device after 180 days but were listed for transplant 1A or 1B at 180 days were also considered successes.

MULTI-CENTER PIVOTAL STUDY

A total of 133 patients were enrolled into the pivotal study at 26 investigational centers in the United States between March 2005 and May 2006. Seven (7) patients with a $\text{BSA} < 1.5 \text{ m}^2$ were analyzed separately in the Small BSA Cohort group. Therefore, the 126 patients from this group with $\text{BSA} \geq 1.5 \text{ m}^2$ will be referred to as the Primary Study Cohort throughout this executive summary and were the only cohort prospectively identified to be part of the primary endpoint analysis.

Enrollment was limited to end-stage, NYHA Class IV heart failure patients listed for transplant without severe end-organ damage that would preclude heart transplantation. Patients with $\text{BSA} \geq 1.5 \text{ m}^2$ were included in the Primary Study Cohort and those with $\text{BSA} < 1.5 \text{ m}^2$ and $\geq 1.2 \text{ m}^2$ comprised the Small BSA Cohort. (See Section 7.13 Study Protocol for the full inclusion/exclusion criteria)

Primary Endpoint

The primary endpoint for the HeartMate II BTT pivotal study was “patient survival to cardiac transplantation or 180 days of LVAD 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 null and alternative hypotheses based on a one-proportion hypothesis test were constructed as follows:

$$H_0: P \leq 65\% \quad \text{vs.} \quad H_A: P > 65\%$$

where P = the true percentage of patients who will survive to transplantation or 180 days of LVAD support while remaining listed status 1A or 1B.

Secondary Endpoints

The pivotal study was not formally powered to detect differences in the secondary endpoints as specified in the HeartMate II Pivotal Study Protocol, Rev. 18 03/31/05, so formal claims regarding secondary endpoints would be problematic. Secondary endpoints consisted of the following: survival to transplant, survival 30 days post-transplant, survival 1 year post-transplant, frequency of adverse events, device reliability, improvement in functional status, quality of life, neurocognitive evaluation, and reoperations.

Primary Study Cohort Results

The data presented in the Primary Study Cohort section includes the 126 pivotal study patients with body surface area $\geq 1.5 \text{ m}^2$ enrolled at 26 investigational sites. Ten (10) patients had deviations from the study entrance criteria. All 10 patients were included in the pre-specified analysis plan.

Baseline Characteristics

Table 1: Baseline Characteristics

	n	Mean	SD	Median	Range
Gender					
	Male 83%	Female 17%			
Race					
	Caucasian 71%	Black 21%	Hispanic 6%	Other 2%	
Etiology					
	Ischemic 39%	Idiopathic 52%	Other 9%		
NYHA class					
	Class IV 99%	Class IIIb 1%			
	n	Mean	SD	Median	Range
Age (years)	126	50.4	12.8	55.0	17.0-68.0
BSA (m ²)	126	2.02	0.27	1.99	1.50-2.62
BMI (kg/m ²)	126	27.3	5.6	26.5	10.3-40.0
Weight (kg)	126	85.5	20.8	85.0	51.3-135.4
Sodium (mM/L)	126	133.0	5.0	133.0	117 -150
Albumin (g/dL)	125	3.5	0.5	3.4	2.2-4.4
Creatinine (mg/dL)	126	1.4	0.5	1.3	0.6 -3.0
Total Bilirubin (mg/dL)	125	1.3	0.8	1.1	0.2-4.0
Heart Rate (bpm)	126	91.5	18.7	90.0	48-128
Systolic BP (mmHg)	122	95.6	14.9	93.0	60-156
PCWP (mmHg)	109	26.6	7.8	26.0	12-60
Cardiac Index (L/min/m ²)	122	2.0	0.6	1.9	0.9 -3.8
LVEF (%)	121	16.6	6.3	15.0	5-45

It is interesting to note that the majority of patients were not ischemic. This is unusual in the patient population today, especially in the men where an ischemic etiology is more common. In addition, the mean total bilirubin of 1.3 mg/dL is mildly elevated. The mean creatinine of 1.4 mg/dL is slightly elevated, which is not unusual for this population. Mean sodium of 133.0 mM/L is low. These laboratory values appear to be consistent with values in transplant listed heart failure patients. Baseline hemodynamics are as expected for this patient population. (See Section 7.5.5 for Patient Baseline Characteristics of the Primary Study Cohort)

Effectiveness Endpoint

Table 2 illustrates the results from the Primary Study Cohort as of September 14, 2007, using the pre-specified primary endpoint. The September 14, 2007 primary study cohort table is provided to show the most recent results (See Section 7.5.6, Table 18 for Primary Study Cohort results as of March 16, 2007 which represents the sponsor's response to FDA's request for an updated primary study cohort dataset with the pre-specified primary endpoint). As of March 16, 2007, the median time to transplant for patients that received a transplant was 96.5 days with a range between 15 and 471 days. Post-transplant survival for these patients was 97% at 1 month and

83% at 1 year. The overall median duration of support was 117 days (mean = 177 days, range = 1 – 672 days). The cumulative duration of support was 61 patient years.

The most recent results show that the lower confidence limit (LCL) of success was 64.0%, thereby not quite meeting the pre-specified agreed-upon LCL endpoint > 65%.

