FDA Executive Summary

Prepared for the
April 25, 2012 meeting of the
Circulatory System Devices Panel
P100047
HeartWare Ventricular Assist System
HeartWare, Inc.

INTRODUCTION

This is the Food and Drug Administration (FDA) Executive Summary for the HeartWare Ventricular Assist System (VAS). This device includes an implantable, centrifugal flow, rotary blood pump with an external driver and power source(s). It is intended for use as a bridge to cardiac transplantation (BTT) in patients who are at risk of death from refractory, end-stage heart failure. The HeartWare VAS is designed for in-hospital and out-of-hospital settings, including transportation via fixed wing aircraft or helicopter. A clinical trial to study the device was approved by FDA on April 30, 2008 under IDE G070199. This is the first left ventricular assist device (LVAD) trial for which data from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) is being used as a contemporaneous control. HeartWare, Inc. (the Sponsor) submitted a premarket approval (PMA) application (P100047) for the device on December 27, 2010. This submission has been reviewed by the Division of Cardiovascular Devices (DCD) within the Center for Devices and Radiological Health (CDRH) of the FDA.

This memorandum summarizes FDA's review of the PMA and highlights the particular areas for which we are seeking your input. These topics include the safety and effectiveness profile of the device as demonstrated by the results of the clinical study conducted by the Sponsor, including a comparison of its benefit to risk profile to data in a registry of currently marketed devices for the same indication.

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1. PROPOSED INDICATIONS FOR USE

The HeartWare VAS is intended for use as a bridge to cardiac transplantation (BTT) in patients who are at risk of death from refractory end-stage heart failure. The HeartWare VAS is designed for in-hospital and out-of-hospital settings, including transportation via fixed wing aircraft or helicopter. The device is contraindicated in patients with a body surface area (BSA) of less than 1.2 m^2.

2. DEVICE DESCRIPTION

Implanted components of the HeartWare VAS include the pump (which includes an integrated inflow cannula), an outflow conduit, a percutaneous driveline, and an apical sewing ring. The HeartWare ventricular assist device (HVAD) pump is a continuous flow blood pump which utilizes magnetic and hydrodynamic forces to elevate and rotate the impeller. Once power is applied to the device, there are no points of mechanical contact between the impeller and the body of the pump. An exploded view of the pump is shown below.

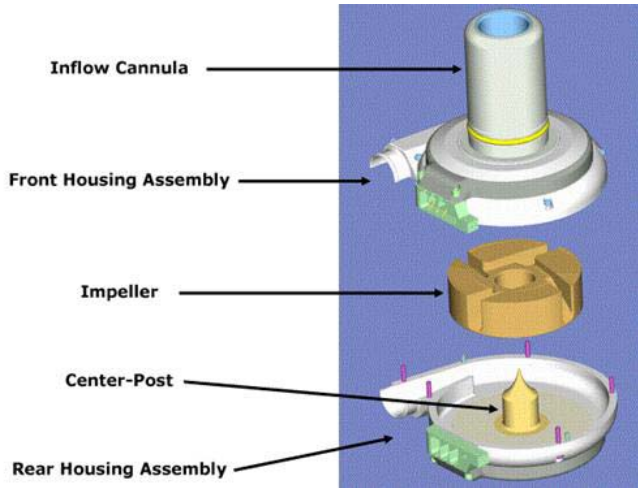


Figure 1. HVAD pump exploded view

The pump displaces 50mL of blood, weighs 160g, and is capable of pumping up to 10 liters per minute (L/min) of blood. It is designed to be implanted entirely in the pericardial space, obviating the need for an abdominal pocket.

Surgical tools include an apical coring tool, tunneler, sewing ring wrench, hex driver, inflow cap, and driveline cover.

External components include the controller, monitor, battery charger, battery packs, AC and DC adapters, driveline extension cable, serial communication cable, universal serial bus (USB) flash drive, patient carry pack and shower bag.

The controller manages the HVAD pump operation and is depicted on the following page. A light emitting diode (LED) screen displays real time pump parameters including

power, speed and flow estimation as well as alarm conditions. The percutaneous driveline connects the pump to the controller. The controller is intended to always be connected to two power sources for safety (2 batteries or 1 battery and an AC adapter or DC adapter (car adapter)). Each battery contains lithium ion cells that, when fully charged, can power the HVAD pump for approximately 4 to 6 hours. The batteries are expected to have a useful operating life of greater than 250 charge and discharge cycles.

Figure 2: HeartWare VAS controller

There have been several modifications to the system throughout the IDE study, and also after study completion. The following significant changes were made to the HeartWare VAS after study enrollment had completed: the addition of a sintered inflow cannula, a controller software update, hardware upgrades to the device controller and monitor, modifications to the driveline, battery pack and associated charging unit, introduction of driveline splice and sheath repair kits, addition of the shower bag, a change in the apical coring tool diameter, addition of a USB key, addition of an electrostatic discharge (ESD) shield, and addition of the air travel claim. Other more minor changes were submitted to FDA under 5-day notices or annual reportable changes. The final device design has undergone pre-clinical testing as outlined in Section 4.

Please see the Sponsor's executive summary for further details regarding the system components.

FDA Comment: In general, FDA does not have significant concerns regarding any of these changes. However, the impact of these changes on the poolability of the results is not clear since the Sponsor has not presented (and FDA did not request) any subgroup analyses based upon any of the above modifications.

3. REGULATORY HISTORY

The Sponsor's first discussions with FDA regarding the HeartWare VAS took place in 2004. Since that time FDA has reviewed multiple regulatory submissions related to this device. A summary of the major regulatory interactions follows below.

3.1 Pivotal BTT Trial

The Sponsor received approval of Investigational Device Exemption (IDE) G070199 for the clinical study of the HeartWare VAS as a bridge to cardiac transplantation device on April 30, 2008. The study was approved for 150 patients at 40 sites. The last subject in this trial was enrolled on February 23, 2010.

3.2 Continued Access Protocol

In order to allow for continued access to a device when there may be a gap between trial completion and final regulatory review, sponsors have the opportunity to request additional patients who are still subject to the same patient protection measures as the IDE trial; such patients are enrolled into an "extension" of the initially approved sample size. The Sponsor submitted a continued access protocol (CAP) for continued use of the device after the last study patient was enrolled (February 23, 2010). The CAP design was based upon the pivotal study's design; the primary difference was the removal of pre-specified comparison to the comparator(s) of the main trial. As of March 14, 2012, the Sponsor is approved for 256 CAP patients. The most comprehensive CAP data that FDA has reviewed comes from mandatory annual reporting for the IDE trial and includes the cohort of patients (n=110) who have follow-up as of a database lock on February 28, 2011.

3.3 Compassionate and Emergency Use

The compassionate use (CU) and emergency use (EU) provisions allow for patients who do not meet the enrollment criteria of a clinical study to receive an investigational device if their treating physician believes the device may provide a benefit in treating and/or diagnosing their disease or condition. FDA approves CU of a device prior to patient use. However, if there is not enough time to obtain prior FDA approval, patients may be implanted emergently if they are considered to have a life-threatening or serious disease or condition with no other appropriate clinical alternative. Compassionate and emergency use cases increased under the CAP. As of March 1, 2012 a total of 36 cases were submitted to FDA. Several of these requests were for right ventricular use of the device and use in the pediatric patient population. Because of the CU and EU volume, FDA has asked the Sponsor to consider additional clinical studies to evaluate right ventricular and pediatric use of the device.

3.4 Premarket Approval (PMA) Application

The Sponsor submitted a PMA on December 27, 2010. It predominantly presents data collected during the G070199 study, but it also includes limited outside-of-United States (OUS), CAP, and compassionate and emergency use patient data. A major deficiency letter was issued to the Sponsor on May 16, 2011. The Sponsor responded to this letter on October 11, 2011.

3.5 Destination Therapy Study

In addition to the IDE study for the BTT indication, the Sponsor also received approval for an IDE to study the use of the HeartWare VAS as destination therapy (DT) for inotrope dependent, transplant ineligible, end-stage heart failure patients. This is a randomized, controlled trial of the HeartWare VAS compared to FDA approved devices for destination therapy. This study is ongoing.

4. PRE-CLINICAL AND ANIMAL STUDIES

The Sponsor conducted significant pre-clinical bench testing, human factors, and animal testing to support initiation of a pivotal study.

4.1 Human Factors

A human factors usability study was conducted during the early development of the external components. The usability study reviewed the external components of the HeartWare VAS including: 1) controller user interface layout; 2) battery and pump connectors; 3) audio alarms; 4) controller wearable preferences; 5) controller user interface functionality; and 6) monitor user interface layout and preliminary functionality. Feedback from this study was incorporated into the development of version 2 of the software. In addition, the Sponsor also conducted human factors testing on the final device design.

4.2 Bench Testing on Implantable Components

Bench testing was performed on the final version of the HeartWare VAS implantable components and the system's associated surgical tools, service support kits, and user accessories to demonstrate that they met their intended functional requirements as defined in the product specifications. The design verification testing for the implantable components included physical, mechanical, environmental, system performance, operating range, stress and integrity, biocompatibility, and accelerated aging tests.

The specific tests conducted on the HVAD pump are as follows: mass and volume displacement testing, pump geometric dimension verification, environmental testing, seal integrity testing, dual and single stator start/stop test, noise level testing, housing temperature increase test, shock and vibration test, performance/flow characteristics test, single stator safety/hazard testing, life cycle reliability test (2 year), and pump driveline header junction flex test.

Since the pump is bolted together, leakage is theoretically possible at the flange joint between the front and rear housings. Seal integrity testing showed that leakage through the pump could occur at a maximum rate of 0.194 mL/hr at an internal pump pressure of 250 mmHg.

Appropriate testing on the other implantable components was also conducted. Testing on the driveline included the following: driveline header junction flex test, driveline connector flex test, cable body flex test, cable tensile strength test, driveline dam (i.e., heat shrinking of a small section of the cable) cable tensile testing, driveline cleaning testing, and driveline connector seal pressure testing. Other tests included integrity testing of the outflow graft, graft strain relief junction, sewing ring inflow tube junction, and sewing ring seal.

4.3 Bench Testing on Peripheral Components and Entire System

Electrical safety and electromagnetic compatibility testing was appropriately conducted on the peripheral components of the device. The testing conducted on the batteries was also deemed to be sufficient. Overall reliability of the device has been studied out to 2 years and was demonstrated to meet the 80% reliability goal with 80% confidence.

The performance of the controller was evaluated for the accuracy of the estimated flow and ventricular suction detection. The estimated flow displayed is within 20% of the actual pump flow in dual stator operation over pump speeds ranging from 1800 rpm to 3900 rpm for both steady flow and expected pulsatile environment operation. Below pump flows of 2 liters per minute, ventricular suction will not be detected and no alarm will be triggered.

Testing of the surgical tools (apical coring tool, tunneler, sewing ring wrench, hex driver, inflow cap, and driveline cover), service kits and user accessories included visual inspection, physical, mechanical, environmental, stress and robustness, and accelerated aging tests. Of note, a driveline splice kit and sheath repair kit are added to the PMA version of the HeartWare VAS. The repair kits are not to be sold. They are to be used in the repair of the driveline by HeartWare personnel only as part of needed intervention in the case of driveline damage.

4.4 Animal Studies

Animal studies were conducted on the device prior to approval of the IDE. This testing is referenced in the PMA and consisted of a study conducted in sheep. The Sponsor also studied the updated sintered inflow cannula design in two animal studies in the sheep model. Results of these animal studies were found to be acceptable.

FDA Comment: FDA identified potential clinical concerns based on the design of the device and requested more information about leakage from the pump and start/stop cycling. The Sponsor claims that leakage at the flange joint would not lead to bleeding or thrombosis issues because “the leakage would clot off quickly, even in an anticoagulated patient, forming a natural tissue seal around the pump periphery.” While objective evidence of this assertion could not be obtained, FDA agrees that the demonstrated leakage rate is low.

FDA was also concerned with repeated start/stop cycling as this could promote thromboembolic events and contribute to blood contacting surface wear or damage with the possibility of particulate generation. The Sponsor generated a reliability plot showing that, with 95% confidence, 95% of patients will experience no more than 93 start/stop cycles in dual stator operation. The Sponsor also provided data showing that the probability of thrombus and stroke events in patients is not correlated with a high number of start/stop events. A comparison of the correlation coefficients between the patients with and without thrombus events is 12.0% versus 12.9%, respectively. A comparison of the correlation coefficients between the stroke and non-stroke patients is 23.5% and

11.2%, respectively. Plots of both the thrombus and stroke data versus the number of start/stop cycles showed complete overlap between the thrombus versus non-thrombus and stroke versus non-stroke populations. FDA therefore agrees that start/stop cycling is not a large contributor to thrombus and stroke events.

Given that start/stop cycling is expected to occur, an analysis of the HVAD pump with respect to blood-contacting surface abrasion, wear, impeller and/or housing damage, and any particulates generated following the 200 cycles of start/stop testing would have been ideal. However, based on the lack of correlation between thrombus and stroke events and start/stop cycles, a request for these test data was felt to be unduly burdensome.

FDA has no remaining concerns regarding the pre-clinical testing of this device.

5. PRIOR CLINICAL EXPERIENCE

To support initiation of the pivotal trial that is the subject of this PMA, the Sponsor presented FDA with preliminary results from a single-arm, BTT trial in Europe and Australia. This OUS study compared the 180-day survival/transplantation rate to a 70% performance goal (PG).

The OUS trial enrolled a total of 50 patients between March 2006 and June 2009 at 5 sites in Europe and Australia. The trial's endpoint was survival to anesthesia induction for transplantation, survival with ongoing LVAD support at day 180, or survival for 60 days after weaning of the HeartWare VAS. The Sponsor received European marketing approval (CE mark) for the device in November 2009 on the basis of results of the first 25 patients in the OUS study.

Of the 50 patients in the OUS study, 84% (n=42) reached the primary endpoint. The average age of patients was 49 years, and 86% of patients were male. Mean duration of support was 349 ± 223 days. Results from longer-term follow up are shown in Figure 3.

