SUMMARY OF SAFETY and EFFECTIVENESS

(Draft 10-Jan-2002)

General Information

Device Generic Name:	Ventricular assist system
Device Trade Name:	HeartMate® VE LVAS
Applicant's Name and Address:	Thoratec Corporation 6035 Stoneridge Drive Pleasanton, CA 94588
PMA Number:	P920014/S016
Date of Panel Recommendation:	*(to be completed by FDA)*
Date of Notice of Approval to the Applicant:	*(to be completed by FDA)*

This device was originally approved in its pneumatic powered configuration on September 30, 1994, as a bridge to transplantation in cardiac transplant candidates. The electrically powered configuration was approved on September 29, 1998 for the same indication under PMA supplement P920014/S007. The sponsor has submitted this supplement for the HeartMate VE LVAS to expand its use to patients who are ineligible for cardiac transplantation.

The preclinical tests that apply to this device were presented in the original application and are not repeated here. For information on the data that were used to support the original device configuration, the summary of safety and effectiveness for the original PMA should be referenced. Written requests for copies can be obtained from the Dockets Management Branch (HFZ-305), Food and Drug Administration, 12420 Parklawn Drive, Rm. 1-23, Rockville, MD 20857, under Docket 94M0404, or through the Internet at http://www.fda.gov\cdrh\pmapage.html.

Indications for Use

The HeartMate VE LVAS is indicated for use as a bridge to transplantation in cardiac transplant candidates at risk of imminent death from nonreversible left ventricular failure. The HeartMate VE LVAS is also indicated for use in patients with end-stage left ventricular failure who are ineligible for cardiac transplantation. The HeartMate VE LVAS is intended for use both inside and outside the hospital.

Contraindications

The patient is considered unsuitable for implant of the VE LVAS if his/her body surface area is less than 1.5 m^2.

Warnings and Precautions

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

Device Description

The HeartMate® VE LVAS (hereafter referred to as VE LVAS) consists of an implanted blood pump, external System Controller and external power supply components. The blood pump, or Left Ventricular Assist Device (LVAD), is a pusher-plate type device that is capable of producing a stroke volume of 83 ml, generating up to 10 liters of blood flow per minute at a beat rate up to 120 beats per minute.

The pump consists of a rigid titanium housing divided in half by a flexible diaphragm. One half functions as the blood chamber, while the opposite half serves as a chamber for the electric motor and rotating cam. This motor chamber is connected to the external control and power components via a Percutaneous Tube. Displacement of the diaphragm by rotation of the cam results in pumping of the blood.

The VE LVAS used in the clinical study supporting this PMA supplement is the same device that has been in commercial use as a bridge to transplant under PMA P920014 / S07 (September, 1998).

Alternative Practices or Procedures

Patients in end-stage heart failure are treated primarily via two treatment modalities, pharmacologic therapy (including digoxin, ACE inhibitors, diuretics and inotropes) and cardiac transplantation. Both treatments have limitations. Pharmacologic therapy is only palliative and improves short-term survival for patients in moderate to severe heart failure. Cardiac transplantation is limited to the number of organs available and criteria for being a transplant candidate. For patients that are considered non-transplant candidates due to comorbidities or age, pharmacologic therapy is currently the only non-investigational treatment option.

Marketing History

To date, over 1,600 HeartMate VE pumps have been implanted worldwide. One hundred thirty six institutions have been trained to implant the VE LVAS in the United States, Canada, Australia, the European Economic Area, Asia, India, Middle East and South America. The VE LVAS has been distributed on a commercial basis in the United States since September 29, 1998 for use as a bridge to cardiac transplantation. The VE LVAS has not been removed from any of the countries listed above for any reasons related to the safety and effectiveness of the device.

