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HeartMate II® Pivotal Clinical Trial Fact Sheet

Pivotal Clinical Trial Overview:

The Thoratec® HeartMate II Left Ventricular Assist System (LVAS) pivotal clinical trial incorporated a number of unique elements, including the use of the device for both Bridge-to-Transplantation (BTT) and Destination Therapy (DT). This was the first time the FDA approved a clinical trial with both indications in one protocol.

BTT Study: The BTT pivotal clinical trial was a non-randomized trial in which all subjects received the HeartMate II LVAS and were compared to an objective performance criterion (OPC). Study enrollment ended with FDA approval in April 2008.

DT Study: The DT pivotal clinical trial was a prospective, randomized evaluation of the HeartMate II LVAS. Patients were randomly assigned to treatment with the HeartMate® XVE LVAS (control group) or to treatment with the HeartMate II LVAS. The DT arm of the study initially involved 200 patients in its primary cohort at up to 38 sites, randomizing the HeartMate II LVAS to the HeartMate XVE LVAS on a 2-1 basis, respectively. After enrollment of the initial 200 patients, hundreds more have been enrolled as part of a continued access protocol.

Primary Study Objectives:

- To determine the safety and efficacy of the HeartMate II LVAS as a BTT in advanced heart failure patients who were cardiac transplant listed but at imminent risk of dying.
- To determine the safety and efficacy of the HeartMate II LVAS as DT in advanced heart failure patients who did not qualify for cardiac transplantation.

Study Population:

BTT Patients—Enrollment for BTT was limited to transplant-listed, advanced heart failure patients. The patients also had to meet specific inclusion and exclusion criteria.

DT Patients—The HeartMate II LVAS was implanted in patients who were not candidates for cardiac transplantation and met specific inclusion and exclusion criteria. The criteria of the trial allowed the DT arm to enroll patients who were not yet as ill as those in the original REMATCH trial, even providing

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for inclusion of some late-stage New York Heart Association (NYHA) Class IIIB heart failure patients.

Both the BTT and DT arms allowed for hospital discharge, based on the patient's condition.

Primary Endpoints:

- The primary outcome measure for the HeartMate II BTT trial was the rate of survival to transplantation or 180 days.
- The primary endpoint of the HeartMate II DT trial was a composite two-year endpoint that, includes patient survival, disabling stroke, and device durability.

Special Considerations:

- The DT protocol also included a separate study group of small patients who, because of their body size, could not be randomized to the larger HeartMate XVE LVAS. These patients may have received the HeartMate II device without randomization.
- Cross-over patients were allowed in the trial, enabling DT patients that were supported by Thoratec's HeartMate XVE LVAS to be implanted with the HeartMate II device on an elective basis in the event of the need for device replacement.

Trial Timeline:

- Pilot Trial: The pilot trial for the HeartMate II LVAS began in November 2003 and consisted of 46 study patients at 15 centers. The pilot trial featured encouraging early results, including 11 patients supported for more than one year and three patients supported for more than two years.
- Pivotal Trial: The HeartMate II LVAS pivotal clinical trial was approved by FDA on Feb. 18, 2005, and successfully enrolled patients at a record pace.
- Conformité Européenne (CE) Mark: The HeartMate II LVAS received European CE Mark in November 2005, allowing for commercial sale of the device in Europe.
- Pre-Market Approval: In December 2006, Thoratec completed the submission of a Pre-Market Approval (PMA) seeking approval for a bridge-to-transplantation (BTT) indication.
- FDA Approval: In April 2008, Thoratec received FDA approval for the commercialization of HeartMate II in the U.S. as Bridge-to-Transplantation.
- In April 2009, Thoratec filed a PMA Supplement to provide data on adjunctive cohorts totaling an additional 409 patients, including those who had originally been supported by an XVE who elected to receive a HeartMate II based on the need for device replacement.
- As of July 24, 2009, enrollment in the DT arm reached 795 patients. In total, 1,149 patients were enrolled in the pivotal trial, by far the largest VAD study ever conducted.