The calculated p-value is 0.0824 with the 89 successes in the September 14, 2007 primary study cohort table.

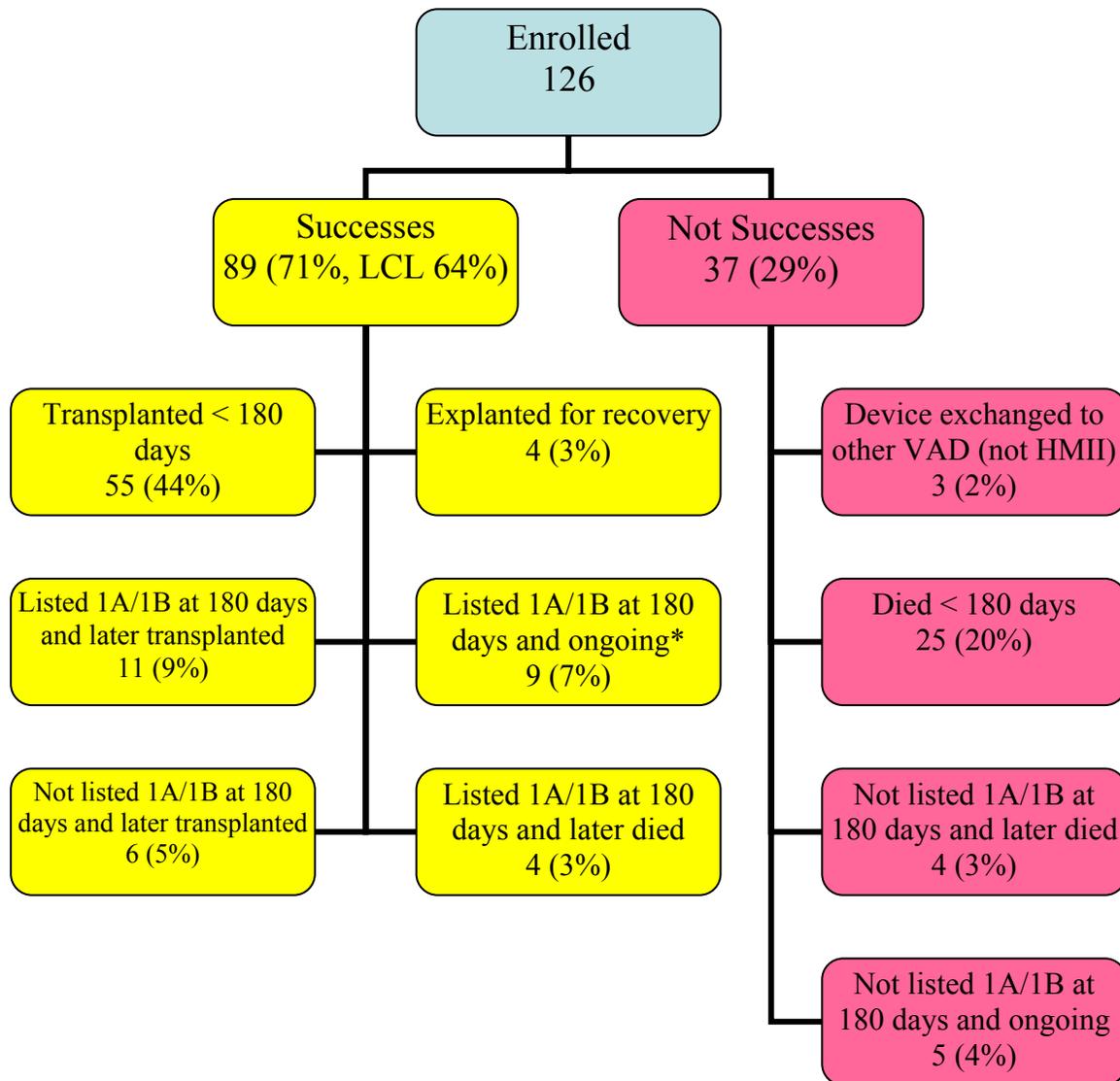
Table 2: Primary Study Cohort Results as of September 14, 2007

Success	# Pts	% Pts	LCL
Transplanted	72	57.1%	
Recovered	4	3.2%	
Supported 180 days and Status 1A or 1B	13	10.3%	
Total Success	89	70.6%	64.0%
Not Success			
Not Success	# Pts	% Pts	UCL
Expired < 180 days	25	19.8%	
Supported 180 days but not Status 1A or 1B	9	7.1%	
Received other VAD; Treatment failure	3	2.4%	
Total Not Success	37	29.4%	36.0%

Within the group of 89 patients counted as a success,

- Two (2) patients had their original HeartMate II replaced (at 24 days and 56 days after initial device implant) with another HeartMate II. Both of these exchanges were related to pump thrombosis;
- Three (3) patients were transplant listed 1A or 1B at 180 days but subsequently expired on the device;
- Four (4) patients were not transplant listed at 180 days but were subsequently transplanted;
- Two (2) patients were transplanted > 180 days but were already counted as successes since they were transplant listed 1A or 1B at 180 days; and
- Four (4) patients were explanted for recovery.

The figure below illustrates the outcome of patients receiving the device in the Primary Study Cohort.