Adverse Events

Table 1 presents the number of patients, percent of patients and the total number of events for each adverse event observed in the REMATCH (Randomized Evaluation of Mechanical Assistance in the Treatment of Congestive Heart failure) study, comparing patients treated with the HeartMate VE LVAS with those treated with optimal medical management (OMM). Adverse events were defined as any observations that may have a deleterious effect on the patient. Adverse Events were classified as serious if they resulted in a fatality, were life threatening, resulted in permanent disability, required hospitalization or prolonged a hospital stay. Due to differences in survival between the two treatment groups, the serious adverse events are presented in Table 2 as event rates (number of events per 100 patient days) in an effort to normalize the data based on patient longevity. As shown in Figure 1, the majority of serious adverse events occurred during the perioperative period for the LVAS patients. Once the LVAS patients recovered from implantation surgery, most adverse event rates were comparable to those observed in the OMM patients.

No new adverse events were observed in the REMATCH study that have not occurred in previous bridge to transplant studies with the LVAS. However, since the adverse event definitions in the REMATCH study differed from those used in the previous studies, the incidences could not be directly compared.

Table 1. Adverse Events, Regardless of Severity

	LVAS (n=67)					OMM (n=61)				
	# pts[a]	% pts	UCL[b]	LCL[c]	Events[d]	# pts[a]	% pts	UCL[b]	LCL[c]	Events[d]
Neurologic Dysfunction	28	42%	50%	33%	40	4	7%	11%	2%	4
Bleeding	22	33%	41%	25%	43	2	3%	6%	0%	2
Local Infection	44	66%	74%	58%	97	21	34%	43%	26%	32
Sepsis	29	43%	52%	35%	41	9	15%	21%	8%	11
Thromboembolic Event[e]	10	15%	21%	9%	10	2	3%	6%	0%	2
Cardiac Arrest requiring defibrillation	3	4%	8%	1%	6	4	7%	11%	2%	7
Sustained ventricular arrhythmia	18	27%	34%	19%	21	13	21%	29%	14%	21
Supraventricular arrhythmia	17	25%	33%	18%	23	5	8%	13%	3%	6
Syncope	3	4%	8%	1%	3	4	7%	11%	2%	5
Perioperative Myocardial Infarction	0	0%	0%	0%	0	0	0%	0%	0%	0
Non-periop Myocardial Infarction	2	3%	6%	0%	2	1	2%	4%	0%	1
Renal Failure	21	31%	39%	23%	23	6	10%	15%	4%	6
Chronic Renal Dysfunction	0	0%	0%	0%	0	0	0%	0%	0%	0
Hepatic Dysfunction	3	4%	8%	1%	3	0	0%	0%	0%	0
Psychiatric Episode	15	22%	30%	15%	18	3	5%	9%	1%	3
LVAD Related Adverse Events										
LVAD Related Right Heart Failure	10	15%	21%	9%	11					
Perioperative Bleeding	28	42%	50%	33%	32					
Percutaneous or Pocket Infection	29	43%	52%	35%	46					
Pump housing, Inflow, or Outflow Infection	13	19%	26%	13%	16					
Device Thrombosis	7	10%	16%	5%	7					
LVAD Failure	2	3%	6%	0%	2					
Confirmed Device Malfunction	25	37%	46%	29%	70					

[a] # Pts = number of patients who experience event
[b] UCL = upper 95% Confidence Limit
[c] LCL = lower 95% Confidence Limit
[d] Events = total number of events reported
[e] TE does not include events resulting in neurologic dysfunction