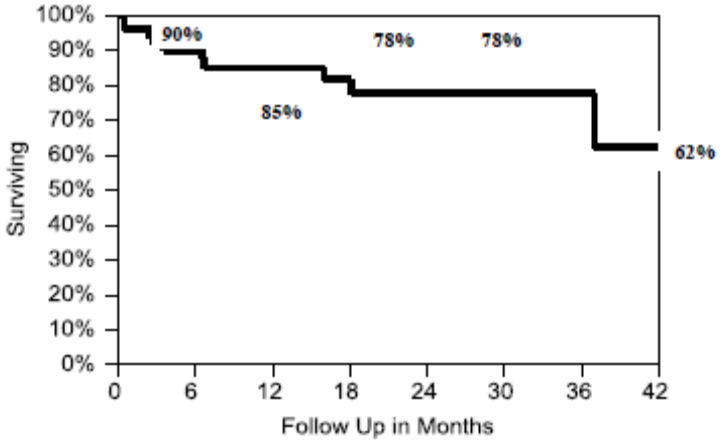


Figure 3. OUS study long term survival

The definition of success was "on device 180 days, transplanted or weaned with 60 day survival." It did not include a component of neurological status, transplant eligibility, or absence of pump replacement. Stroke and pump replacement rates at 180 days are highlighted in Table 1 below.

Table 1. OUS Patient Status at 180 Days

Day Status	Number of patients	Percentage of patients
Alive	42	84%
Stroke	2	4%
Pump replacement	6	12%

FDA Comment: FDA believed the data collected OUS were sufficient (in conjunction with the results from pre-clinical and animal testing) to initiate a pivotal study in the US.

6. IDE CLINICAL STUDY DESIGN

The G070199 clinical study was a multi-center, prospective, non-randomized ventricular assist device (VAD) trial compared against a contemporaneous control. This is the first VAD trial for which data from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) is being used as a contemporaneous control. At the time of the trial design, the INTERMACS registry was assuming prominence within the mechanical circulatory support community. FDA recognized the benefit of having a more dynamic, contemporaneous comparator for newer VAD devices than the previously used PG derived from experience with what are now somewhat obsolete technologies.

The IDE study was designed to evaluate non-inferiority of the proportion of study patients alive, transplanted, or explanted for recovery at 180 days to the same proportion obtained from the INTERMACS cohort. The study's statistical plan allowed for a traditional, PG-based primary endpoint analysis if it was determined that the patients in the two study arms were not similar enough in baseline characteristics to justify a treatment-control comparison.

6.1 History of BTT Trial Design and Use of INTERMACS

Initial BTT trial designs were limited due to small target populations and difficulties in achieving enrollment within a reasonable period of time. Although the primary endpoint of survival to transplant is an objective endpoint, FDA recognized that this approach required long and unpredictable follow-up periods resulting in trials lasting more than 2-3 years. FDA believed that establishing a prospectively identified criterion to define success for bridging patients to cardiac transplantation would facilitate single-arm clinical trials and allow for these life-supporting devices to be made available to the patients that need them. In 2002, the FDA conducted an extensive literature review of approved BTT devices at the time. Six publications[1-6] were used as the basis for development of a performance goal where the 95% lower confidence limit for the point estimate for the success rate had to be greater than 65% for bridging to cardiac transplantation in order to

facilitate single-arm clinical trials for BTT devices. FDA considered several factors when developing the performance goal, including a well understood patient population, extensive history with BTT devices, a well known standard of care, consensus in the clinical community that there is an expectation of significant positive results, and sufficient published data to support a robust performance goal.

In 2006, INTERMACS was launched as a result of a collaborative effort between the VAD community and the National Institutes of Health (NIH), the Center for Medicare and Medicaid Services (CMS) and the FDA. The registry collects information on all patients implanted with approved mechanical circulatory support devices (MCSDs), including approved VADs, total artificial hearts and extracorporeal circulatory support devices. One of the objectives of the registry is to advance the development and regulation of existing and next generation MCSDs. At the time, FDA believed that the amount of data available for outcomes and adverse events could allow it to serve as an appropriate contemporaneous control for BTT studies.

In order to help overcome difficulties related to subjectivity and accuracy in determining the health and capability levels of high risk patients based upon the New York Heart Association (NYHA) classification scale, INTERMACS also developed patient profile levels to classify potential MCSD patients. A description of the INTERMACS patient profiles is provided in the Table 2:

Table 2. INTERMACS Patient Profile Descriptions

Description (per study protocol)	Official Shorthand[7,8]	General Time Frame for Support[7]
Profile 1: Critical cardiogenic shock – Patient with life-threatening hypotension despite rapidly escalating inotropic support, occasionally with IABP placement as well, with critical organ hypoperfusion, often confirmed by worsening acidosis and/or lactate levels.	"Crash and burn"	Hours
Profile 2: Progressive decline – Patient who has been demonstrated "dependent" on inotropic support but nonetheless shows signs of continuing deterioration in nutrition, renal function, fluid retention, or other major status indicator. Level 2 can also describe a patient with refractory volume overload, perhaps with evidence of impaired perfusion, in whom inotropic infusions *cannot be maintained* due to tachyarrhythmias, clinical ischemia, or other intolerance.	"Sliding on inotropes"	Few days
Profile 3: Stable but inotrope dependent – Clinical stability on mild-moderate doses of intravenous inotropes after repeated documentation of failure to wean without symptomatic hypotension, worsening symptoms, or progressive organ dysfunction	"Dependent stability"	Weeks to few months

(usually renal). It is critical to monitor nutrition, renal function, fluid balance, and overall status carefully in order to distinguish between patients who are truly stable at Level 3 and those who have unappreciated decline rendering them Level 2.		
Profile 4: Resting symptoms – Is the level of "recurrent" rather than "refractory" decompensation. After interventions such as hospitalization for intravenous diuretics, these patients can be stabilized briefly on an oral regimen at close to normal volume status. However, they experience brief relapses into fluid retention. These patients should be carefully considered for more intensive management and surveillance programs, by which some may be recognized to have poor compliance that would compromise outcomes with any therapy.	"Frequent flyer"	Weeks to few months
Profile 5: Exertion intolerant – Describes patients who are comfortable at rest but are exercise intolerant for most activity, living predominantly within the house or housebound. They have no congestive symptoms, but may have chronically elevated volume status, frequently with renal dysfunction, and may be characterized as housebound.	"Housebound"	Variable, depends on maintenance of nutrition, organ function and activity
Profile 6: Exertion limited – Patient who is generally without any evidence of fluid overload and able to do some mild activity. Activities of daily living are comfortable and minor activities outside the home such as visiting friends or going to a restaurant can be performed, but fatigue results within a few minutes or any meaningful physical exertion.	"Walking wounded"	Variable, depends on maintenance of nutrition, organ function and activity
Profile 7: Advanced NYHA class III – Describes patients who are clinically stable with a reasonable level of comfortable activity, despite history of previous decompensation that is not recent. Any decompensation requiring intravenous diuretics or hospitalization within the previous 2 weeks should make the person a Level 4 or lower.	Advanced Class III	Transplantation or circulatory support may not currently be indicated

6.2 Objective

The objective of the trial was to evaluate the safety and effectiveness of the HeartWare VAS in patients listed for cardiac transplantation with refractory, advanced heart failure at risk of death.

6.3 Primary Endpoint

The primary endpoint for this study included both a safety and effectiveness component. It was dependent upon the comparability of the HeartWare VAS treatment group and the INTERMACS control group. Two different primary endpoints were pre-specified depending on whether or not the treatment and control groups were comparable based on a propensity score analysis. Propensity score is the probability of treatment exposure conditional upon certain pre-specified covariates. The statistical comparability determination is discussed in more detail in Section 6.6.2. This section describes the two options, in detail, for evaluating the primary endpoint when the treatment and control patient populations are comparable or somewhat comparable, and when they are not comparable.

6.3.1 Scenarios 1 and 2: Treatment and Control Arms are Comparable or Somewhat Comparable

In this case, the primary endpoint was pre-specified as survival at 180 days, which is defined as alive on the originally implanted device or transplanted or explanted for recovery. The patient must survive 60 days post-explant for recovery to be considered successful. These success criteria do not consider transplant eligibility at 180 days.

The primary endpoint was to be evaluated by non-inferiority testing. Per the study protocol, the rates of interest are the proportion of treatment group patients implanted with the HeartWare VAS and the proportion of control group patients in the INTERMACS subset who survive to 180 days on device, heart transplantation, or 60 days post-device explant for recovery. The null and alternative hypotheses are:

$$H_0: \pi_{INT} - \pi_{HW} \geq \delta$$

$$H_A: \pi_{INT} - \pi_{HW} < \delta, \text{ where}$$

π_{HW} is the proportion of treatment group patients who survive to 180 days on HeartWare VAS support, heart transplantation, or 60 days post-explant for recovery;
π_{INT} is the proportion of patients in the INTERMACS registry control group who survive to 180 days on left ventricular assist device (LVAD) support, heart transplantation, or explant for recovery; and δ is a positive value (15%). At the time of trial design, the success rate of patients in INTERMACS was assumed to be approximately 80%. FDA therefore agreed that a 15% non-inferiority margin was clinically appropriate.

For Scenario 1, the primary endpoint analysis will be unadjusted for propensity score. The difference in the treatment success rates between the treatment group and the control group would be statistically compared to the non-inferiority margin of 15% using a non-inferiority Z-test of the difference in proportions. A one-sided 95% upper confidence limit (UCL) on the difference of success rate (control-treatment) would be computed. If the UCL is less than 15%, non-inferiority would be inferred.

In the original protocol, for Scenario 2, the primary endpoint analysis will be stratified by propensity score quartiles. Patients will be sorted into four strata based upon the propensity score such that patients with a similar probability of being assigned to either

the treatment or control arm of the study will be grouped into the same strata. The differences of the success rates between the treatment and the control arms will first be evaluated within each stratum, then the Mehrotra and Railkar minimum risk (MR) weights method would be applied to get an overall evaluation across these strata.[9] A one sided 95% UCL on the difference of success rates (control-treatment) would be computed using the MR weights method. If the UCL is less than 15%, non-inferiority would be inferred.

6.3.2 Scenario 3: Treatment and Control Arm are Not Comparable

Primary endpoint success or failure was to be based upon an agreed-upon analysis in which the 95% lower confidence limit for the point estimate for the success rate had to be greater than the PG of 65%.

Success in this case is defined by the following criteria, per the study protocol:

- Cardiac transplanted,
- Survival on device to 180 days and listed 1A or 1B,
- Survival on device greater than 180 days but not listed for cardiac transplantation based upon the United Network for Organ sharing (UNOS) listing status of 1A or 1B at day 180, and subsequently received a cardiac transplantation by proposed date of the study's data lock, or
- Device removal for recovery and survival to 60 days after device removal.

Failure in this case would be defined as follows:

- Device removal for recovery and death < 60 days after device removal,
- Survival on device greater than 180 days and not listed for cardiac transplantation UNOS 1A or 1B at day 180, and still ongoing,
- Survival on device greater than 180 days and not listed for cardiac transplantation UNOS 1A or 1B at day 180 for any reason (i.e., patient preference, in the process of weaning for recovery, compliance or social problems, etc.), or
- Patient received different device due to a failure of the original HeartWare VAS.

The treatment success rate will be compared to the PG. The null and alternative hypotheses are given below:

$$H0: \pi_{HW} \leq PG$$

$$HA: \pi_{HW} > PG, \text{ where}$$

π_{HW} is the proportion of successes in the treatment group. PG is set as 65%. The success rate

in the HeartWare VAS group would be statistically compared to the performance goal (PG) of 65% using a one-sided binomial exact test (i.e., the lower 95% one-sided confidence limit would have to exclude 65%).

FDA Comment: Although FDA agreed to the 65% survival performance goal in 2008, it is important to note that aggregate INTERMACS results (from published literature in 2010), for LVAD BTT therapy between 2006 and 2009, reflected 12 month BTT survival of 88%.[10] FDA acknowledges that this value includes patients who may have received a device exchange and/or were no longer listed for transplant. This is shown in Figure 4.

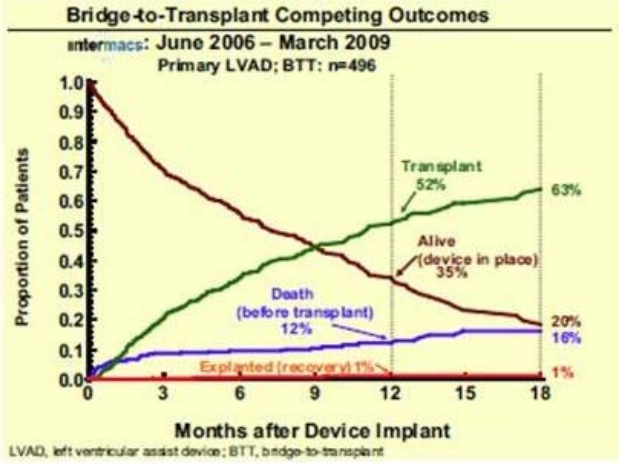


Figure 4. Survival according to device strategy at the time of implant[9]

6.4 Secondary Endpoints

A series of secondary endpoints related to safety and effectiveness were also pre-specified:

1. Overall survival;
2. Incidence of all serious adverse events (SAEs), including neurocognitive status and unanticipated adverse device effects;
3. Incidence of all device failures and device malfunctions;
4. Quality of Life improvement, as measured by Kansas City Cardiomyopathy Questionnaire (KCCQ) and European Quality of Life (EuroQoL EQ-5D); and
5. Functional status improvement, as measured by New York Heart Association Classification (NYHA) for heart failure and 6-minute walk.

FDA Comment: During the time of trial development, FDA encouraged the Sponsor to propose specific hypotheses regarding key secondary endpoints such as SAE rates. However, the Sponsor believed that the lack of clarity regarding the adjudication of the INTERMACS data did not allow for valid and direct inter-group comparisons of adverse event rates such as severe strokes (or other intercurrent events) affecting transplant eligibility. As a result, the

Sponsor specified in the protocol that "no formal statistical hypothesis tests or comparative analyses will be conducted. Secondary endpoint analyses will be conducted for the HeartWare treatment group only." In addition to general SAE comments, FDA also stressed that a full presentation of rigorously identified neurological events would be critical to the device's overall benefit to risk assessment.