* includes 2 patients who received another HeartMate II

The primary endpoint was observed in several subgroups such as ethnicity, etiology, age, gender and the need for concurrent procedures at implant surgery. The difference in the primary endpoint was only observed between the two age subgroups (age \geq 55 and age < 55) with younger patients achieving marginally better outcomes: 57% (37/65) versus 77% (47/61). Results can be seen in Section 7.5.7.2.

Deaths

As of March 16, 2007, 29/126 (23%) patients in the Primary Study Cohort had died on the HeartMate II and the following table below presents the causes of death. All of these deaths were adjudicated by the Clinical Events Committee (CEC). The sponsor did provide updates on additional deaths between March 16 and September 14, 2007 for the following causes: 2 sepsis, 1 ischemic CVA, and 1 pocket infection, but the following table is not updated because the Serious Adverse Event table below has not been updated.

Table 3: Primary Study Cohort - Causes of Death as of March 16, 2007

Cause of Death	# Pts	Pt duration (days)	% of Implanted Patients (n=126)	% of Deaths (n=29)
Sepsis	6	10, 59, 74, 80, 133, 191	5%	21%
Ischemic CVA	5	7, 13, 30, 102, 127	4%	17%
Multi-System Organ Failure	4	8, 38, 64, 141	3%	14%
Hemorrhagic CVA	3	15, 18, 93	2%	10%
Anoxic Brain Injury	2	10,10	2%	7%
Device Related: External Components, Loss of Power, Operator Dependent	2	184, 326	2%	7%
Right Heart Failure	2	26, 144	2%	7%
Adenocarcinoma	1	104	1%	3%
Bleeding	1	20	1%	3%
Device Related: Implanted Components, VAD Dysfunction/Failure, Inflow Cannula Twist	1	6	1%	3%
Respiratory Failure	1	672	1%	3%
Unknown	1	59	1%	3%

The majority of deaths, as adjudicated by the sponsor's independent CEC, were due to sepsis or neurological causes. FDA reviewed the sponsor's summary timeline for each death and has no additional comments on the adjudication. The most common cause of death in LVAD patients in the REMATCH trial^(7, 8) was sepsis, which continues to be a leading cause of death in the LVAD patients in this trial (6/126 = 5%). FDA notes that 5/6 HeartMate II Primary Study Cohort patients who died of sepsis had events that occurred after the first 30 days of implantation. Neurological events leading to death occurred in 10/126 (8%) HeartMate II Primary Study Cohort patients. These results appear to be similar to data published on approved ventricular assist devices.

Serious Adverse Events

The table below illustrates the serious adverse events (SAE) experienced in the Primary Study Cohort. Adverse events were classified as serious if they resulted in death or were life-threatening, resulted in permanent disability, required hospitalization or a prolonged hospital stay. The expected SAEs were defined prospectively. (See Section 7.14 for Adverse Event Definitions)

Table 4: Primary Study Cohort - Serious Adverse Events as of March 16, 2007

	# Pts	% Pts	UCL	LCL	# Events
Death	29	23%	30%	16%	
Bleeding*	74	59%	67%	50%	132
Bleeding requiring surgery	37	29%	37%	21%	42
Stroke	11	9%	14%	4%	11
Peri-operative (\leq POD2)	5	4%	7%	1%	5
Post-operative ($>$ POD2)	6	5%	8%	1%	6
Other Neurological**	10	8%	13%	3%	11
Local Infection	25	20%	27%	13%	41
Percutaneous Lead Infection	9	7%	12%	3%	11
Pocket Infection	2	2%	4%	0%	2
Sepsis	25	20%	27%	13%	36
Right Heart Failure	22	17%	24%	11%	23
Peripheral TE	9	7%	12%	3%	10
Respiratory Failure	32	25%	33%	18%	41
Cardiac Arrhythmias	55	44%	52%	35%	91
Renal Failure	17	13%	19%	8%	18
Hepatic Dysfunction	3	2%	5%	0%	3
Device Thrombosis	2	2%	4%	0%	2
Hemolysis	3	2%	5%	0%	3
Psychological	2	2%	4%	0%	4
Myocardial Infarction	1	1%	2%	0%	1
Confirmed Malfunctions	8	6%	11%	2%	8

*Bleeding requiring Packed Red Blood Cells \geq 2 units or surgery

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

The adverse events experienced by the HeartMate II Primary Study Cohort are comparable to those that were experienced in the HeartMate VE BTT study and Thoratec IVAD BTT study. The study was not powered for a specific analysis of the adverse events. The definitions of adverse events were comparable with 5 previous definitions from the HeartMate VE BTT study and 8 definitions from the Thoratec IVAD BTT study. There were no significant differences between the 5 comparable adverse events relative to the HeartMate VE. The rates of bleeding and infection were consistent with previous devices.

FDA acknowledges the sizeable proportion of Primary Study Cohort patients (29%) that required reoperation because of bleeding. It is possible that this serious adverse event's rate may drop as

clinicians gain more experience with the device's implantation; accordingly, subsequent clinical use of the HeartMate II will need to incorporate continued monitoring of the bleeding rate.