Table 2. Serious Adverse Event Rates per 100 Patient Days

Event	LVAS (n=67)	OMM (N=61)	Risk Ratio	P[a]
	events / 100 pt days	events / 100 pt days	(95% Confidence Limits)	
Total Follow Up (days)	18411	11841		
All Serious Adverse Events	1.66	0.73	2.29 (1.80 – 2.91)	< 0.0001
Neurologic Dysfunction	0.12	0.03	3.54 (1.22 - 10.27)	0.0145
Bleeding	0.16	0.02	9.65 (2.31 - 40.38)	<0.0001
Localized Infection	0.12	0.07	1.85 (0.83 – 4.14)	0.1437
Sepsis	0.14	0.08	1.61 (0.77 – 3.35)	0.2281
Thrombembolic Event	0.04	0.02	2.25 (0.47 - 10.84)	0.4971
Cardiac Arrest requiring Defibrillation	0.03	0.05	0.54 (0.15 – 1.76)	0.3586
Sustained ventricular arrhythmia	0.06	0.10	0.59 (0.26 – 1.33)	0.2068
Sustained supraventricular arrhythmia	0.03	0.03	1.29 (0.32 – 5.14)	1.0000
Syncope	0.01	0.00	----	0.5236
Perioperative Myocardial Infarction	0.00	0.00	----	----
Non-perioperative myocardial infarction	0.01	0.00	----	1
Renal Failure	0.05	0.04	1.29 (0.44 – 3.76)	0.7938
Chronic Renal Dysfunction	0.00	0.00	----	----
Hepatic Dysfunction	0.01	0.00	----	1.0000
Psychiatric Episode	0.02	0.01	1.93 (0.20 - 18.55)	1.0000
LVAS EVENTS				
LVAS Related Right Heart Failure	0.05			
Perioperative Bleeding	0.13			
Percutaneous site or pocket infection	0.11			
Pump housing , inflow or outflow tract infection	0.06			
Device Thrombosis	0.02			
Confirmed Device Malfunction	0.10			
LVAS System Failure	0.01			

[a] Fisher Exact Test (2-tailed)

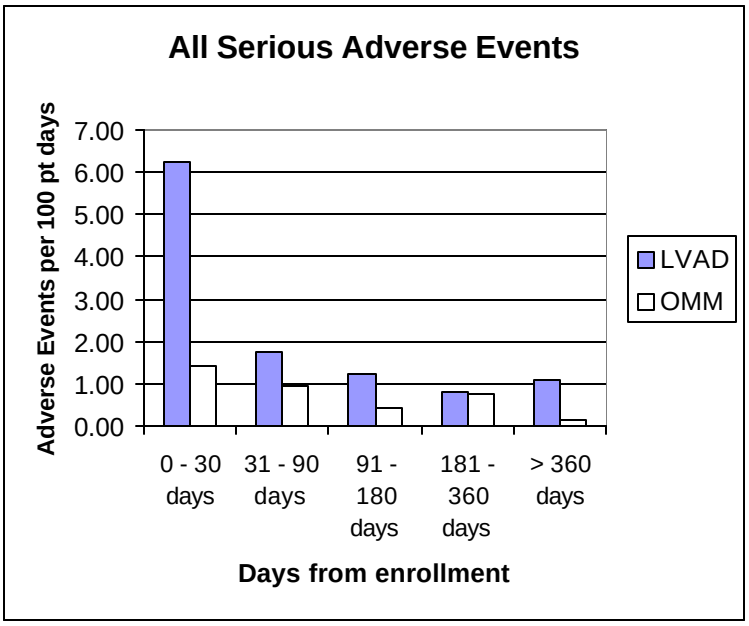


Figure 1. Summary of Serious Adverse Events Over Time

Summary of Pre-Clinical Studies

Non-clinical laboratory studies presented in the Summary of Safety and Effectiveness for the original PMA of the pneumatic device (P920014) and the vented electric device configuration (P920014/S007) are equally applicable to use of the HeartMate VE LVAS in patients who are ineligible for cardiac transplantation.

Reliability: Based on *in vitro* testing to a confidence interval of 90%, there is 98% chance that this device will be free of critical failures at two (2) months of use, an 88% chance that this device will be free of critical failures at one (1) year of use, and a 76% chance that this device will be free of critical failures at two (2) years of use. The mean-time-to-failure (MTTF) for the device is estimated to be 3.1 years at the 90% confidence interval.