FDA also notes that when testing the primary endpoint by means of non-inferiority compared to the INTERMACS control group, there is no explicit consideration of patients possibly having developed an intervening major stroke. The alternative PG analysis (Scenario 3) defined success on the basis of 180 days of support with continuing UNOS 1A/1B transplant status of the patient; as such, the PG may have better identified patients with disabling strokes as treatment failures than did the non-inferiority hypothesis. Accordingly, FDA requested an adjunctive analysis of the primary endpoint using the pre-specified PG methodology, and these results are discussed in the Clinical Study Results, Section 9.

6.5 Key Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for those patients receiving the device as well as those patients who were entered into the INTERMACS control group are discussed here.

6.5.1 Treatment group inclusion criteria:

- HeartWare VAS implant is planned as a bridge to transplant
- Patient is NYHA Class IV
- Patient listed for cardiac transplantation, UNOS Status 1A or 1B
- Body Surface Area (BSA) ≥ 1.2 m^2
- Age $\geq$ 18 years

6.5.2 Treatment group exclusion criteria:

- Ongoing mechanical circulatory support other than intra-aortic balloon pump (IABP)
- Ventilator support for > 72 hours within the four days enrollment
- Serum creatinine greater than 3.0 times the upper limit of normal
- Requiring dialysis (no time frame)
- Severe right ventricular failure (includes right atrial pressure > 20 mmHg on multiple inotropes)
- Prior cardiac transplant
- Acute myocardial infarction within 14 days of implant
- Cardiothoracic surgery within 30 days of enrollment
- Symptomatic cerebrovascular disease (> 80% carotid stenosis)
- Pulmonary artery systolic pressure > 60mmHg and pulmonary vascular resistance (PVR) > 5 Wood units

6.5.3 INTERMACS control group inclusion criteria:

- LVAD implanted and patient prospectively included in INTERMACS
- LVAD is first VAD implant for the patient

- LVAD planned as BTT by the implanting physician
- Currently listed for transplant
- BSA $\geq 1.2\ m^2$
- Age ≥ 18 years
- Not on ventilator support within 24 hours of implant
- Creatinine ≤ 5 mg/dl
- Not on dialysis within 24 hours of implant

FDA Comment: FDA accepted that the trial design incorporated differing degrees of specificity with regard to the characterization of the two arms' inclusion and exclusion criteria. FDA believes that the HeartWare VAS treatment arm of the trial was comprised of a more narrowly defined patient population than was in the INTERMACS control arm (e.g., lack of recent cardiac events, designation of pulmonary hypertension). Furthermore, some of the analogous criteria could conceivably have allowed for enrollment of patients into the control arm with relatively worse clinical presentation than in the HeartWare VAS arm (e.g., degree of renal impairment, degree of pulmonary impairment). Accordingly, FDA believes that appropriate clinical balance between groups for the eight pre-specified propensity score covariates (see Section 8) may be quite important when considering the overall comparability of the HeartWare VAS and INTERMACS patients at baseline.

6.6 Statistical Analysis Plan

The following sections describe the analysis populations, in addition to the methodologies associated with analyzing the data when the control and treatments group are similar and different.

6.6.1 Analysis Populations

There are three analysis populations defined for this trial: the intent-to-treat population (ITT), the Safety population (SAF) and the Per Protocol population (PP). The ITT population for the treatment group includes all enrolled patients who underwent anesthesia for implantation of the HeartWare VAS. The SAF population for the treatment group includes all ITT patients who received the HeartWare VAS. The study's ITT population is identical to the SAF population. The PP population for the treatment group includes SAF patients who did not have protocol criteria violations.

The primary analysis population is the ITT population. All primary and secondary analyses were to be performed on the ITT and Per Protocol populations. All safety analyses were to be performed on the Safety Population.

The INTERMACS contemporaneous control group consists of patients enrolled in the registry who met the pre-specified control group inclusion criteria (over the same enrollment period as the HeartWare VAS treatment group).

6.6.2 Analysis Plan Based on Treatment and Control Group Comparability

The Sponsor pre-specified the manner in which it was to decide if the contemporaneous INTERMACS patients were acceptable as a control group. According to the protocol, the comparability between the HeartWare and INTERMACS patient characteristics was to be evaluated using a propensity score analysis with pre-specified baseline covariates.

For subjects with missing baseline covariates, the missing data were to be imputed by replacing the missing value with the treatment group median.

As per the protocol, the C-Statistic was employed to evaluate the use of the propensity score model. The C-statistic is intended to serve as a measure of concordance between two groups. One of three conclusions was to be made based on the results of the propensity score analysis and the number of patients in the INTERMACS control group:

1. The treatment groups are well balanced with the baseline covariates providing little to no predictive value for treatment group as evidenced by a C-statistic < 0.60. In this case (Scenario 1), a non-inferiority test was to be carried out without a propensity score adjustment.

2. The treatment groups are somewhat imbalanced with the regression model providing sufficient predictability of the treatment group as evidenced by a C-statistic of ≥ 0.60 and sufficient overlap "as evidenced by propensity score quartiles that contain no fewer than five (5) subjects in each treatment group" between the distributions of propensity score. In this case (Scenario 2), a non-inferiority test was to be conducted with propensity score stratification and a weighted average of the stratum specific differences in proportions was to be computed and tested against the non-inferiority margin of 15% using minimum risk (MR) weights.

3. The treatment groups are found to be not comparable as evidenced by insufficient overlap in the distribution ("one or more strata with fewer than five (5) subjects in a given treatment group") of propensity scores in the two treatment groups or an inadequate number of patients enrolled into the INTERMACS registry who qualify for inclusion in the control group. In this case (Scenario 3), a performance goal comparison was to be conducted.

7. CLINICAL STUDY CONDUCT and DATA PRESENTATION

The overall conduct of the study is presented in this section and highlights events that occurred in both the treatment and control arms. Enrollment for the treatment arm took place between August 18, 2008, and February 23, 2010. The corresponding window for the INTERMACS control arm was between August 18, 2008, and February 18, 2010. Patient accountability for both the treatment and control groups is presented in addition to a discussion regarding pre-screen and screen failures, protocol deviations, and adverse event adjudication.

7.1 Patient Accountability-Treatment Group

A total of 273 patients were screened for this trial; 160 HeartWare VAS patients signed Informed Consents and were thus enrolled in the trial. The treatment-arm patient accountability is shown in Figure 5:

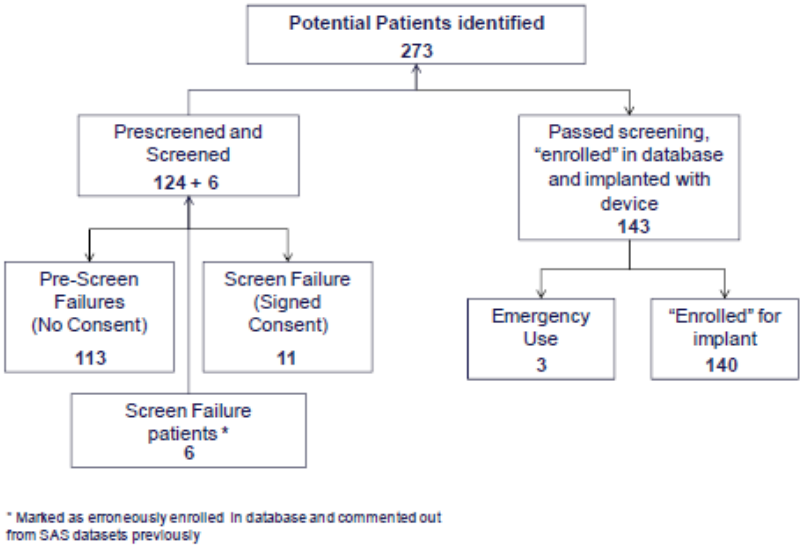


Figure 5. Breakdown of Screened Patients

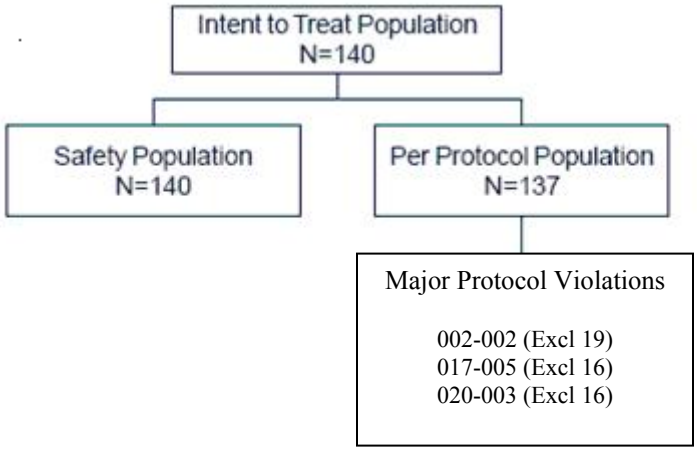


Figure 6. Analysis Populations

Three of the ITT patients enrolled with waivers of major protocol violations were removed from the Per Protocol analysis population, but remained within the ITT Safety population (which included all implanted HeartWare VAS patients). Three other patients did not meet specific Inclusion/Exclusion criteria, but did undergo HeartWare VAS placement on an "emergency use" basis; the reasons for exclusion from the analysis cohort were age, NYHA class, ongoing MCS other than IABP, and cardiothoracic surgery within 30 days.

ITT enrollment by center was as follows:

Table 3. HVAS Treatment Group Site Enrollment

Site	Total	Site	Total	Site	Total
001	10	015	3	033	2
002	14	016	5	034	5
003	2	017	7	035	4
004	3	019	3	039	4
005	12	020	3	041	3
006	8	022	1	044	2
008	1	024	2	046	1
009	4	025	1		
010	9	026	1		
011	7	027	12		
014	4	030	4		

7.2 Pre-Screen and Screen Failures

Overall, 49% of patients (133/273) screened for the trial were not eligible to receive the HeartWare VAS implantation according to the protocol. The four highest enrolling centers, accounting for 34% (48/140) of ITT implantations, had a screening failure rate of 30%, whereas two of these highest enrolling centers, accounting for 17% (24/140) of implantations, had no screening failures. Conversely, nearly 60% of all screening failures occurred at four low enrolling sites that collectively contributed 10% (14 patients) to the ITT analysis population.

There were 160 HVAD patients who signed informed consent forms and were enrolled in the trial. Seventeen of these consented patients were enrolled in error (having not met all of the inclusion/exclusion criteria) and therefore were not considered part of the pre-specified ITT analysis cohort. None of these 17 patients underwent anesthesia for HeartWare VAS placement, and the Sponsor considered and defined them as "screen-failures." However, three other patients likewise did not fulfill the inclusion/exclusion criteria, but did undergo HeartWare VAS placement on an "emergency use" basis. These three patients are not included in the ITT population.

Since 17 "screen failure" patients had been enrolled, FDA requested further follow-up data for this cohort. Six of the 17 patients had been enrolled by a single site (#017). Three of the "screen failures" were on the basis of either physician decision or patient preference to receive alternative heart failure treatment, as shown in Table 4.

Table 4. Treatment of Enrolled "Screen Failure" Patients

Treatment post screen-	Number of patients	Percentage of patients
HeartMate II	12	71%
Abiomed	1	6%
Transplant	2	12%
None	2	12%

Of the 17 "screen failure" patients, 15 were alive at 6 month follow-up; 1 of 12 HeartMate II patients (8%) and 1 of 1 Abiomed patients (100%) had died, both in the immediate peri-operative period.

FDA Comment: FDA noted that the trial's screening and enrollment logs assigned screening failures on the basis of inclusion/exclusion criteria that were waived for other enrolled and implanted patients. Based on the specifics of the cases involving the identified enrollment disparities, FDA accepted the Sponsor's *post hoc* justifications for why these documented disparities did not unduly bias the trial results. However, FDA notes that screening and subsequent enrollment practices were not homogenous. At several times throughout the IDE period, FDA conveyed to the Sponsor the Agency's concerns about screening, enrollment, and compassionate/emergency use possibly reflecting a lack of investigator equipoise that could potentially introduce bias adversely affecting data interpretability.

7.3 Patient Accountability-INTERMACS

During the August 2008 to February 2010 trial enrollment period, 1513 patients were entered into INTERMACS. Of these, 544 patients were adult patients receiving an LVAD and listed for transplantation. As noted earlier, the transplant list status of UNOS 1A or 1B is not captured in INTERMACS.

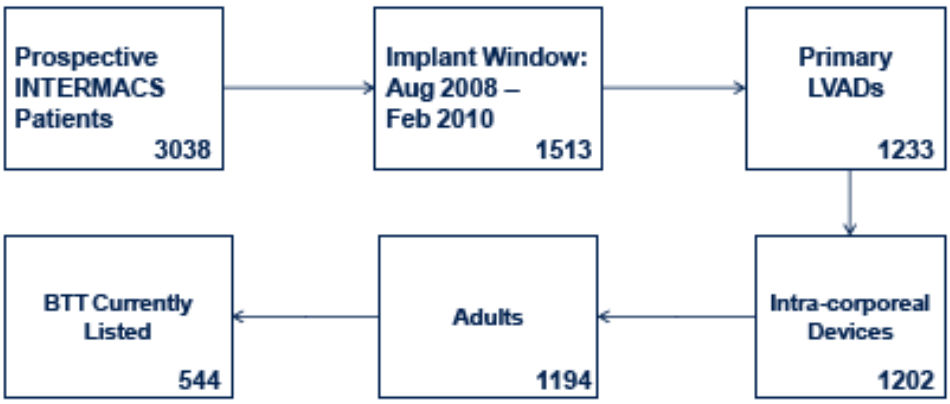


Figure 7. INTERMACS control group

Forty-five of these patients were excluded from the control group because they did not meet the inclusion criteria for the trial. The cohort of INTERMACS patients therefore consisted of 499 patients that were subject to a propensity score analysis with the HeartWare VAS treatment arm. However, two INTERMACS patients withdrew consent upon transferring their care from the implanting centers. The endpoint analyses were

based upon an INTERMACS population of 499, with the two patients who withdrew consent being counted as missing data. The comparability of the treatment and control groups is further discussed in Section 8.1.