As in any patient with an implanted foreign body, infection in the HeartMate II BTT patients had serious ramifications. Of the Primary Study Cohort patients, 20% developed sepsis according to Table 4 above, 24% of those sepsis episodes were lethal to the patient, and 21% of all HeartMate II deaths were due to sepsis based on Table 3. This incidence of sepsis occurred despite a very low rate of pump pocket infections (2%), and thus there is no clear explanation for this Serious Adverse Event rate. Comparison of the HeartMate II's sepsis rate to rates from the sponsor's other studies of implantable devices for BTT (HeartMate VE and Thoratec IVAD) was not possible because of differing definitions for sepsis among the studies.

Secondary Endpoints

New York Heart Association (NYHA) Functional Classification

The table below illustrates the New York Heart Association (NYHA) functional classification at baseline and post-implant at 1, 3, and 6 months. NYHA functional classification was assessed independently by a nurse, cardiologist, or other medical staff not directly involved with patient care at that time.

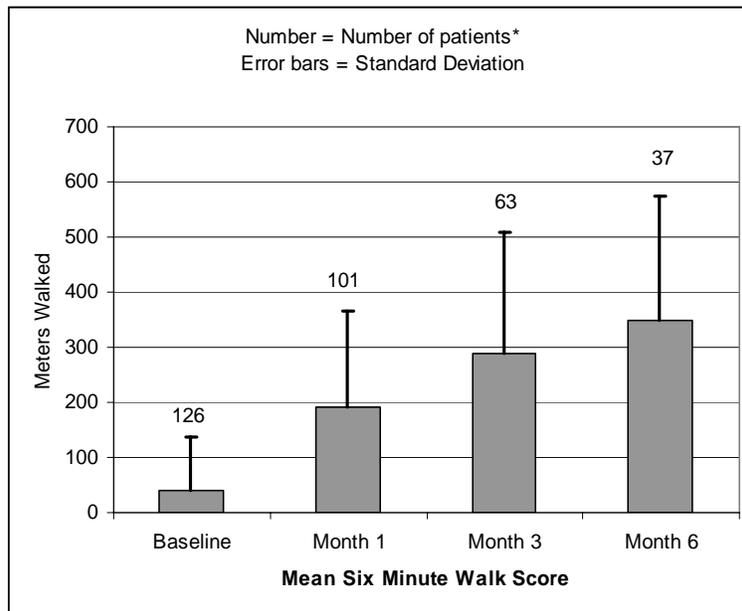
Table 5: Primary Study Cohort - NYHA Functional Classification

Interval	Baseline	Month 1	Month 3	Month 6
Number of patients at interval	126	107	75	41
Number of patients with missing data (%)	0	8 (7%)	4 (5%)	0
Patients at NYHA IV	125 (99%)	4 (4%)	2 (3%)	0 (0%)
Patients at NYHA IIIB	1 (1%)	13 (13%)	2 (3%)	1 (2%)
Patients at NYHA IIIA	0 (0%)	18 (18%)	7 (10%)	2 (5%)
Patients at NYHA II	0 (0%)	47 (47%)	36 (51%)	19 (46%)
Patients at NYHA I	0 (0%)	17 (17%)	24 (34%)	19 (46%)

There is an improvement in NYHA Class over time with patients generally in NYHA Class I or II by month 3. However, because this is an unblinded study, the magnitude of the placebo effect and assessment bias are unknown.

Six Minute Walk Test

The figure below illustrates the change in mean six minute walk score over time. The sponsor assigned a score of 0 meters walked for patients who were unable to perform the test. Patients with missing data due to non-medical reasons were ignored in the first analysis and then assigned a score of 0 meters walked to represent a worst case scenario. The results illustrated that the mean distance walked in 6 minutes increased at each interval, but the results are difficult to assess because this is an unblinded study, the placebo effect may be significant, and there is no concurrent control. However, the increase in 6 minute walk is consistent with the improvement in NYHA.



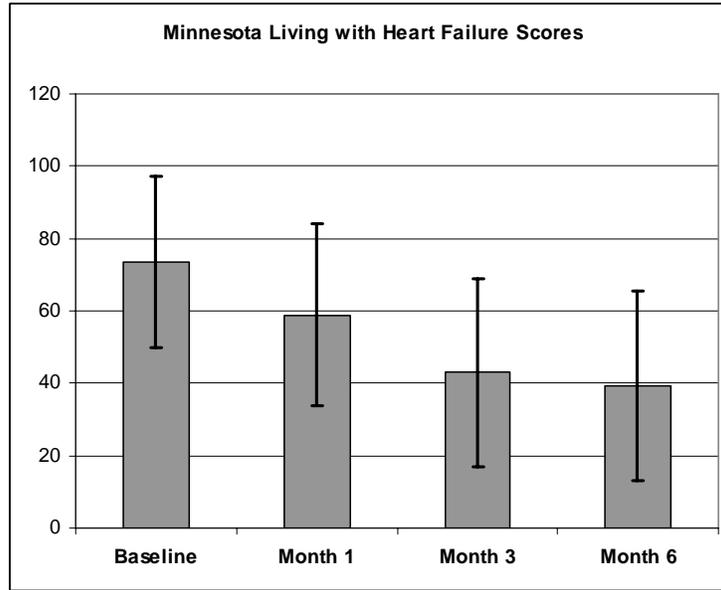
* Patients with data who performed test, or who are medically unable to perform test and assigned zero