Summary of Clinical Study

Study Objectives

REMATCH is an acronym for Randomized Evaluation of Mechanical Assistance in the Treatment of Congestive Heart failure. This study was conducted by a cooperative agreement between Thoratec Corporation, the National Institutes of Health (NIH) and Columbia University. The overall purpose of the REMATCH study was to evaluate the efficacy and safety of the VE LVAS versus optimal medical management (OMM) in the treatment of end-stage heart failure. The primary objective of the study was to determine the effect of the VE LVAS on all-cause mortality in patients with end-stage chronic heart failure who are on OMM and are not candidates for cardiac transplantation. Adverse events and the incidence of device malfunction

and failure were also documented in LVAS patients. A number of secondary objectives were evaluated during the REMATCH study, including a comparison of the functional status, quality of life, days alive and out of hospital, and the incidence of cardiovascular mortality between the two groups.

Study Design

The study was a multi-center, non-blinded, randomized study in which eligible patients were randomized to treatment with the VE LVAS or to OMM in a 1:1 ratio. The randomization was stratified by center and blocked to ensure approximately equal numbers of patients per arm at each center over time. The block sizes were selected at random to prevent centers from manipulating the treatment assignment. The goal was to enroll up to 140 patients in the study until the study endpoint of the 92nd death was reached. Three interim analyses were performed (every 23 deaths) and the results were reviewed by the Data Safety Monitoring Board (DSMB). The DSMB meetings were closed meetings and the interim analysis results were not divulged beyond the DSMB members.

A baseline assumption was drawn from review of the scientific literature suggesting that the 2-year mortality rate for patients receiving medical management is approximately 75%. Therefore it was hypothesized that use of the LVAS would reduce this rate by a third to 50% or more. This is a minimal clinically significant effect in that patients and surgeons may not be willing to adopt the LVAS with its invasive surgery and subsequent risks and discomforts unless all-cause mortality over 2-years was reduced by one third or more. To ensure that the OMM mortality had not been overestimated, and to ensure at least 80% power, mortality rates of 60% in the OMM and 40% in the LVAS were used (1/3 reduction). Using these more conservative rates and assuming that survival is roughly exponential, the hazard ratio for LVAS to OMM is 0.56. To detect a difference of this magnitude with 80% power in a Logrank test, a total of 92 deaths are needed.

The primary objective of the study was to determine the effect of LVASs on all-cause mortality. This was analyzed using the product-limit method of Kaplan and Meier. Differences in survival distributions between patients supported with an LVAS and those receiving only OMM were compared using Logrank analysis. Data were analyzed based on intention-to-treat.

The study was powered to determine the efficacy of the device for this intended purpose and not safety. Safety of the device was well established in the bridge to transplant population. However, the incidence of adverse events experienced by patients supported with an LVAS and OMM patients were reported. Additional secondary objectives included the quality of life between the LVAS and OMM patients, functional status and rehospitalizations.

Patient Population

The patients enrolled into the REMATCH study were patients who were in end stage heart failure and ineligible for a heart transplant due to either advancing age, a significant co-morbidity or renal dysfunction. All study candidates were screened to meet the specific study inclusion and exclusion criteria. A total of 968 patients were screened from April 29, 1998 to