7.4 Protocol Deviations

A total of 990 protocol deviations occurred from the start of enrollment to December 2010. The majority of the deviations occurred between initiation of the study to April 2010, a time period accounting for 88% of device implantations and for which site management and monitoring were performed by a Clinical Research Organization (CRO) independent of the Sponsor.

Table 5. Protocol Deviations Based on Study Monitor

	Sites Active	Patients Implanted	Deviations Noted
August 2008-Start of Enrollment to April 2010- Annual IDE Report (CRO monitoring)	29	123	635
April 2010-Annual IDE Report to December 2010 (Sponsor monitoring)	1	27	355
Total	30	140	990

The majority of the deviations were identified by the Sponsor as "protocol deviations:"

Table 6. Protocol Violation Types and Numbers

Violation Type	Enrollment to December 2010
Good Clinical Practice	50
Protocol Deviation	938
Protocol Violation	2
Total	**990**

FDA Comment: FDA agrees with the Sponsor's assessment that the captured deviations' had a minimal impact on trial interpretability. However, FDA also accepts the Sponsor's statement that "the performance of the monitoring during this crucial phase of the trial [enrollment to April, 2010] was inadequate. Monitoring visit frequency was insufficient to maintain pace with enrollment, training on the protocol required procedures, and follow-up on site deficiencies was ineffectively executed." As a result of the suboptimal monitoring on the part of the CRO, FDA must also consider the possibility that the true number of protocol deviations and violations may have been inaccurately captured.

7.5 Clinical Events Committee (CEC) and Adverse Event Adjudication

During the course of the IDE, the Sponsor made multiple modifications to the membership of the CEC. The CEC's adjudication process required review of events by two voting members; in the event of disagreement of adjudication between the two

members, final adjudication was decided by the CEC Chairman. The following changes were made to the CEC:

- October 2008: Three member CEC (Chair + two voting members) formulated.
- July 2010: Three member CEC reconstituted with replacement of Chairman and one voting member.
- August 2010: CEC expanded to eight members (Chair + seven voting members). Adjudications now reviewed by up to 21 distinct two-member sub-committees.
- December 2011: CEC reduced to three members (same individuals as noted in July 2010).

The CEC adjudicated nearly 80% of all the investigator-reported events during the primary endpoint period. The number of adjudicated events is outlined in the table below. Although the adjudicated adverse events total to 763, the investigator reported adverse events total to 776, as the CEC counted some adverse events as linked.

Table 7. Adverse Event Adjudication

	Total	**%**
Events Not Adjudicated	158	20.7%
Events Adjudicated	605	79.3%
Total	763	100%

The Sponsor originally identified that 265 of the 605 adjudicated events (44%) involved differences of opinion among the two voting members and the Chairman. Forty-three of the differences concerned the characterization of the event as being protocol-defined, whereas the remaining 223 differences concerned device-relatedness and/or designation as a serious adverse event. Nearly half of all adjudicated events were initially disputed internally by the CEC and then reconciled by one of two Chairmen.

The lack of clarity surrounding the adjudication of events is highlighted in the review of the rate of neurological events (discussed in further detail in Section 10). FDA identified at least 15 events that were formally adjudicated by the CEC as strokes. The CEC evaluated the neurological event of subject [redacted] on two occasions (February and March, 2010), with the two voting members agreeing that the event was a device-related SAE (ischemic stroke). The CEC adjudicated an event for subject [redacted] in February, 2009, involving neurological findings and brain imaging. In January 2011, the Sponsor contacted the former CEC Chairman (previously not involved with either patient's adjudications) and solicited his opinion "post hoc since the patient was adjudicated as an ischemic stroke." On the basis of a brief patient narrative, the former Chairman suggested that there was "no definitive evidence that the patient had a stroke." As a result, in all subsequent accountings to FDA of neurological events, the Sponsor represented subject [redacted] as having "metabolic encephalopathy" rather than a true stroke, and subject [redacted] was excluded from all accounting of neurological events. Furthermore, the Sponsor opted in its PMA amendment to revise downward the total accounting of ischemic stroke

SAEs, most notably when providing FDA with comparisons to the literature. Recently, the Sponsor again revised the stroke rate, but ambiguity regarding the Sponsor's reconciling of neurological events in subjects [redacted] and [redacted] persists (see Sponsor's executive summary). Because of the multiple discrepancies, FDA's calculation of the observed ischemic stroke rate (Table 22 below) differs from the sponsor's.

FDA Comment: FDA believes (and conveyed to the Sponsor during the course of the trial) that multiple changes to the CEC may have affected the reproducibility of SAE adjudications and the interpretability of the adjudicated safety results. The volume, nature, and outcome of internally disputed AEs may have been different had the CEC membership remained consistent throughout the course of the trial. Additionally, FDA questions the appropriateness of selective, *post hoc* revisions of previously categorized adverse events on the part of the unblinded Sponsor. FDA acknowledges the Sponsor's statement that the adjudication process specifically allowed for standardization and consistency of the events' reviews by the CEC, however, the accounting of discrete stroke events by the Sponsor has in FDA's view been repetitively inconsistent.

7.6 Data Presentation

Since the review of the of the PMA amendment, the Sponsor has provided FDA with multiple versions of adverse event data.

For example, the Sponsor identified to FDA two additional patients who experienced ischemic CVA but were not consistently represented in data tables that FDA relied upon for its safety assessment.

Prior to such discoveries, FDA had noted several inconsistencies in the adverse event data provided within the PMA amendment, and between the PMA amendment and the original PMA. When questioned further, the Sponsor identified programming errors and inconsistencies with definitions of patient populations analyzed as explanations for the datasets' variability. Data from at least three separate adverse event analyses were presented to FDA without an explanation of the differences.

FDA Comment: The Sponsor's accounting of adverse events does raise concerns to FDA regarding data interpretability. The Sponsor's updated accounting of adverse events is represented in Section 10.

8. PATIENT COMPARISONS – TREATMENT and CONTROL GROUPS

The comparability between the treatment and control groups was evaluated based on 8 pre-specified covariates: age, gender, blood urea nitrogen (BUN), right atrial pressure (RAP), creatinine, body surface area (BSA), prior cardiac surgery (Yes/No),and INTERMACS patient profile (scale 1-7). A propensity score stratification analysis using quartiles (this method was pre-specified) and quintiles (as requested by FDA) was conducted in order to determine the comparability of the treatment and control groups. However, due to missing data and a direct comparison of patients' individual covariates, the conclusions that can be drawn from a statistical and clinical perspective are different.

Boxplots of the propensity score of the two groups are shown in Figure 8 after a statistical analysis of the data.

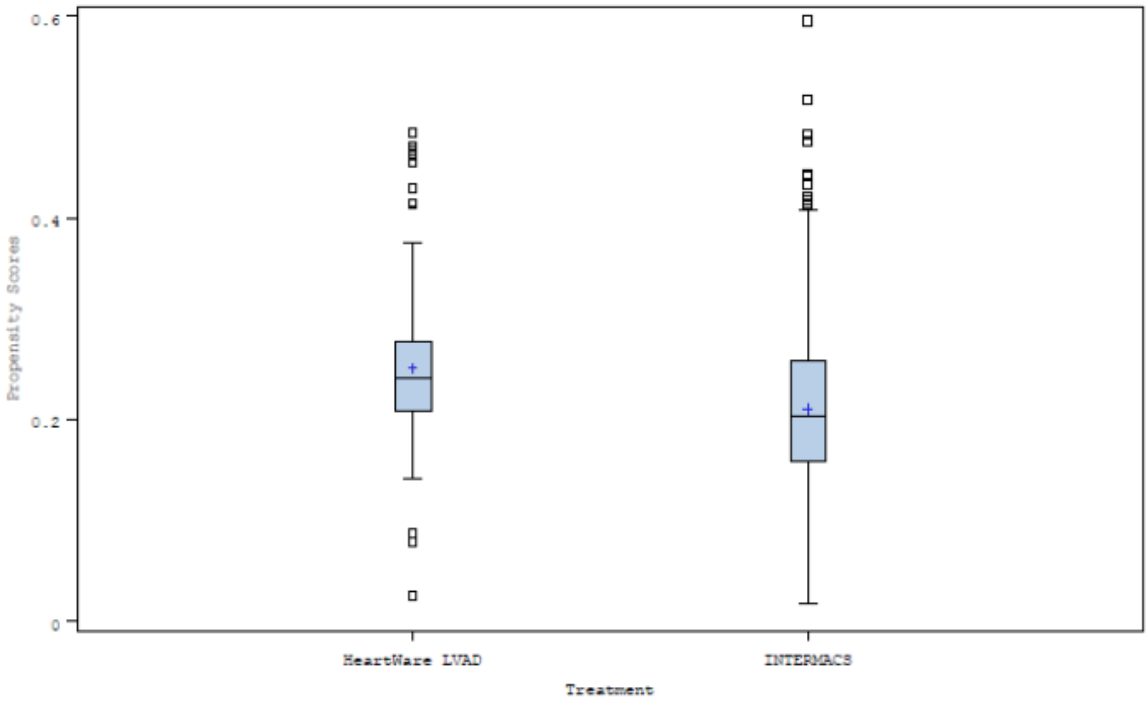


Figure 8. **Propensity score boxplots**

8.1 Missing Baseline Covariate Data

It is important to note that among the eight covariates, there were missing data for three of them – RAP, BSA and INTERMACS patient profile.

Table 8. Missing Baseline Covariate Data

	RAP n (%)	**BSA n (%)**	**INTERMACS Profile n (%)**
HeartWare VAS Group	112 (80%)	3 (2.1%)	2 (1.4%)
INTERMACS Group	222 (44.5%)	2 (0.4%)	0 (0%)

As noted in the table above, RAP data were missing for 80% of patients in the HeartWare VAS group and 44.5% of patients in the INTERMACS group. FDA acknowledges that sites were instructed to collect either central venous pressure (CVP) or RAP, but not both. However, even with a combination of both parameters, only a total of 51% of patients are represented.

For subjects with missing baseline covariates, the missing data were imputed by replacing the missing value with the treatment group median. Thus, all missing RAP data

for HeartWare were replaced with a value of 9.5 mmHg and all missing RAP data for INTERMACS were replaced with a value of 11 mmHg.

FDA Comment: The need to impute missing data may have added an increased bias to the propensity score analysis. The ability to draw conclusions about propensity score stratification is a challenge as a result of the missing data.

8.2 Comparability Assessment using Quartiles

The propensity score analysis using the pre-specified covariates yielded a C-statistic of 0.65. The number of patients in each stratum is summarized in Table 9.

Table 9. Patient Number per Quartile

	Quartiles				
	1	2	3	4	Total
HeartWare® LVAD, N=140	13	28	53	46	140 (100.0)
INTERMACS, N=499	146	132	107	114	499 (100.0)

Since the C-statistic is ≥ 0.60, Scenario 2 (see Section 6.6.2) is selected and the treatment and control groups, from a statistical perspective, can be considered somewhat comparable with a propensity score adjustment.

8.3 Comparability Assessment using Quintiles

FDA requested that the Sponsor evaluate comparability of the treatment and control groups using quintiles to further reduce potential biases.

The number of patients in each stratum is summarized below.

Table 10. Patient Number per Quintile

	Quintiles					Total
	1	2	3	4	5	
HeartWare LVAD, N=140	8	21	25	50	36	140 (100.0)
INTERMACS, N=499	119	107	103	78	92	499 (100.0)

Again the treatment and control groups can be considered somewhat comparable with a propensity score adjustment (from a statistical perspective).

8.4 Assessment of Covariate Balance after Propensity Score Stratification Using Quintiles

For each of the covariates, balance checking was performed after propensity score stratification using quintiles to further evaluate the comparability of the two groups.

For continuous variables and ordered categorical variables (age, BUN, RAP, creatinine, BSA and INTERMACS profile), a two-way analysis of variance (ANOVA) model (2 treatment x 5 propensity score quintiles) was used. For each of the covariates, the two-way interaction of the treatment and propensity score quintile as well as the treatment comparison after stratification were checked. None were found significant at a significance level of 0.15. The above analysis was performed using imputed values when missing data existed.

Additionally, for the covariate balance checking after stratification for RAP, the 2-way ANOVA was also performed deleting all missing data (the quintiles are still marked by the propensity score model built using imputed RAP). The two-way interaction of the treatment and propensity score quintile has a p-value of 0.7017. The p-value for the treatment effect is 0.1066. Due to the large amount of missing data, an evaluation on the true RAP balance is not possible.

For other categorical variables (gender and prior cardiac surgery), a Mantel-Haenszel test was used and no covariate was found to be significantly different at a significance level of 0.15 after propensity score stratification.

FDA Comment: Although the treatment and control groups can be considered statistically comparable based on the propensity score box plot and covariate balance checking, the large amount of missing data on RAP may add an increased amount of bias to the propensity score analysis. The clinical relevance of the propensity scores is discussed in the next section.

8.5 Direct Between-Group Comparisons of Individual Covariates

Although the overall propensity score analysis shows the treatment and control groups are somewhat comparable, clinically relevant differences were seen when certain individual covariates were compared.

FDA agrees that the following six covariates had no statistically significant differences between the HeartWare VAS and INTERMACS groups: age, gender, BSA, BUN, creatinine, and prior cardiac surgery. However, FDA believes that clinically significant differences in the groups' renal function, based upon heterogeneity, may have been present based upon Figure 9.