Interval	Baseline	Month 1	Month 3	Month 6
Number of patients at interval	126	106	75	41
Number of patients with missing data (%)	0 (0%)	5 (5%)	12 (16%)	4 (10%)

Health Status

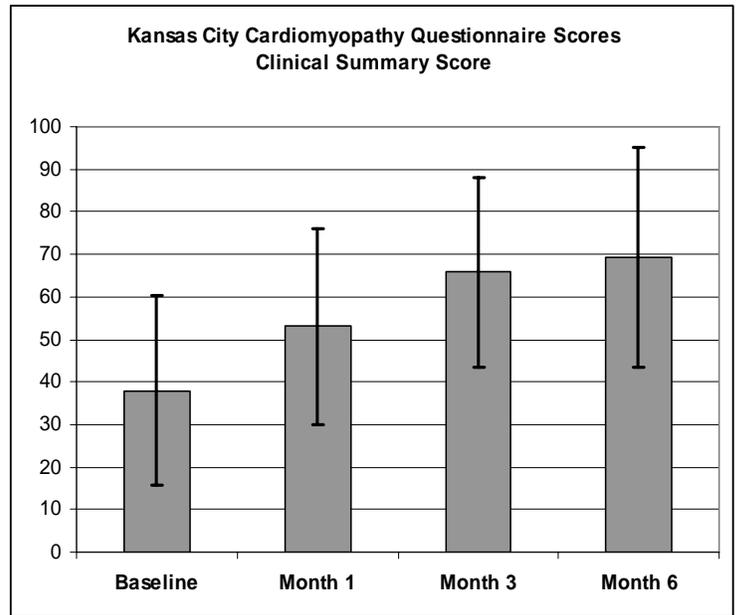
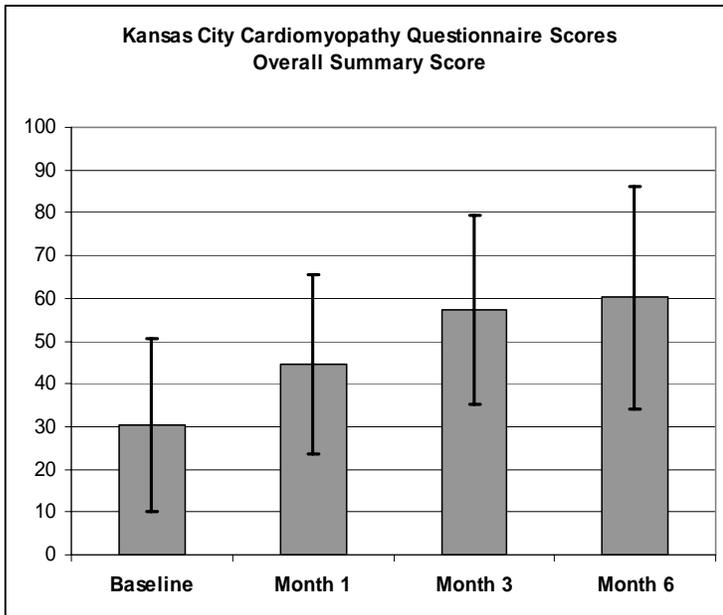
Health status was measured using the Minnesota Living with Heart Failure Questionnaire (MLWHF) and the Kansas City Cardiomyopathy Questionnaire (KCCQ). The MLWHF questionnaire score is lower with improvement while the KCCQ is higher. The KCCQ overall summary score is derived by combining scores in each domain (physical function, symptom {frequency and severity}, social function and quality of life) while the KCCQ clinical summary score is derived from combining the physical function and symptoms scores. Although these quality of life assessment tests have not been validated in NYHA Class IV patients, the results suggest that quality of life improved at each interval. The patient numbers decrease due to deaths and cardiac transplantation. The contribution of the placebo effect to the improvement in health status is unknown.

Minnesota Living with Heart Failure Questionnaire



Interval	Baseline	Month 1	Month 3	Month 6
Number of patients at interval	126	105	74	41
Number of patients with missing data (%)	18 (14%)	12 (11%)	7 (9%)	2 (5%)

Kansas City Cardiomyopathy Questionnaire Overall and Clinical Summary Scores



Interval	Baseline	Month 1	Month 3	Month 6
Number of patients at interval	126	105	75	41
Number of patients with missing data (%)	17 (13%)	12 (11%)	7 (9%)	2 (5%)

Patient Activity Evaluation

A third measure to assess functional improvement was documenting the patient's level of activity via a Metabolic Equivalent score (METs; 1 MET is approximately 3.5 ml/min/kg of oxygen uptake, as these values are estimated). Patients were asked to describe their highest level of activity for the reporting period. This was collected at baseline and post-implant at 1, 3, and 6 months. It appears that patients experienced improvement in patient activity score after device implantation, although the contribution of the placebo effect to the improvement is unknown.