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- FDA Approval: In January 2010, Thoratec received FDA approval for the commercialization of HeartMate II in the U.S. as Destination Therapy (i.e. long-term support for patient ineligible for cardiac transplantation).

Outcomes:

BTT: The BTT Pivotal Clinical Trial results were published in the *Journal of the American College of Cardiology* by HeartMate II investigators Francis D. Pagani, MD, PhD, Leslie W. Miller, MD, Stuart Russell, MC, et al. As of July 2009, actuarial survival of 281 patients observed in a prospective, multi-center study (based on Kaplan-Meier analysis) was 82% at six months, 73% at 12 months, and 72% at 18 months. The conclusion: a continuous-flow LVAD provides effective hemodynamic support for at least 18 months in patients awaiting transplantation, with improved functional status and quality of life.[1]

Note: The BTT Post-Approval Study, which was published in the *Journal of the American College of Cardiology* by Randall C. Starling, MD, MPH, Yoshifumi Naka, MD, Andrew J. Boyle, MD, et al, included 169 patients across 77 institutions. Post-approval study data demonstrated 91% survival at six months and 85% survival at one year.[2]

DT: The DT arm of the Pivotal Clinical trial was published in the *New England Journal of Medicine* by HeartMate II investigators Mark S. Slaughter, MD, Joseph G. Rogers, MD, Carmelo A. Milano, MD, et al. Treating patients with HeartMate II leads to dramatically improved survival (68 and 58 percent at one and two years, comparing favorably to data on patients managed on medical management alone), functional capacity (80% restored to and maintained at Class I or II at two years; doubling in six-minute walk test) and substantial improvement in quality of life unequaled by any other heart failure therapy.[3]

Note: The latest multicenter results with HeartMate II for destination therapy demonstrate 75% survival at one year.[4]

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[1] *Journal of American College of Cardiology, Pagani, MD, PhD; et. al. - Volume 54, Issue 4, Pages 312-321 (21 July 2009)*

[2] *Results of the Post-U.S. Food and Drug Administration-Approval Study With a Continuous Flow Left Ventricular Assist Device as a Bridge to Heart Transplantation; Journal of American College of Cardiology; R. Starling, Y. Naka, A. Boyle, G. Gonzalez-Stawinski, R. John, U. Jorde, S. Russell, J. Conte, K. Aaronson, E. McGee; 2011; 57-1890-1898, doi:10.1016/j.jacc2010.10.062*

[3] *NEJM 10.1056/NEJMoa0909938, Slaughter MS, Rogers JG, Milano CM, et al. Advanced Heart Failure Treated with Continuous-Flow Left Ventricular Assist Device*

[4] *Park SJ, et al. Outcomes in Advanced Heart Failure Patients with Left Ventricular Assist Devices for Destination Therapy. Circulation Heart Failure. 2012.*

Product: The HeartMate II is a mechanical circulatory support (MCS) device intended for a broad range of advanced-stage heart failure patients. An axial flow device, the HeartMate II can pump up to 10 liters of blood per minute, the full output of a healthy heart, and is designed to provide long-term cardiac support. The device is implanted alongside a patient's native heart and is designed to supplement or take over the pumping function of the weakened heart's left ventricle. It is easier to implant than prior devices, and with only one moving part, the HeartMate II is designed to provide exceptional reliability and improved patient quality of life. The device is designed to have a much longer functional life than the previous generation of devices and to operate more simply and quietly.

In total, more than 18,000 patients have been implanted with HeartMate II through trial enrollment and commercial use worldwide.[5]

DEVICE	REGION	STATUS
HeartMate II LVAS	• United States	• Bridge-to-Transplantation – Received FDA approval in April 2008. • Destination Therapy – Received FDA approval in January 2010.
	• Europe	• Authorized to bear the Conformité Européenne (CE) Mark in November 2005.

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[5] Thoratec data on file