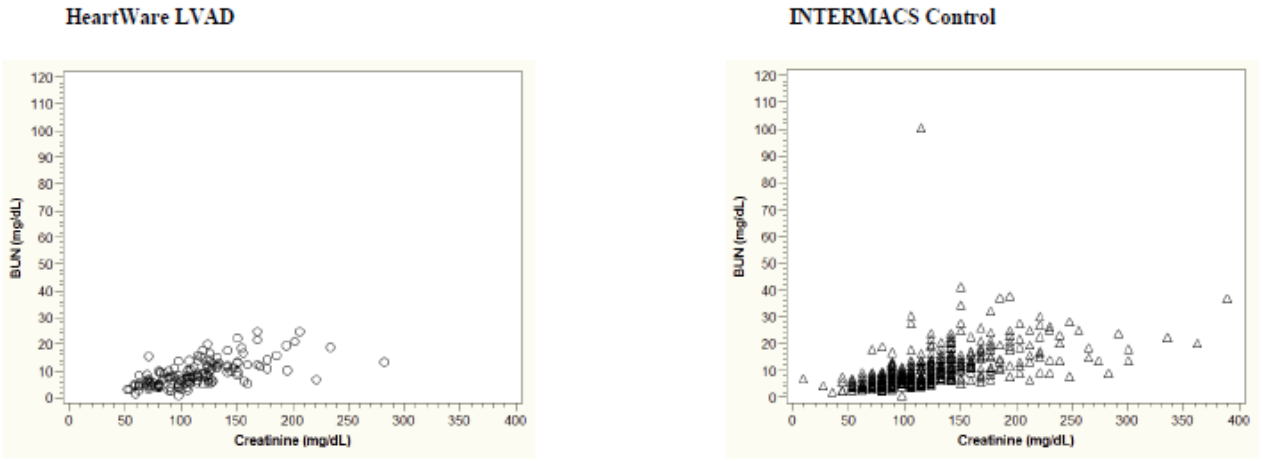


Figure 9. Scatterplot of the creatinine covariate for treatment and control groups

Imputation of the missing RAP values (based upon the median values of the available data) identified a statistically significant difference, as shown in the table below.

Table 11. Imputed RAP for Treatment and Control Groups

Imputed RAP	HeartWare	INTERMACS	P-value (t-test)
n	140	499	0.0002
Mean	9.8	11.5	
Standard Deviation	3.23	5.07	
Median	9.5	11	
Min – Max	2 – 34	1 – 39	

Figure 10 may further suggest clinically significant differences between the treatment and control groups in terms of RAP.

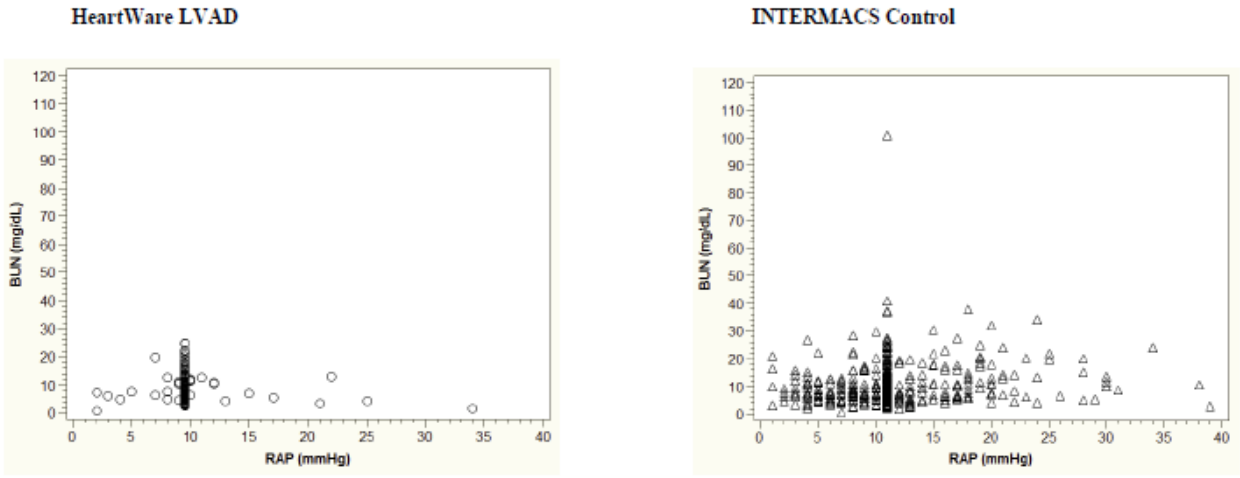


Figure 10. Scatterplot of the RAP covariate for treatment and control groups

There was also a statistically significant difference between the two arms of the trial for the eighth covariate of INTERMACS patient profile.

The table below shows the distribution of the patients in each profile.

Table 12. Patient Distribution Based on INTERMACS Profile

	HeartWare® LVAD N=140	INTERMACS N=499
	n (%)	n (%)
INTERMACS 1	7 (5.0)	39 (7.8)
INTERMACS 2	39 (27.9)	259 (51.9)
INTERMACS 3	62 (44.3)	103 (20.6)
INTERMACS 4	17 (12.1)	60 (12.0)
INTERMACS 5	7 (5.0)	15 (3.0)
INTERMACS 6	2 (1.4)	9 (1.8)
INTERMACS 7	6 (4.3)	14 (2.8)

At baseline, the distributions of patients by INTERMACS profile were found to be statistically significantly different between the treatment and the control groups (p-value = 0.0015 by a t-test).

The protocol stipulated that the INTERMACS profile score be assigned (in the HeartWare VAS treatment arm) by an individual at each site not otherwise involved with the study, so as to limit investigator bias or confounding. Profile levels 1 and 2 represent the most critically ill heart failure patients who are being considered for LVAD therapy. Proportionately, nearly twice as many patients in the INTERMACS control arm were in profile 1 or 2 (60%) as compared to the HeartWare VAS arm (33%); more specifically, profile level 2 patients comprised 52% of the INTERMACS control arm and only 28% of the HeartWare VAS arm.

In the propensity score model, the p-value for INTERMACS patient profile was 0.0031 and the 95% CI of the odds ratio for this parameter within the propensity score model was [1.075-1.426], suggesting that INTERMACS profile may have been a major determinant of the observed patient distribution within quartiles, and by extension a major determinant of a given patient's propensity to receive the HeartWare VAS (see Table 9 in Section 8.2).

FDA Comment: Inferences regarding the comparative clinical condition of patients on the basis of the imputed RAP data are limited. However, the clinical and statistical comparisons of key covariates – cardiac function/volume status (RAP), renal function (BUN and creatinine values) and global patient condition (INTERMACS profiles) – suggest to FDA that clinically important differences existed between the treatment and control groups involved with this trial.

9. CLINICAL STUDY RESULTS – PRIMARY ENDPOINT

9.1 Primary Endpoint Analysis

The primary endpoint was analyzed under Scenario 2 based on the comparability evaluation of the HeartWare VAS and INTERMACS control group baseline covariates using a propensity score analysis. See Sections 6.3.1, 8.2 and 8.3 for more details regarding the statistical analysis plan and propensity score analysis.

Under Scenario 2 the study compared the success rate of patients surviving to 180 days with the original LVAD, transplant, or 60 days post-explant for recovery between the HeartWare VAS group and the INTERMACS control group.

As no patient in either arm of the trial underwent (successful) VAD explantation for recovery, success was based on the rate of either transplantation or ongoing LVAD support with the originally implanted device at 180 days after implantation. The overall study results are shown in Table 13. The 95% one-sided upper confidence limit is based on the difference in success rates for the treatment and control groups (Control-Treatment), calculated under Scenario 2 using quartiles (four strata) and MR weights.

Table 13. Pivotal BTT Study Success Based Upon Quartiles

	Implanted	**Successes (rate, %)**	**p-value (non-inferiority test)**	**95% one-sided upper confidence limit on the difference in success**
Safety Cohort – HeartWare VAS	140	127 (90.7)	<0.0001	4.5
Safety Cohort – INTERMACS	497	448 (90.1)		
Per Protocol Cohort – HeartWare VAS	137	126 (92.0)	<0.0001	0.9
Per Protocol Cohort – INTERMACS	497	448 (90.1)		

Note: The table accounts for 497 of the 499 INTERMACS patients; the remaining 2 patients withdrew consent before 180 days and have a missing success/failure outcome.

There are two INTERMACS patients with missing primary endpoint information and no missing data on the primary endpoint for HeartWare VAS patients. A worst-case analysis was performed where the outcomes for the two (of 499) INTERMACS patients with missing endpoint data (1 each from Quartile 1 and 2) were imputed to be successes, and no marked change in the results was noted.

Based on the pre-specified statistical analysis alone, the HeartWare VAS is not inferior to devices used in patients who are in the control group by more than 15%.

As previously discussed, FDA also requested a primary endpoint analysis using quintiles. As such, the following is a discussion of the primary endpoint analysis based on quintiles. Under Scenario 2, using quintiles (five strata) and MR weights, the upper bound of the

one-sided 95% confidence interval of the difference between the success rates (control minus treatment) is 1.6% on the ITT/SAF population and 0.093% on the PP population.

Table 14 breaks down the primary endpoint results in the context of quintile distribution:

Table 14. Number (%) Success by Quintile for Each Treatment Group

Treatment Group	Success	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
HeartWare VAS	Yes	8 (100)	19 (90.5)	22 (88.0)	46 (92.0)	32 (88.9)
	No	0	2 (9.5)	3 (12.0)	4 (8.0)	4 (11.1)
	Total	***8 (100)***	***21 (100)***	***25 (100)***	***50 (100)***	***36 (100)***
INTERMACS	Yes	99 (84.0)	102 (95.3)	90 (88.2)	71 (91.0)	86 (93.5)
	No	19 (16.0)	5 (4.7)	12 (11.8)	7 (9.0)	6 (6.5)
	Total	***118 (100)***	***107 (100)***	***102 (100)***	***78 (100)***	***92 (100)***

Note: This table excludes the two INTERMACS control group patients who withdrew consent.

Quintile 1 contained 5.7% (8/140) of the HeartWare VAS treatment arm patients (as per Table 10) and 0% of HeartWare VAS treatment patient failures. However, Quintile 1 contained 24% (118/499) of the INTERMACS control patients (per Table 10), but 39% (19/49) of INTERMACS control patient failures.

Aggregate success and failure are illustrated by competing risk plots in Figure 11. (Note: The INTERMACS control is n=499 for these graphs. The two patients lost-to-follow up are handled as censored patients at 36 days and 63 days, respectively.)

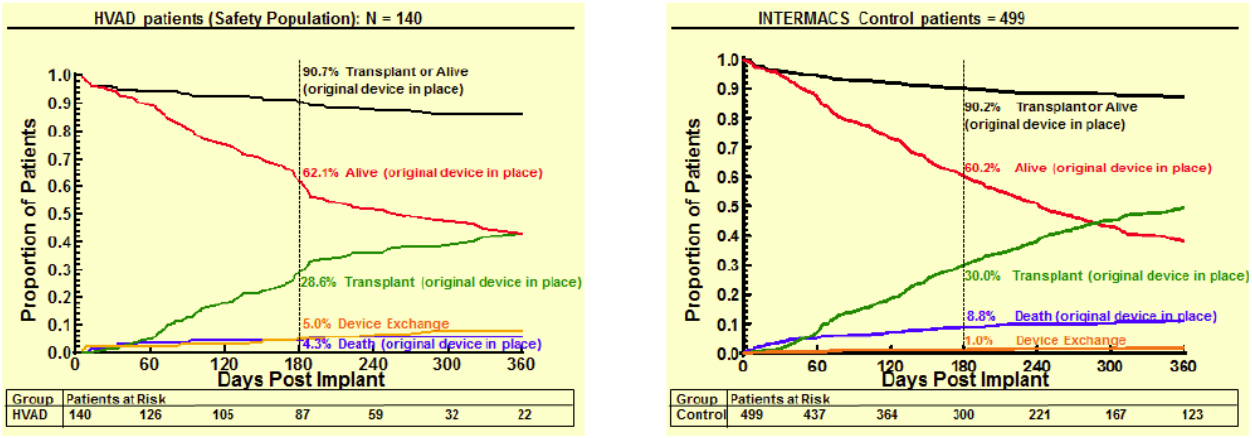


Figure 11. Overall survival after device implant

Although at 6 months the rates of transplantation or survival with original device were clinically equivalent between treatment (HeartWare VAS) and control (INTERMACS) groups, the predominant mode of failure was different in the two groups. Of the

treatment arm's 13 failures (9.3% rate), 6 (46%) were death and 7 (54%) were device exchanges; of the control arm's 49 failures (9.8% rate), 44 were death (90%) and 5 (10%) were device exchanges.

As indicated in Table 12, profile level 2 patients comprised only 28% of the HeartWare VAS arm, compared to 52% of the INTERMACS control arm. However, half of the deaths in both arms occurred in INTERMACS profile level 2 patients, and most of the deaths appeared to have occurred within the first two months. FDA also noted a slight increase in level 2 HeartWare VAS transplantations (compared to INTERMACS control patients) just prior to day 180, as noted on the left in Figure 12.