	# of Patients			
	Baseline	Month 1	Month 3	Month 6
# Patients at interval	126	106	75	41
# Patients with missing data	2 (2%)	1 (1%)	4 (5%)	2 (5%)
Very Low (METs < 1)	64	12	4	0
Low (METs 1-2)	54	68	22	9
Moderate (METs 2-4)	6	23	25	10
High (METs 4-6)	0	2	12	13
Very High (METs >6)	0	0	8	7

Neurocognitive Tests

The data from the Primary Study Cohort indicates that neurocognitive testing data was collected at 11 of the investigational sites. These sites enrolled 50% (64/129) of the Primary Study Cohort patients. Five cognitive domains were evaluated and the 1 month post-implant data were used for baseline values. The patients were evaluated at 3 and 6 months and if the patient experienced a stroke.

The assessment of cognitive function is limited because a small number of patients had paired baseline and 6 month data for each of the ten tests in the suite of cognitive tests (only 6 – 10 patients had paired data for each test, see Section 7.12 Neurocognitive Evaluations, Table 10). A Serious Adverse Event (SAE) was prospectively defined as a score on any one test three standard deviations below the normative standard for the general population (a profoundly abnormal score). Using the available data in the submission, eighteen (18) of the 24 eligible patients had 6 month data, and no patients had a SAE at that time period that was not present at baseline. Therefore, the amount of missing data makes it difficult to make any conclusions regarding neurological damage or improvement from baseline.

Reoperations

Eighty (80) of the 126 patients underwent additional operations after device implant with 73% of the reoperations occurring within the first 30 days of device implant. Bleeding was the most common cause of reoperation and was the cause of half of the reoperations in the first 30 days. Reoperations for all other causes occurred in 48% of the patients at risk in the first 30 day timeframe and 82% of the patients at risk after 30 days. (See Section 7.5.11 Reoperations for Primary Study Cohort)

Reops occurring	# Pts	# Pts at risk	% Pts at risk	# Events	Reason for Reoperation		
					HeartMate II Replace	Bleeding	Other
≤ 30 days	72	126	57%	118	3	58	57
> 30 days	25	107	23%	44	2	6	36
Total	80*	126	63%	162	5	64	93

*A few patients had reoperations in each interval

Pump Replacements for the Primary Study Cohort

Of the 126 primary cohort patients, five patients (4%) required a HeartMate II pump replacement or exchange to another device. Two patients underwent HeartMate II to HeartMate II pump exchanges on post-implant days 24 and 56. Both exchanges were related to pump thrombosis. The patients remained in the study and were both deemed “successes” for the primary endpoint since they were alive at 180 days after device implantation and were still listed for cardiac transplantation (UNOS 1B). The other three pump replacements (two to HeartMate XVE and one to Thoratec PVAD) occurred on post-implant days 1, 15 and 32, respectively. Because these three patients received non-HeartMate II devices, they were considered failures and were withdrawn from the study at the time of HeartMate II removal. (See Section 7.5.12 Pump Replacements for Primary Study Cohort)

Continued Access Protocol Results

The Continued Access Protocol (CAP) was an extension of the original HeartMate II Pivotal Study Protocol, Rev. 18 03/31/05, which allowed the investigators and investigational sites access to the device during the time that the sponsor was analyzing their data and when FDA was reviewing their PMA application. The CAP patients were enrolled and followed using the identical protocol as the Primary Study Cohort. The CAP included a total of 32 investigational sites compared to the 26 sites in the Primary Study Cohort. The current approved limit of CAP patients is 280 subjects.

A total of 139 CAP patients were implanted from May 25, 2006 to March 16, 2007. All patients are included in the analysis except for one patient who had previously been implanted with the HeartMate XVE. Thus, the CAP cohort included 138 patients. As of March 16, 2007, 58

patients had reached an endpoint. The lower confidence limit of the successes was 55.3%, which is below the Performance Goal of 65% as illustrated in Table 6.

Table 6: Continued Access Protocol Cohort Results as of March 16, 2007

Success	# pts	% Pts	LCL
Transplanted	26	44.8%	
Recovered	1	1.7%	
Supported 180 days and Status 1A or 1B	11	19.0%	
Total Success	38	65.5%	55.3%
Not Success	# pts	% Pts	UCL
Expired < 180 days	11	19.0%	
Supported 180 days but not Status 1A or 1B	9	15.5%	
Total Not Success	20	34.5%	44.7%

Pump Replacements for the Continued Access Protocol

Of the 138 continued access patients, two patients (1%) required a HeartMate II pump replacement or exchange to another device. These two patients underwent HeartMate II to HeartMate II pump exchanges on post-implant day 0 and 123. Both exchanges were related to pump thrombosis and both patients subsequently expired on the device. (See Section 7.6.12 Pump Replacements for Continued Access Cohort)

Small BSA Cohort Results

The protocol pre-specified that the patients with body surface area (BSA) less than 1.5 m² would be analyzed separately from the primary cohort. Seven patients with BSA <1.5 m² were enrolled during the multi-center pivotal study and 8 patients were enrolled during the Continued Access phase. Ten (10) of these 15 patients have been followed for at least 180 days as of the March 16, 2007 dataset. The sample size is small and there was no pre-specified statistical analysis plan for pooling from the two cohorts nor was there a pre-specified statistical analysis plan for the small BSA data. The small BSA data (Primary Study Cohort and Continued Access Protocol Cohort) are presented in Table 7 to determine if labeling can be extended to this cohort.

