

DRAFT

**FDA Questions for Circulatory System Devices Panel
November 30, 2007
P060040
Thoratec HeartMate II Left Ventricular Assist System**

Evaluation of Safety and Effectiveness

The multi-center pivotal study for the HeartMate II was a single arm bridge to cardiac transplantation study that included 126 primary study cohort patients. The study would be determined successful if the one-sided 95% lower confidence limit of the true success rate exceeded 65%, the performance goal. Patients were deemed successful if they met the primary endpoint of survival to transplantation or 180 days of LVAD support while remaining transplant listed as a status 1A or 1B. The results as of September 14, 2007 showed that the lower confidence limit of success was 64.0%, thereby not meeting the success criteria.

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	# 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%

- 1. Please provide your clinical and/or statistical interpretation of the results from the HeartMate II study and whether the results demonstrate a reasonable assurance of effectiveness even though the data did not meet the performance goal.**

The causes of deaths and serious adverse events for the Primary Study Cohort are shown in Tables 3 and 4 in the FDA's executive summary as well as Sections 7.5.7.3 and 7.5.8 in the panel package.

- 2. Please provide your clinical and/or statistical interpretation of the results as to whether any class of serious adverse events (i.e., Infection, Bleeding, or Neurological Event) raises clinical concerns for a left ventricular assist device in bridge-to-transplant patients.**

The small patient cohort group included patients with a body surface area (BSA) $< 1.5 \text{ m}^2$ and $\geq 1.2 \text{ m}^2$, thus allowing the device to be implanted in smaller-sized patients who met all other inclusion and exclusion criteria. Seven (7) small BSA patients were enrolled during the multi-center pivotal study and eight (8) small BSA 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 follow-up dataset. Seven (7) small BSA patients met the pre-specified primary endpoint.

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			
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%

3. Please provide your clinical and/or statistical interpretation of the results for the small patient cohort with a body surface area (BSA) $< 1.5 \text{ m}^2$ and $\geq 1.2 \text{ m}^2$ and discuss whether the results from the Primary Study Cohort can be extrapolated to the small BSA patients. If not, please discuss what concerns that you may have.

Labeling

One aspect of the pre-market evaluation of a new product is the review of its labeling. The labeling must include which patients are appropriate for treatment, identify potential adverse events with the use of the device, and explain how the product should be used to maximize clinical benefit and minimize adverse events. If you recommend approval of the device, please address the following question regarding product labeling.

The proposed indication for use of this device: “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 intended for use both inside and outside the hospital, or for transportation of 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 m^2 .

4. **With regard to the indications for use, labeling, and clinical data, please comment on the following:**
 - a. **Please comment as to whether the indications for use adequately reflect the HeartMate II study's patient population and for which the device may be marketed.**
 - b. **Please discuss whether the device should be contraindicated for patients with $BSA < 1.3 \text{ m}^2$, or if the decision to implant the device should rather be based on an individualized assessment of body habitus and device fit.**
5. **Please discuss whether you think that additional warnings, precautions, or contraindications should be included in the labeling to assist practitioners in using the HeartMate II. For example, please comment on the use of anticoagulation given that the device is an axial flow pump.**

Post-Approval Study

The sponsor has proposed to use the Interagency Registry of Mechanical Assisted Circulatory Support (INTERMACS) as the vehicle to collect post-market data on the HeartMate II. The sponsor proposes to include in the post-approval study the first fifty (50) patients who give their consent for inclusion in the INTERMACS registry. The rate of survival to transplantation, rate of death, and rate of explant for recovery along with the frequency of adverse events, clinical reliability (rates of device malfunction or failure), improvement in function and quality of life as measured by directional trends, and assessment of general cognitive function will be compared to results from the clinical trial. Patients will be followed in the registry until study outcome: transplant, death or explant for recovery with an assessment at one year post-explant.

As of September 2007, 334 patients were enrolled in that registry, from 81 sites, and 18 additional sites were pending.

6. **With regard to the post-approval study, please comment on the following:**
 - a. **Based on the clinical data provided in the panel pack, please comment on the design of the post-approval study proposed by the sponsor. Is follow-up of 1 year post-transplant with data collection for adverse events and functional assessments appropriate?**
 - b. **Please comment on whether there should be a separate subgroup analysis for women. In addition, please comment on whether any other subgroup analyses should be performed.**

In the pre-market study, success was defined as patients either transplanted or supported with the device for at least 180 days while remaining transplant listed with status 1A or 1B. The HeartMate II was prospectively determined to be successful if the one-sided 95% lower confidence limit of the true success rate exceeded 65%.

- c. Please comment on whether or not this success criterion for device effectiveness is adequate for a post-approval study or if instead it would be better to utilize a concurrent control group in order to assess post-market effectiveness.**

The sponsor proposes to use the Trail Making Neurocognitive Test, Part B to assess Neurocognitive function in the post-approval study.

- d. Please comment on whether that test is adequate to assess neurocognitive function or a complete battery of neurocognitive tests including the 5 cognitive domains should be administered.**