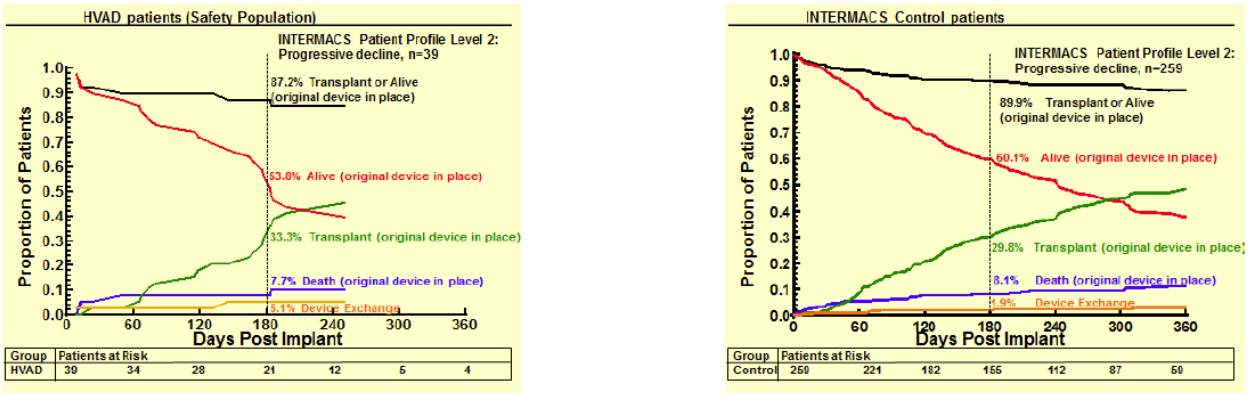


Figure 12. Survival after device implant in INTERMACS level 2 patients

The following table presents success rates stratified by INTERMACS profiles:

Table 15. Success Based on INTERMACS Profile

INTERMACS Profile Level	HVADHeartWare VAS Group Success (%)	INTERMACS Group Success (%)
Overall (1-7)	127/140 (92.0%)	448/497 (90.1%)
1-3	96/106 (90.6%)	359/399 (90.0%)
4-7	29/32 (90.6%)	89/98 (90.8%)
1	7/7 (100%)	32/38 (84.2%)
2	34/39 (87.2%)	232/258 (89.9%)
3	55/60 (91.7%)	95/103 (92.2%)
4	19/19 (100%)	52/60 (86.7%)
5	6/7 (85.7%)	15/15 (100%)
6	2/2 (100%)	9/9 (100%)
7	4/6 (66.7%)	13/14 (92.9%)

FDA Comment: FDA agrees that the study met the trial's primary endpoint of non-inferiority based upon Table 13. However, interpretation of these data must be considered in the context of statistical and clinical comparison of the HeartWare VAS and INTERMACS control patient populations. Although the success rates appear to be similar between trial arms when stratified by INTERMACS profiles, there is a relative paucity of failure due to device exchange in the control arm but similarly high mortality rates of more critically-ill patients

(INTERMACS profile 1 and 2 patients) in the two arms. FDA therefore questions whether the inference of non-inferiority would have persisted if there had been equivalent proportions of INTERMACS profile 1 and 2 patients in both study arms and plans to seek panel input on this issue. Drawing clinical inferences of non-inferiority is further complicated by FDA's inability to audit and review patient line data available in INTERMACS.

9.2 Gender Analysis

Using the definition for the primary endpoint under Scenarios 1 and 2, males have higher success rates in the HeartWare VAS treatment group compared to males in INTERMACS, whereas females in the INTERMACS control group have higher success rates compared to females on the HeartWare VAS.

Table 16. Success by Gender

Gender	HeartWare VAS (% success)	INTERMACS (% success)
Male	94/101 (93.1)	339/377 (89.9)
Female	33/39 (84.6)	109/120 (90.8)

The gender by treatment interaction from a logistic regression model with treatment, gender, and treatment by gender interaction has a p-value of 0.15 in the ITT/Safety population. When including other covariates (age, BUN, RAP, creatinine, BSA, patient profile, and cardiac surgery history) the gender by treatment interaction has a p-value of 0.14.

The proportions of male and female treatment group subjects who experienced an SAE during the trial were similar (85% and 82%, respectively). However, the rate of death while on the HeartWare VAS was higher in women (7.7% versus 3%).

FDA Comment: The findings for women in the treatment group appear to be consistent with both control group women's results and the results overall. However, the gender by treatment interaction (after adjusting for covariates) has a p-value of 0.14, which would be considered statistically significant using a significance level of 0.15.

9.3 BSA-specific Primary Effectiveness Results

The Sponsor believes the size and implantation technique of its device may make it "suitable for smaller patients who would not otherwise be candidates for implantable LVAD support." However, the trial only enrolled one patient with a BSA <1.5 m^2, whereas there were 11 patients in the control group:

Table 17. Success by BSA

BSA (m^2)	HeartWare VAS (% success)	INTERMACS (% success)
<1.5	1/1 (100.0)	10/11 (90.9)
>1.5	126/136 (92.6)	434/484 (90.5)

Note: Patients with missing BSA at baseline are not included

The primary effectiveness endpoint did not appear to be dependent upon clinically significant differences in BSA of the groups' patients.

No statistical evaluation on the treatment by BSA interaction was conducted because there is only one subject in one subgroup.

FDA Comment: FDA agrees with the Sponsor's plan to collect additional clinical data supporting a labeling claim for patients with BSA <1.5m^2 in a post-approval study.

10. CLINICAL TRIAL RESULTS – SAFETY ASSESSMENT – ADVERSE EVENTS

The trial's safety evaluation is based primarily upon the rate of adverse events. As noted earlier, mortality was incorporated into the overall primary endpoint for this trial, and is discussed in greater detail here, in addition to other adverse events.

Serious adverse events included deaths and unanticipated adverse device effects (UADEs). Non-serious events included infection, bleeding, hemolysis, thromboemboli/thrombus, neurologic events, cardiac arrhythmia, hepatic dysfunction, myocardial infarction, psychiatric episode, renal dysfunction, respiratory dysfunction, right heart failure, and device malfunction or failure.

The CEC reviewed and adjudicated both serious and non-serious adverse events. The events for adjudication were either pre-specified by definitions contained within the INTERMACS registry (the so-called "INTERMACS events") or *ad hoc* ("Other" events that are considered clinically relevant by the investigator but that did not meet the organ- or event-specific definitions previously described by INTERMACS). As mentioned previously, although identically-defined INTERMACS events data were collected for both the treatment and control arm patients, the protocol did not pre-specify any consideration of the control arm's adverse events rates or, consequently, any direct comparison of event rates between the HeartWare VAS treatment and INTERMACS control arms. Justification at the time of the protocol design included differing methods of handling events (monitoring and adjudication for the treatment arm versus auditing and adjudication of events in the registry control arm).

FDA Comment: FDA's inferences regarding safety are dependent upon comparison to the current state of the field, rigorous data collection, and consistent adjudication of treatment arm adverse events. As noted above, FDA had concerns that the reporting and adjudication of serious adverse events, including neurological events, may have underrepresented the true rate of SAEs in HeartWare VAS patients. FDA therefore requested that detailed adverse event rates for the 499 INTERMACS control patients be provided to allow for an adjunctive comparison of key serious adverse events. FDA believed that this adjunctive, *post hoc* analysis would be informative given that "the adverse events in INTERMACS are collected and managed according to precise data protocols and…are of higher quality than can be found in a typical registry."[11] To date, FDA has been unable to conduct direct comparisons to

INTERMACS control group patients due to the unavailability of patient line data from the INTERMACS database and has had to interpret only aggregate data available in the published literature. Please refer to the correspondence between the Sponsor and INTERMACS in Appendix B. FDA acknowledged that the comparison of adverse event rates was not pre-specified for the reasons cited above and that differing methods of SAE data collection and adjudication/auditing would limit inferences to be drawn. However, FDA has maintained that the rigorously collected SAE data within the INTERMACS database would help to inform interpretation of the contemporaneously collected SAE data from the HeartWare VAS patients. The Sponsor was not able to provide patient line data for FDA review and comparisons of HeartWare VAS adverse event rates to the contemporaneous control arm are not possible. FDA seeks panel input on this issue.

10.1 Treatment Arm Adverse Events

The following section discusses the adverse events that occurred in the treatment arm of the trial. Investigators' identified 776 adverse events throughout the trial, of which 452 were believed to be SAEs.

Table 18. Adverse Events

HeartWare VAS (N = 140)	**Events**	**Subjects n (%)**
Total Adverse Events	776	132 (94.3)
INTERMACS Events	437	116 (82.9)
"Other" Adverse Events	338	105 (75.0)
Unanticipated Adverse Device Experiences	1	1 (0.7)

Despite the broad characterization of LVAD adverse events described by the INTERMACS definitions, the investigators independently identified "Other" events as having occurred at a rate equivalent to 82% of the universal well-defined INTERMACS Events (338/437 as shown in Table 18). Unlike the discretely defined INTERMACS Events, characterizations of "Other" events were more investigator-specific and not described consistently across sites. "Other" is defined by INTERMACS as "An event that causes clinically relevant changes in the patient's health (e.g. cancer)." Per Table 19 below, 36% (164/452) of AEs classified as SAEs by investigators were "Other." CEC adjudication resulted in that rate being decreased to 28% (145/523), though the CEC ultimately identified 16% (71) more SAEs than did the investigators (see Table 19 below).

Of note, if a patient had more than one event simultaneously in a single INTERMACS adverse event category, then the CEC adjudicated this as one event. For example, if a patient had both a driveline and a localized infection, while the CEC did adjudicate both events, they were considered as a single, linked event. As such, the overall number of CEC reported adverse events is 763, while the number of investigator reported adverse events is 776. Overall, assessment of SAE device-relatedness was similar between investigators and the CEC (Table 20).

Table 19. Serious Adverse Events

HeartWare VAS (N = 140)	Investigator Reported (n)	CEC Reported (n)
Serious Adverse Events	452	523
INTERMACS Events	287	377
"Other" Adverse Events	164	145
Unanticipated Adverse Device Experiences	1	1

Note: See Table 18 for the total number of adverse events in each category. The exceptions are that the total number of CEC reported events is 763 and the total number of CEC reported INTERMACS events is 398

Table 20. Serious Adverse Event Relationship to Device

Relationship to Device	Investigator Count of Event	Adjudicated Count of Event
Not Related	241	281
Unlikely Related	77	89
Possibly Related	83	97
Probably Related	22	19
Related	28	36
UADE	1	1
Grand Total	452	523

The Sponsor did provide a listing of the specific "Other" events. The most commonly occurring events are categorized under cardiac disorders, nervous system disorders and respiratory, thoracic, and mediastinal disorders.

The INTERMACS events included the following categories: bleeding, cardiac arrhythmia, hemolysis, hepatic dysfunction, infection, myocardial infarction, neurological events, psychiatric episodes, renal dysfunction, respiratory dysfunction, right heart failure, thromboembolism and device malfunction. These event definitions can be found in the Sponsor's executive summary. A table summarizing the observed INTERMACS event rates in the treatment group out to the primary endpoint time period (180 days), as well as a table summarizing these rates out to the date of the last patient's last visit (August 23, 2010), are included in this Executive Summary's Appendix.

FDA Comment: FDA believes the observed rates for the majority of the pre-specified INTERMACS adverse events in the HeartWare treatment group were clinically acceptable. However, FDA believes the observed rates of neurological events and device malfunction may not be similarly acceptable, and the peri-operative device associated infection rate was notable. These events are discussed in further detail below (Sections 10.3-10.5).

A large proportion of SAEs were dependent upon the vague definition of "Other." FDA reviewed the specifics of the "Other" events and believes that most were not likely to be associated with an SAE. However, many "Other" events (e.g., visual disturbances, multi-organ failure, post-procedure hemorrhage, mediastinal hematoma) could have obscured an important SAE such as a neurological event or bleeding episode. FDA remains concerned that variability in what investigators considered "Other" adverse events may have affected the interpretability of the SAE rate generated by the trial. FDA's ability to draw definitive

conclusions about the safety profile of this device is further complicated by the inability to compare these adverse event rates and occurrences to line data available in INTERMACS.

The Sponsor did provide a comparison of clinical trial data to that published by Miller, et al.[12], Pagani, et al.[13] and Starling, et al.[14]. Miller, et al. and Pagani, et al. are comparable clinical trials, while Starling et. al is a postmarket study that utilized the INTERMACS database.

Comparisons of the adverse events in the peri-operative period and through August 23, 2010 are shown in Tables 21 and 22 respectively. August 23, 2010 corresponds to the date of the last enrolled patient's last visit.

Table 21. Adverse events through day 30

	Patients Affected (%) 0-30 Days			Event Rate (events PPY) 0-30 Days		
	HW003	Miller et al	Pagani et al	HW003*	Miller et al	Pagani et al
Bleeding						
Re op	14.3	30	23.8	2.03	4.41	3.32
Infections						
Local (non-device)	14.3	21	22.8	1.79	3.63	3.59
Driveline exit	3.6	0	0.7	0.45	0	0.09
Sepsis	2.1	13.5	9.3	0.27	1.77	1.24
Neurological Events						
Ischemic CVA	5.0	3.8	2.8	0.63	0.49	0.37
Hemorrhagic CVA	1.4	1.5	1.4	0.18	0.2	0.18
TIA	1.4	1.5	1.1	0.18	0.2	0.14
Respiratory Dysfunction	15.7	21.8	21.7	2.89	3.14	3.18
Arrhythmia						
Ventricular	10.0	18	13.2	1.34	2.55	1.89
Right Heart Failure						
Inotropes	12.1	9	10	1.52	1.18	1.34
RVAD	2.1	3	5.7	0.27	0.39	0.74
Thrombus/Thromboembolism	2.9	6	5.7	0.36	0.78	1.02
Renal Dysfunction	5.7	11.3	8.5	0.72	1.47	1.11
Psychiatric event	3.6	4.5	4.6	0.45	0.59	0.6
Hepatic dysfunction	2.1	1.5	1.4	0.27	0.2	0.18
Hemolysis event	1.4	2.2	2.1	0.18	0.29	0.28

*Event rate for the HVAD was calculated by events/11.2 patient-years.