Table 7: Small BSA Cohort Results as of March 16, 2007

Success	# Pts	% Pts	LCL
Transplanted	6	60.0%	
Recovered	0	0.0%	
Supported ≥ 180 days and Status 1A or 1B	1	10.0%	
Total Success	7	70.0%	46.2%
Not Success	# Pts	% Pts	UCL
Expired < 180 days	0	0.0%	
Supported ≥ 180 days but not Status 1A or 1B due to reversible reason	1	10.0%	
Supported ≥ 180 days but not Status 1A or 1B due to irreversible reason	2	20.0%	
Received other VAD; Treatment failure	0	0.0%	
Total Not Success	3	30.0%	53.8%

With regard to the safety results for the Continued Access Protocol Cohort and Small BSA Cohort, the adverse events and deaths appear to be similar to that seen with the Primary Study Cohort. FDA notes that no small BSA patients have required a HeartMate II pump exchange or replacement to another device

GENDER ANALYSIS

FDA requested that the sponsor perform a *post hoc* data analysis to assess any differences in patient outcome by gender. This analysis includes comparison of the primary study outcome according to the pre-specified endpoint, adverse events, quality of life, 6-Minute Walk Test, NYHA Classification, reoperations and baseline demographics. This dataset is comprised of 194 patients, all of which have reached an endpoint. The 194 patients include the Primary Study Cohort (n=126), the Continued Access Protocol Cohort (n=58) and Small Patient Cohort (n=10). These 194 patients are also referred to in the sponsor's portion of the panel pack as the Thoratec Proposed Labeling Cohort. The analyses are based on data follow-up as of March 16, 2007.

The following baseline differences were noted between groups: 74% of the males were Caucasian while 59% of the females were Caucasian; mean total bilirubin was 1.3 mg/dL in males and 1.0 mg/dL in females; mean creatinine was 1.5 mg/dL in males and 1.2 mg/dL in females; mean sodium was 133.0 mM/L in males and 134.9 mM/L in females.

The results showed that females were observed to have a higher incidence of stroke compared to men (18% vs. 5%). Females had a higher percentage of patients at risk of a reoperation than men (31% vs. 18%) after the first 30 days, and females had a higher rate of reoperation for bleeding than men within the first 30 days (60% vs. 47%). Please refer to Section 7.10 in the Panel Package for other Gender-Specific information and note that the p-values that are included have not been adjusted for multiplicity.

The results also show that there do not appear to be differences with primary study outcome, NYHA Classification, 6 minute walk, MLWHF, and KCCQ assessments.

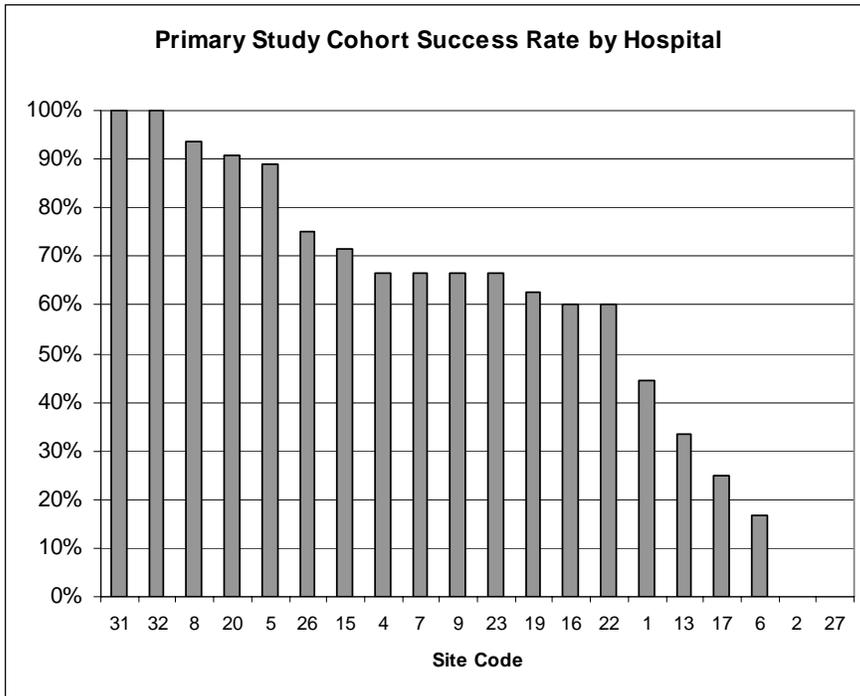
ADJUNCTIVE ANALYSES

The “alternative” primary endpoint of “survival to transplant or 180 days of LVAD support while remaining listed status 1A or 1B or 180 days of LVAD support but not status 1A or 1B due to reversible reasons” that is presented by the sponsor was neither proposed nor pre-specified in the approved investigational plan (HeartMate II Pivotal Study Protocol, Rev. 18 03/31/05). This alternative primary endpoint represents a *post hoc* data analysis since the modification of the endpoint definition was generated after the study data had been made available. FDA notes that there could be the possibility that the proposal was inspired by the results of the study data. The interpretation of the results for the modified endpoint is very difficult from a statistical perspective, especially since a performance goal is involved. FDA does not consider this *post hoc* analysis provided by the sponsor to be appropriate for the primary analysis of this multi-center pivotal study. FDA will consider the analysis and the totality of data submitted as additional information in the evaluation of the safety and effectiveness of the HeartMate II as a bridge to cardiac transplantation device. There was no pre-specified analysis plan for the Thoratec Proposed Labeling Cohort. Therefore, no additional comments will be provided regarding the “alternative” primary endpoint analysis or the additional cohorts provided by the sponsor.