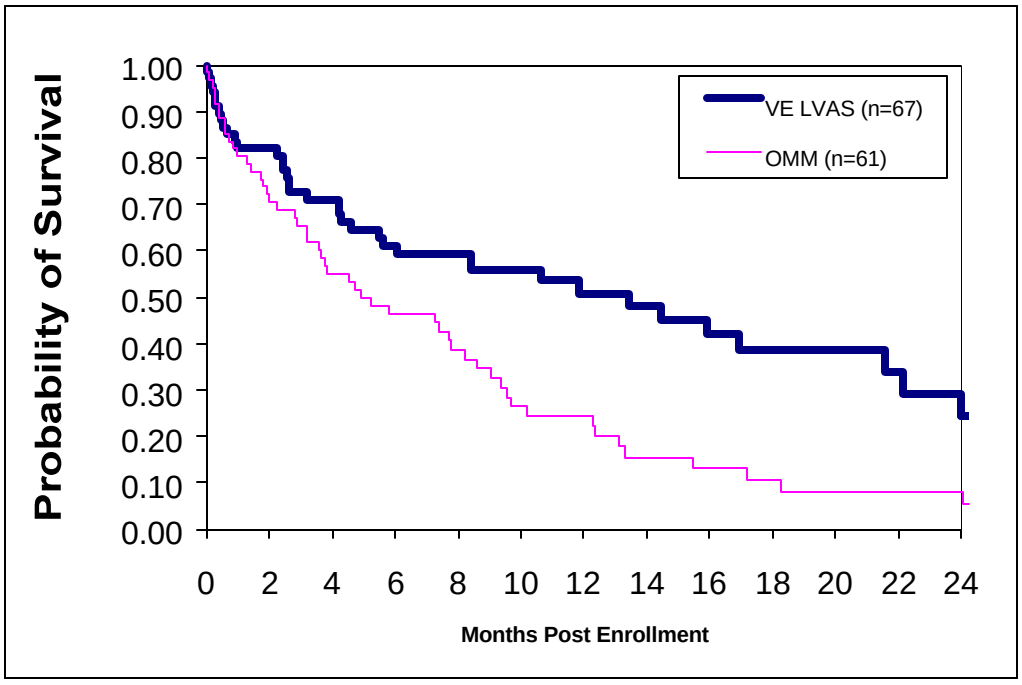
June 25, 2001 to yield the total of 128 enrolled into the study at 21 investigational centers in the United States. Of the 128 patients enrolled, 67 patients were randomized to the LVAS and 61 patients were randomized to OMM. All patients were followed for two years, or until death or withdrawal from the study, whichever occurred first. For those patients in either group who survived after two years, only mortality and explant data were collected, including autopsy and adverse events identified at explant/autopsy.

Study Results – Primary Safety and Effectiveness

The Kaplan-Meier analysis (see Figure 2) showed a 46% reduction in the risk of all cause mortality over two years in the LVAS group (risk ratio = 0.54; p = 0.003). The probability of surviving one year (± standard error) was 50.8 ± 6.7% for the LVAS arm and 24.4 ± 5.9% for OMM patients. Predicted two year survival was 24.2 ± 8.1% for LVAS patients and 8.0 ± 4.1% for OMM patients. Median survival was 408 days for LVAS patients and 150 days for OMM patients. The causes of death are summarized in Table 3.

The Kaplan-Meier analysis conclusively proves the efficacy of the HeartMate VE LVAS in reducing all-cause mortality in patients with end-stage chronic heart failure who are receiving optimal medical management and are not candidates for cardiac transplantation.

Figure 2. Kaplan-Meier plot illustrating the probability of survival, VE LVAS versus Optimal Medical Management. Logrank analysis: P=0.003



VE LVAS						
	Time Interval (Months)					
	0 - 1	1 - 3	3 - 6	6 - 12	12 - 18	18 - 24
Number of patients starting interval	67	54	46	36	19	11
Number of patients who died during this interval	12	6	7	5	4	3
Number of cumulative patient deaths	12	18	25	30	34	37
Number of patients censored[1] in interval	1	2	3	12	4	3
Number of cumulative censored[1] patients	1	3	6	18	22	25
Probability of surviving interval	0.819	0.726	0.613	0.508	0.387	0.242
+/- 95% Confidence Limit at end of interval	0.09	0.11	0.12	0.16	0.18	0.18
Optimal Medical Management						
	Time Interval (Months)					
	0 - 1	1 - 3	3 -6	6 - 12	12 - 18	18 - 24
Number of patients starting interval	61	49	38	27	11	4
Number of patients who died during this interval	12	9	11	11	6	1
Number of cumulative patient deaths	12	21	32	43	49	50
Number of patients censored[1] in interval	0	2	0	5	1	0
Number of cumulative censored[1] patients	0	2	2	7	8	8
Probability of surviving interval	0.803	0.653	0.464	0.244	0.106	0.080
+/- 95% Confidence Limit at end of interval	0.10	0.12	0.13	0.13	0.10	0.09

[1] Censored patients are those who remain alive at the time of analysis (6/28/01)
5 LVAD pts survived beyond 24 months (2 ongoing at 24.5 and 30 months, 3 expired at 24.7 25.7 and 25.9 months).
3 OMM pts survived beyond 24 months (1 ongoing at 26.1 months, 2 expired at 24.0 and 24.8 months).