Table 22. Adverse events through August 23, 2010 (last patient's last visit)

	HeartWare BTT		Miller et al		Pagani et al		Starling et al	
	Subjects Affected %	Events PPY	Subjects Affected %	Events PPY	Subjects Affected %	Events PPY	Subjects Affected %	Events PPY
Bleeding		1.59		2.87		2.12		1.44
Reoperation	17.1	0.33	31	0.78	26	0.45	UNK	UNK
Transfusion: >=4 within 7 days	7.9	0.13	UNK	UNK	UNK	UNK	UNK	UNK
Transfusion: Any after 7 days	29.3	1.02	UNK	UNK	UNK	UNK	UNK	UNK
Cardiac Arrhythmia								
Ventricular	19.3	0.39	24	0.79	20	0.4	27	0.49
Supraventricular	19.3	0.41	UNK	UNK	UNK	UNK	UNK	UNK
Hemolysis	3.6	0.06	3	0.06	4	0.06	3	0.04
Hepatic Dysfunction	2.9	0.05	2	0.05	2	0.04	7	0.08
Infection								
Local Non-device	25.0	0.47	28	1.13	30	0.85	29	0.61
Percutaneous Site/Pocket	12.1	0.31	14	0.37	16	0.33	20	0.35
Sepsis	11.4	0.22	20	0.62	17	0.35	19	0.33
Myocardial Infarction	0.7	0.01	UNK	UNK	UNK	UNK	2	0.02
Neurological Event		0.28		0.31		0.18		0.14
TIA	4.3	0.08	4	0.1	2	0.04	UNK	UNK
Ischemic CVA	*7.1**	0.12	6	0.13	5	0.1	5	0.08
Hemorrhagic CVA	4.3	0.07	2	0.05	3	0.05	1	0.01
Other	0.7	0.01	6	0.16	5	0.09	5	0.06
Psychiatric Episode	7.9	0.13	7	0.18	6	0.1	8.3	0.12
Renal Dysfunction	8.6	0.16	14	0.31	11	0.17	10	0.13
Respiratory Dysfunction	19.3	0.42	26	0.7	26	0.48	20	0.29
Right Heart Failure		0.34		0.36		0.29		0.18
RAVD	2.9	0.04	4	0.08	6	0.09	UNK	UNK
Inotropes/NO	16	0.30	13	0.28	13	0.2	UNK	UNK
Arterial Thromboembolism	2.9	0.05	7	0.15	6	0.14	1	0.01
Venous Thromboembolism	6.4	0.11	UNK	UNK	UNK	UNK	6.5	0.09
Device Malfunction								
Pump Failure	5.7	0.09	4	0.08	4	0.07	1	0.01
Non-pump Failure	14.3	0.34	UNK	UNK	UNK	UNK	UNK	UNK

* FDA believes that the ischemic CVA rate is 7.9%

FDA Comment: Although most adverse event rates seem comparable to those cited in the literature, FDA notes a higher level of peri-operative ischemic stroke events seen with the HeartWare VAS as shown in Table 21. In addition, as previously mentioned, FDA does not agree with the Sponsor's *post hoc* reclassification of some neurological events and seeks panel input on the significance of the longer term neurological event rates (as demonstrated in part by Table 22).

10.2 Deaths on Device

In the HeartWare VAS primary cohort, there were six deaths, summarized in Table 23.

Table 23. Summary of Patient Deaths in BTT Study

Subject ID	Study Day Death Occurred	Cause of Death	Device Related (CEC Adjudication)
[redacted]	12	Hemorrhagic CVA	No
	24	Hepatic failure	Unknown
	94	Cardiovascular	Yes
	50	Multi-organ Failure	No
	11	Hemorrhagic CVA	Yes
	33	Multi-organ failure	Unknown

Three of the six patients were profile level 2, two were profile level 3, and one was profile level 7. The rate of death on the original device the in HeartWare VAS treatment group (4.3%) was lower than that seen for the INTERMACS control group (8.8%). At least two of the deaths in the treatment arm were device-related.

Of note, two additional treatment group patients died within the six month endpoint timeframe, but after first undergoing HeartWare VAS replacement with a second device. These deaths occurred after explantation of the original HeartWare VAS and therefore do not appear to have been formally adjudicated by the CEC.

- Subject [redacted] (INTERMACS profile [redacted] died six weeks after initial HVAD pump implantation. The patient developed intra-ventricular/pump thrombosis in the peri-operative period; this complication was treated first medically (tissue plasminogen activator [tPA] and anti-platelet infusions) and then with device exchange to a second HeartWare VAS on post-operative day eight; the patient suffered a hemorrhagic stroke 10 days thereafter. Cause of death was listed as multi-system organ failure (MSOF).

- Subject [redacted] (INTERMACS profile [redacted] died 4 months after the initial HeartWare VAS implantation. The patient's clinical course deteriorated on post-operative day 83, and was associated with "blood stagnation around inflow resulting in a clot formation." The patient underwent device exchange to biventricular support (post-operative day 86). The cause of death was listed as MSOF.

These patients were counted as failures in the trial.

FDA Comment: FDA acknowledges the CEC adjudications; however, FDA's review of the detailed patient narratives for the six patients who died raises questions about the assigned device-relatedness:

- Subject [redacted]s hemorrhagic CVA ("spontaneous subdural hematoma") occurred in the setting of obligatory anticoagulation.

- Subject [redacted]'s hepatic failure developed subsequent to hemorrhagic shock associated with apparent apical inlet cannula bleeding.

- Subject [redacted]'s cause of death (MSOF) included a subarachnoid hemorrhage that developed in the setting of an INR "found to be above target range." Subject [redacted]'s MSOF developed in the setting of the need to keep the patient's chest open after post-implantation bleeding.

10.3 Device Exchange

The INTERMACS event device malfunction defined a failure of the HeartWare VAS. The malfunctions were further classified as being either a pump or a non-pump failures. Twenty treatment arm patients (14.3%) experienced 26 device malfunctions involving their original HeartWare VAS. Twelve of these events were adjudicated as SAEs.

According to the Sponsor's records, seven of these SAEs (involving seven patients) required exchange of the HVAD pump within 180 days of the initial implantation.

Table 24. Device Exchange Information

ID	Total Days on Original Pump	Death Date	Alive at 180 days post implant
[redacted]	152	N/A	Yes
	146	N/A	Yes
	180	N/A	Yes
	86	23-Apr-10	No
	8	11-Aug-09	No
	6	N/A	Yes
	9	N/A	Yes

Six of the patients received a second HVAD pump and one patient was implanted with biventricular VADs. According to FDA's review of the patient narratives, all cases of device exchange were associated with signs and/or symptoms of ventricular or pump thrombosis.

None of the BTT patients with ongoing post-exchange support at the time of data lock (n=8) were actively listed for a donor organ; one patient had been de-listed due to stroke, and seven were UNOS status 7. Two exchange patients died within the 180 day time period. Details of their clinical course are presented in Section 10.2.

As of a data cut-off date of July 15, 2011, 16 device replacements had occurred in the 140 patients from the HeartWare VAS treatment group.

FDA Comment: As noted previously, device exchange accounted for 54% of the treatment arm's 13 failures. FDA is concerned that the rate of device exchange and thrombosis for the HVAD pump is clinically significant and seeks panel input on this issue.

10.4 Stroke

Four patients experienced a hemorrhagic stroke and 11 patients experienced an ischemic stroke on the original device as of Day 180. Information regarding these patients, including their outcomes after stroke, is outlined in Table 25.

Table 25. Patient Outcomes after Stroke

Patient Identifier	Type of Stroke	Days from Implant	Modified Rankin Score Following Stroke	Modified Rankin Score In Recovery Phase	Vital Status
[redacted]	HCVA	9	Death	3	Death
	HCVA	11	Death	Not recorded	Death
	HCVA	40	Death	4	Death
	HCVA	145	5	4	Alive, Not transplant eligible
	ICVA	1	4	0	Transplant
	ICVA	1	4	2	Transplant
	ICVA	2	2	2	Alive, Transplant Eligible
	ICVA	2	1	1	Alive, Transplant Eligible
	ICVA	1	4	Not recorded	Death
	ICVA	2	3	1	Death
	ICVA	16	2	2	Transplant
	ICVA	68	3	2	Transplant
	ICVA	129	4	2	Transplant
	ICVA	2	unknown	unknown	unknown
	ICVA	141	5	4	Alive, Not transplant eligible

* Patient not counted by Sponsor

As noted in Section 7.5, FDA disagrees with the *post hoc* censoring of an adjudicated SAE of ischemic cerebrovascular accident (ICVA). Further, FDA agrees with the Sponsor that *post hoc* "corrections and mitigations" (e.g. due to patient fall or multi-

organ failure) are clinically relevant when considering the adjudicated SAEs of hemorrhagic CVA (HCVA). Therefore, as shown in Table 25, FDA considers the observed ischemic stroke rate (patients affected) to be 8% (11 patients), and the observed hemorrhagic CVA rate to be 3% (4 patients).

FDA Comment: The PMA data indicate 27% of ischemic stroke patients either died or lost transplant eligibility and 100% of the hemorrhagic stroke patients died or lost their transplantation eligibility as a result of these neurological events.

FDA accepts the Sponsor's statement that a discrete portion of strokes were in the immediate peri-operative period and therefore likely related, in part, to "procedural" factors. However, in FDA's view, procedural factors (e.g., implantation techniques) and management factors (e.g., degree of anticoagulation required) are not immediately separable from the device's overall safety profile. In addition, the comparison made to the recent datasets seem to suggest a trend toward higher stroke rates with the HVAD pump in the peri-operative time frame and perhaps in the longer-term. FDA believes the neurological event rate and the sequelae are of significant impact and requests panel input on the rate of occurrence of these events.

10.5 Infection

As indicated in Table 21 above, the peri-operative driveline (pump pocket) infection rate for the HeartWare VAS is 0.45 events/patient year. Driveline infection affected 3.6% of patients in the peri-operative time period. These rates of device related infection are substantially higher when compared to the cited literature. It is also of interest that the literature values are based upon devices that require an abdominal pocket, while the HVAD pump does not require creation of a pump pocket.

Table 26 presents longer term post-implantation infection rates. The rate of infection seen with the HeartWare VAS as of the last enrolled patient's last visit on August 23, 2010 was compared to that seen in the literature. These data show that long-term infection rates for patients with the HeartWare VAS are less than or comparable to literature values.

Table 26. Cumulative Infection Rate of HeartWare VAS (out to August 23, 2010) Compared to Literature Rates

	HeartWare BTT		Miller et al		Pagani et al		Starling et al	
	Subjects Affected (%)	Events PPY	Subjects Affected (%)	Events PPY	Subjects Affected (%)	Events PPY	Subjects Affected (%)	Events PPY
Infection								
Local Non-device	25.0	0.47	28	1.13	30	0.85	29	0.61
Percutaneous Site/Pocket	12.1	0.31	14	0.37	16	0.33	20	0.35
Sepsis	11.4	0.22	20	0.62	17	0.35	19	0.33

FDA Comment: The peri-operative driveline infection rate appeared to be substantially greater than other approved LVADs. FDA recognizes, however, that the rate of infections associated

with the HeartWare VAS driveline appears to have improved with extended implantation times. Overall, FDA agrees that the rates of INTERMACS defined infection events for the HeartWare VAS is similar or less than the three comparison groups selected.

11. CLINICAL TRIAL RESULTS – QUALITY OF LIFE and FUNCTIONAL ASSESSMENT

11.1 Quality of Life

Quality of Life was assessed using the KCCQ and the EuroQOL Measure for Heart Failure.

Table 27. KCCQ Score Summary

Overall Summary Score	Baseline	Month 6	Change from Baseline
N	128	74	70
Mean (SD)	34.86 (18.89)	67.5 (20.38)	30.94 (26.51)
Median	31.50	71.40	34.50
Min, Max	0.0, 8.41	19.3, 100.0	-49.4, 80.5
95% CI	31.56, 38.17	62.78, 72.23	24.62, 37.26

There were 56/70 patients with paired data who demonstrated at least a 10 point increase in KCCQ Summary Score at 6 months.

EuroQoL EQ-5D responses were similar in treatment and control arms. Data from the HeartWare VAS treatment arm are shown in Table 28.

Table 28. EuroQoL EQ-5D Score Summary

Overall Health State Score	Baseline	Month 3	Change from Baseline	Month 6	Change from Baseline
N	130	89	86	75	72
Mean (SD)	39.65 (23.54)	69.54 (19.96)	31.29 (27.52)	69.80 (19.82)	29.53 (25.18)
Median	40.00	75.00	30.00	75.00	30.00
Min, Max	0.0, 92.0	8.0, 100.0	-50.0, 85.0	4.0. 100.0	-36.0, 80.0
95% CI	35.57, 42.74	65.33, 73.74	25.39, 37.19	65.24, 74.36	23.61, 35.44

FDA Comment: Of the initial baseline data from 140 patients, there are KCCQ missing data for 12 patients. By week four, there were 24 missing assessments from the initial 128. Since eight patients died in the first six months, there are 58 missing assessments at six months. The Sponsor has not supplied a rationale for the missing KCCQ assessments and the scores have a wide variability. There is a similar amount of missing data for the EuroQol. FDA agrees that the quality of life of patients who remained alive and had data provided on the HeartWare VAS improved. However, in the setting of an unblinded trial with a significant amount of data missing, the quality of life is difficult to interpret.

11.2 Functional Status

Functional status was assessed by the 6-minute walk test and change in NYHA classification.

Table 29. Patient Change in NYHA Functional Status

	Class I n (%)	Class II n (%)	Class III n (%)	Class IV n (%)
Baseline (n=139)	0 (0%)	1 (1%)	5 (4%)	133 (96%)
Discharge (n=89)	4 (5%)	48 (55%)	26 (31%)	8 (9%)
Month 6 (n=17)	9 (53%)	8 (47%)	0	0

Table 30. Patient Change in 6-minute Walk Distance

Distance Walked (m)	Baseline	Month 6	Change from Baseline
N	132	75	74
Mean (SD)	89.4 (141.31)	246 (203.85)	150.14 (214.13)
Median	0.00	274	108.25
Min, Max	0.0, 600.2	0.00, 991.8	-273.1, 700.9
95% CI	65.07, 113.73	199.09, 292.90	100.53, 199.75

FDA Comment: Both NYHA and 6-minute walk were used for functional assessment. There was a substantial amount of missing data at six months, especially for NYHA classification, as the NYHA variable was deleted from the data collection form. Although the patients were severely limited (<300 meter 6-minute walk distance) at baseline and improved, at six months, they remained significantly impaired. This 6-minute walk distance is lower than with comparable LVAD devices. The variability is also high as shown by the standard deviation. FDA has concerns about the persistent limitation at six months for the 6 minute walk and the availability of paired data for functional assessments was minimal. The setting of an unblinded trial further complicates the ability to draw conclusions from these data.

12. CLINICAL STUDY RESULTS – ADJUNCTIVE ANALYSIS - Primary Endpoint Analysis Using Performance Goal

Despite the results of the propensity score analysis, questions remain regarding the clinical comparability of the treatment and control groups due to the differences in baseline characteristics between the two groups as well as the lack of clarity surrounding critical adverse event rates and adjudication. As a result, FDA was interested in understanding device performance against the pre-specified PG (Scenario 3).

Patient success for ongoing support at day 180 under the PG assessment required either UNOS listing status of 1A/1B or transplantation by the date of data lock, whereas testing for non-inferiority to the INTERMACS control group did not include consideration of transplant eligibility. FDA therefore reasoned that the presence of disabling strokes or similarly important SAEs would be partially reflected by the difference in endpoint success rates between the non-inferiority and PG methods.