DATA POOLING ACROSS CENTERS

Assessment of data poolability across investigational sites is challenging since the primary success rates are different among centers as shown below. As illustrated in the information below, some investigational sites had higher success rates than others, but no obvious conclusion could be determined regarding these differences.

Table 8: Primary Study Cohort Success rate by Hospital as of March 16, 2007



Site Code	# pts	# Success	% Success
1	9	4	44.4%
2	1	0	0.0%
4	3	2	66.7%
5	9	8	88.9%
6	12	2	16.7%
7	3	2	66.7%
8	16	15	93.8%
9	3	2	66.7%
10	2	2	100.0%
13	6	2	33.3%
15	7	5	71.4%
16	5	3	60.0%
17	4	1	25.0%
18	1	1	100.0%
19	8	5	62.5%
20	11	10	90.9%
21	1	1	100.0%
22	5	3	60.0%
23	3	2	66.7%
24	3	3	100.0%
25	1	1	100.0%
26	8	6	75.0%
27	1	0	0.0%
29	1	1	100.0%
31	2	2	100.0%
32	1	1	100.0%

POST-APPROVAL STUDY

FDA believes that a post-approval study is necessary for this first of a kind left ventricular assist device with life-sustaining capabilities if the Thoratec HeartMate II is approved. The sponsor has recognized that a post-approval study is necessary and has proposed that subjects for this study be recruited from the Interagency Registry of Assisted Circulatory Support (INTERMACS), which, as of July 24, 2007, was comprised of patients from 81 transplant centers that voluntarily joined the registry. They propose to enroll the first 50 patients who give their consent for inclusion in the INTERMACS registry and meet the indications for and receive the device. Since the registry is voluntary, patients can refuse to have their data collected by INTERMACS even if they receive an FDA-approved durable (i.e., hospital dischargeable) ventricular assist device.

The sponsor is working interactively with the FDA on the development of the hypothesis and the justification for the study sample size for the post-approval study.

The primary objectives of the proposed study are to: (1) assess patient outcome with respect to transplant, death, and explant for recovery; and (2) obtain information about rehospitalizations to assess the number of days that patients spend in the hospital.

Proposed secondary endpoints include:

- Adverse events, particularly neurologic assessment;
- Clinical reliability (malfunctions/failures);
- Information on quality of life, measured by EuroQOL instrument;
- Reoperations;
- Assessment of cognitive function, measured by the Trail Making Neurocognitive Test, Part B; and
- 1 year post-explant survival.

It is proposed that patients will be followed in the registry until study outcome: transplant, death or explant for recovery with an assessment at one year post-explant. (See Section 8 for Post-Market Study Protocol)

REFERENCES

1. Frazier OH, Rose EA, Oz MC, Dembitsky W, McCarthy P, Radovancevic B, et al. Multicenter clinical evaluation of the HeartMate vented electric left ventricular assist system in patients awaiting heart transplantation. *J Thorac Cardiovasc Surg* 2001 Dec; 122(6): 1186-95.
2. El-Banayosy A, Korfer R, Arusoglu L, Kizner L, Morshuis M, Milting H, et al. Device and patient management in a bridge-to-transplant setting. *Ann Thorac Surg* 2001 Mar; 71(3 Suppl): S98-102.
3. El-Banayosy A, Arusoglu L, Kizner L, Tenderich G, Minami K, Inoue K, et al. Novacor left ventricular assist system versus Heartmate vented electric left ventricular assist system as a long-term mechanical circulatory support device in bridging patients: a prospective study. *J Thorac Cardiovasc Surg* 2000 Mar; 119(3): 581-7.
4. Di Bella I, Pagani F, Banfi C, Ardemagni E, Capo A, Klersy C, et al. Results with the Novacor assist system and evaluation of long-term assistance. *Eur J Cardiothorac Surg* 2000 Jul; 18(1): 112-6.
5. Minami K, El-Banayosy A, Sezai A, Arusoglu L, Sarnowsky P, Fey O, et al. Morbidity and outcome after mechanical ventricular support using Thoratec, Novacor, and HeartMate for bridging to heart transplantation. *Artif Organs* 2000 Jun; 24(6): 421-6.
6. Farrar DJ, Hill JD, Pennington DG, McBride LR, Holman WL, Kormos RL, et al. Preoperative and postoperative comparison of patients with univentricular and biventricular support with the Thoratec ventricular assist device as a bridge to cardiac transplantation. *J Thorac Cardiovasc Surg* 1997 Jan; 113(1): 202-9.
7. Rose EA, Gelijn AC, Moskowitz AJ, Heitjan DF, Stevenson LW, et al. Long-Term Use of a Left Ventricular Assist Device for End-Stage Heart Failure. *N Engl J Med* 2001;345: 1435-43.
8. Holman WL, Park SJ, Long JW, Weinberg A, Gupta L, et al. Infection in Permanent Circulatory Support: Experience from the REMATCH Trial. *J Heart Lung Transplant* 2004;23: 1359-65.