Table 3. Summary of Causes of Death

Cause of Death	LVAS (N=67)	OMM (N=61)
Cardiac Related		
LV Dysfunction	2	49
Acute MI, documented	0	0
Acute myocardial ischemia or suspected MI	0	1
Cardiac Procedure	0	1
LVAD Failure	2	0
Other Cardiovascular	4	0
Unknown Cause	3	0
Subtotal Cardiac Related	***11***	***51***
Non-Cardiac Related		
Cerebrovascular Disease	4	0
Aortic, mesenteric, renal or peripheral vascular disease	0	0
Pulmonary Embolism	2	0
Sepsis	17	1
Bleeding	1	0
Other, Non-cardiovascular	5	0
Subtotal Non-Cardiac	***29***	***1***
Total, all deaths	***40***	***52***

Table 1 presents the number of patients, percent of patients and the total number of events for each anticipated adverse event in the REMATCH study. There were no unanticipated adverse events. Rates of serious adverse events and the incidence of adverse events over time are presented in Table 2 and Figure 1, respectively. Overall,

- No new adverse events occurred that have not been observed in previous bridge to transplant studies.
- The incidence of serious adverse events was 2.74 times as likely to occur to LVAS patients as OMM patients. This, however, did not impact the LVAS patient's survival, functional status or quality of life.
- Confirmed device malfunctions occurred at a rate of 0.10 events / 100 patient days and LVAS failures occurred at a rate of 0.01 events / 100 patient days. There were a total of 2 LVAS failures that occurred in the study.
- The majority of the adverse events in the LVAS patients occurred within the first 30 days of implantation. Thereafter, adverse events rates were comparable between the LVAS and the OMM patients.

Study Results – Secondary Objectives

The secondary objectives that were studied in both treatment groups included quality of life, functional status, days alive and out-of-hospital, and cardiovascular mortality. These data were compared between the LVAS and OMM groups. In summary,

- The quality of life between the two groups was significantly improved in the LVAS patients as evidenced by the Minnesota Living with Heart Failure score, the Becks Depression Inventory score, EuroQOL, and SF36 physical function scores. LVAS patients, despite major heart surgery and increased adverse event rates, demonstrated improved quality of life as compared to baseline scores and achieved improved quality of life when compared to OMM patients in domains that measure general health, physical functioning and depression.

- The functional status, as measured by the NYHA class was significantly improved in the LVAS patients as compared to the OMM patients. Within one month, the LVAS patients had statistically improved functional status, which was maintained through month 12. After month 12 the sample sizes were too small for calculation of meaningful statistical comparisons.

- LVAS patients lived longer and had more days out-of-hospital than the OMM patients.

- Cardiovascular mortality was significantly reduced in the LVAS patients compared to the OMM patients.

Conclusions Drawn from the Studies

Preclinical *in vitro* and *in vivo* studies in the original PMA and its supplements demonstrated that the LVAS is reliable, biocompatible, sterile, non-pyrogenic, able to perform within the design specifications, and that the design meets the intended user requirements.

The analysis of the REMATCH clinical study data indicates a statistically significant survival advantage for patients supported with an LVAS as compared to patients treated with OMM. This significant (P=0.0012) survival advantage in conjunction with the improvement in Quality of Life and functional status outweighs the risks associated with the adverse events.

Panel Recommendation

(To be completed by FDA)

FDA Decision

(To be completed by FDA)

Approval Specifications

(To be completed by FDA)

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