Under the performance goal method, using the Scenario 3 definition of primary endpoint for treatment success, a total of 109 out of 140 (77.9%) patients reached endpoint success. The lower bound of the one-sided 95% confidence interval is 72.09%, exceeding the performance goal with statistical significance ($p<0.0001$). Thus the primary endpoint is met under this scenario and the treatment success rate of the HeartWare VAS is higher than 65%. As discussed previously, however, this success should also be considered in the context of INTERMACS results for BTT LVAD therapy between 2006 and 2009, which reflected a survival rate of ~88%.[10]

Eighteen of the 127 (14%) successes under the INTERMACS-comparison analysis became failures under the PG analysis. Sixteen of these patients were UNOS status 7; two patients were UNOS status 2. One of these 18 additional failures was a patient who had an ischemic stroke (modified Rankin Score [mRS] 1).

FDA Comment: The lower one-sided 95% confidence bound for the point estimate of success was 72%., which is greater than the pre-specified PG of 65%. FDA does note, however, that the PG success rate is substantially less than the primary ITT analysis of 90.7%. In addition, current, published results for BTT are ~88% as found in the INTERMACS registry.[9] FDA notes that these performance goal analysis results should also be considered in the context of the totality of the data from this trial.

13. ADDITIONAL CLINICAL EXPERIENCE

13.1 Continued Access Protocol(CAP)

The CAP was based upon the pivotal study design; the primary difference was the removal of pre-specified comparison to the comparator(s) of the main trial. A detailed analysis plan is pre-specified in the CAP protocol. The Sponsor provided the following information on CAP patients:

- Data on 87 CAP patients who had been implanted as of December 2010 (original PMA submission);
- Selected, updated data for the 101 CAP patients implanted prior to January 2011 (Sponsor's October 2011 response to FDA); and
- Baseline, endpoint, and partially adjudicated adverse event data for 110 CAP patients through February 28, 2011 (April 2011, Annual Report).
- The combined total of CAP and IDE is 250 patient implants.

FDA requested that the Sponsor formally update and expand the CAP dataset to more comprehensively address FDA concerns identified in the PMA review. However, the Sponsor chose not to submit updated line data for these patients. FDA has therefore assimilated CAP patient data from the above sources and used them to augment our interpretations of the pivotal trial data where appropriate. However, FDA notes that our sources for CAP data are neither completely mutually consistent nor reflective of a thoroughly audited dataset.

Data through February 28, 2011, indicate that 15 of 250 combined IDE and CAP HVAD pump implantations have experienced pump failure necessitating exchange: 11 due to thrombus, three due to "iatrogenesis" (i.e., ingestion of tissue fragments/blood clots in the immediate post-operative period), and one due to connector malfunction. At least five additional patients (of the 250) were identified as having pump failures from thrombosis that were salvaged with intraventricular tissue plasminogen activator (tPA). FDA also notes that one patient who underwent exchange to bi-VAD support had intraventricular/pump thrombus, but is not considered a thrombus associated pump failure by the sponsor. Therefore, FDA believes that cumulatively, 21 of 250 HVAD pump implantations (8.4% of the combined CAP and IDE cohorts) required device exchange or could be considered thrombus associated pump failures:

- pump failure (8%);
- pump failure due to thrombosis (6.4%);
- pump failure due to thrombosis necessitating device exchange (4.4%); and
- pump failure due to ingested material (surgical technique) (1.2%).

Additionally, as of February 28, 2011 the ischemic stroke rate for implanted patients remains of substantial clinical consequence:

Table 31. Adverse events in 250 patients (combined study and CAP patients)

Neurological Events	**Events 0-30 Days**	**Events > 30 Days**	**Disabling (MRS ≥ 4)**
Ischemic CVA	12	6	6
Hemorrhagic CVA	3	5	6
TIA	2	7	0

FDA Comment: Although caution is necessary when using the CAP data to corroborate or refute findings from the pivotal study, available data suggest to FDA that the pump failure rate due to thrombosis (i.e., necessitating device exchange or tPA) in the CAP population of 110 patients does not differ from the aggregate IDE results. The peri-operative ischemic stroke rate has also not decreased during the CAP. These findings, taken in context of the training and patient management modifications already implemented by the Sponsor, suggest to FDA that the pump failure/thrombosis rates and neurological event rates are unlikely to substantially decrease. Although the Sponsor suggested that device exchange may not be an appropriate component of VAD therapy "failure," FDA continues to believe that the need for device exchange is a relevant consideration when assessing the device's safety and effectiveness and seeks panel input on this issue.

13.2 Compassionate/Emergency Use (CU/EU)

The Sponsor indicated that 21 compassionate and emergency use patients have been implanted under the CAP as of February 2012. Most of these requests were for right ventricular use of the device and use in the pediatric patient population.

Regarding right ventricular use of the device, a publication in the journal Circulation[15] reports on a series of seventeen patients treated with the HeartWare device in both the right ventricular and left ventricular position, with 50% survival at 6 months and 59% survival to hospital discharge.

FDA Comment: Although FDA is interested in the panel's perspective on this issue for labeling purposes, the Sponsor has not submitted an IDE to study either the right ventricle or pediatric use indication.

13.3 Destination Therapy Trial

As FDA considers the totality of the data available to make a safety and effectiveness determination, data from the ENDURANCE trial for long-term use of the HeartWare VAS in DT patients are also considered. This trial is an ongoing, randomized controlled study of 450 patients assessing for non-inferiority at 2 years of the HeartWare VAS to LVAD therapy approved for DT in the United States. As of December 2010, 32 patients had been randomized to the HeartWare VAS and 16 patients to a control device; in their PMA, the Sponsor states that available data are limited to the following:

- 1 device exchange occurred (HVAD pump patient); and
- 4 patients have died with the device (all HVAD pumps).

FDA Comment: FDA has reviewed updated data from this trial, including approximately one-third of the total participants to be enrolled. Although caution is necessary when using data from the ongoing DT trial to corroborate or refute findings from the pivotal study, FDA's review of the DT trial's accumulating safety data necessitated our further consideration of detailed Sponsor and DSMB interactions. These findings cannot be discussed in an open forum, however, the trial is ongoing without modifications.

14. POST-APPROVAL STUDY

Note: The inclusion of a Post-Approval Study section in this summary should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The presence of a post-approval study plan or commitment does not in any way alter the requirements for premarket approval and a recommendation from the Panel on whether the risks outweigh the benefits. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study could be considered. The issues noted below are FDA's comments regarding potential

post-approval studies, for the Panel to include in the deliberations, if FDA finds the device approvable based upon the clinical premarket data.

FDA believes that if the HeartWare VAS is approved, post-approval studies (PAS) should be required as a condition of approval for this device for the treatment of advanced heart failure. Through review of the premarket data, FDA has identified the following postmarket concerns and recommends that, in addition to continued follow-up of the premarket cohort, a Newly Enrolled PAS be should be conducted to:

1. assess the safety and effectiveness of the device by body surface area (BSA);
2. assess quality of life, neurocognitive status, and functionality out to 5 years from the date of implant;
3. monitor the occurrence of mortality, neurological events, device malfunction and exchange, and other adverse events; and
4. evaluate the effectiveness of a training program.

The Sponsor has proposed conducting three separate PAS: (1) Extended Follow-up of Premarket Cohort, (2) Newly Enrolled Cohort Study, and (3) Evaluation of the Training Program.

The Sponsor did not submit a protocol covering the *Extended Follow-up of Premarket Cohort* in the postmarket. The Sponsor has submitted a PAS protocol for the *Newly Enrolled Cohort* and *Clinical Training Program* (March 15, 2012).

14.1 Extended Follow-up – PAS 1

A study plan for the extended follow-up study was not submitted. Although safety and effectiveness was assessed at 180 days in the premarket study, these participants are consented for 5 years post-implant in order to capture longer-term performance. FDA expects the post-approval study plan for the extended follow-up to evaluate potential long-term safety signals (an increase in adverse events or unexpected adverse events) and effectiveness early within the postmarket phase and to include an analysis plan and reporting reschedule.

14.2 Newly Enrolled – PAS 2

Objective
The objective of the newly enrolled study is to compare the safety and effectiveness data collected in a commercial setting with that collected in the pivotal clinical trial, the CAP, and from INTERMACS..

Hypotheses
Rejection of the null hypothesis for the primary objective of survival would denote non-inferiority of the HeartWare VAS group to the control group results with a 10% margin (one-sided 5% alpha).

Data Collection (endpoints)
With the newly enrolled study, the primary endpoint is defined as survival (alive on the originally implanted device or transplanted or explanted for recovery). Due to concerns regarding thrombus and device malfunctions, the secondary endpoint also includes device malfunctions (which would be analyzed per the INTERMACS definitions) and adverse events associated with the malfunctions. The Sponsor should provide the power calculations for these additional analyses based on the approved sample size.

In the premarket study, seven out of seven pumps exchanged were associated with signs and/or symptoms of thrombus. Four of these devices malfunctioned due to high power alarms, and two transplants occurred as a result of these device malfunctions. Therefore, high-power alarms may be an issue to be followed in the postmarket phase as it is a non-urgent cause for transplant. FDA believes that the Sponsor should monitor the sequence of the events to determine which occurs first: thrombus necessitating transplant, or device malfunction. The type of device malfunction associated with transplants should also be monitored in the PAS.

HeartWare intends to pursue a labeling claim for patients with a BSA<1.5m^2. However, the Sponsor cannot make any such a labeling claim based on the premarket study data, as only one patient with a BSA < 1.5m^2 was enrolled in the study. Although data from the CAP, CU, and EU cases had been considered to address this need, currently there are only 8 patients out of 150 (5%) with BSA<1.5m^2. Therefore, a separate analysis of patients enrolled with a BSA<1.5m^2 will be conducted. Of note, any study of off label use in patients with right heart failure or in pediatric population will require an IDE.

Additionally, conclusions regarding NYHA cannot be made due to lack of post-baseline premarket data. The PAS protocol will therefore capture NYHA (as well as 6-minute walk) as a secondary endpoint.

Sample Size (Patients and Sites)
The sponsor states that "at least" 155 HeartWare and 155 Control (INTERMACS) patients are to be enrolled for 180 days of follow-up data to detect non-inferiority with a 10% margin, using a one-sided 5% significance level at 90% power. However, the Sponsor did not formally account for attrition over time or give justification for a 10% margin. Furthermore, the ability to draw any conclusions about patient outcomes and adverse events in the INTERMACS control group needs to be discussed given FDA's inability to access the line data for these patients.

Statistical Plan
The statistical plan for the newly enrolled study will use a Kaplan Meier survival analysis to assess the primary endpoint of survival, exchange, or recovery. Due to the device exchange data collected in the premarket study, the sponsor has provided an adequate plan to conduct detailed analyses for stroke, pump thrombosis, and pump exchange. As long-term IDE data is not yet conclusive, it is premature to demonstrate non-inferiority of the PAS cohort with these rates. The Sponsor also states that there will be a prospective comparison of patents that adhere to anticoagulation and blood pressure regulation

guidelines. The Sponsor has agreed that a learning curve for physician training will be analyzed by assessing the poolability of the patient data between IDE and non-IDE sites, followed by comparison of AEs by site type.

FDA Comment: FDA seeks panel input on the association between device malfunctions and adverse events (namely thrombus necessitating transplant) and if the order in which these events occur should be monitored in the postmarket setting. FDA also seeks panel input on if the type of device malfunction associated with transplants should be monitored postmarket. Additionally, FDA requests panel input on whether or not a 10% margin for non-inferiority is clinically acceptable for the Newly Enrolled PAS.

14.3 Clinical Training Program – PAS 3

Objective
A clinical training program will be implemented to train new physicians in order to describe compliance, competency and outcomes across sites The study will also measure the correlation between adherence to the program and patient outcomes.

Study Design and Study Population
Teams of clinicians new to HeartWare will participate in the 5-part training program. These teams will most likely be exclusive to the non-IDE sites; however, this is not stated.

Hypotheses
No formal hypotheses are presented, as this is an observational study.

Data Collection (endpoints)
The Sponsor has provided details regarding data collection for both the interventionalist teams and the patient outcome data. Data will be collected through an assessment following each of the training parts in order to test the teams' understanding of the material. Patients' outcome data will be collected in PAS 2 (Newly Enrolled).

Sample Size (Patients and Sites)
The number of sites within the training program will be based on those that participate in the registry. The Sponsor has not estimated the number of sites within the registry that will be in the training program.

Statistical Plan
Statistics for the observational study are descriptive and similar to those used in the Newly Enrolled Cohort study. These are adequate.

15. CONCLUSIONS

The Sponsor seems to have statistically met the primary endpoint using both a propensity score stratification and performance goal analysis method. However, due to concerns regarding missing data, treatment and control group comparability, device exchange and

neurological event rates, the data require careful consideration of what clinical conclusions can be drawn. FDA requests input from the Advisory Panel in interpreting the totality of the data and rendering a recommendation. Furthermore, FDA also requests input on the development of the proposed post-approval study.

APPENDIX A.

The following tables were provided by the Sponsor and include summaries of post-implantation INTERMACS events.

Table 1. INTERMACS Events at Primary Endpoint (Day 180)

	HeartWare LVAD (N=140)								
				Onset Day of Event					
	Overall			Day 1-30			Day 31-180		
Subject Years (Cumulative) [1]:	56.7			11.2			45.5		
INTERMACS Event Type [2]	Events n	Events/ Subject Year	Subjects n (%)	Events n	Events/ Subject Year	Subjects n (%)	Events n	Events/ Subject Year	Subjects n (%)
Total Events	437	7.71	116 (82.9)	246	21.99	98 (70.0)	191	4.20	66 (47.1)
Bleeding	120	2.12	58 (41.4)	67	5.99	48 (34.3)	53	1.17	22 (15.7)
Re-operation	27	0.48	23 (16.4)	23	2.06	20 (14.3)	4	0.09	4 (2.9)
Transfusion: >=4 within 7 days	10	0.18	10 (7.1)	10	0.89	10 (7.1)	0	0	0
Transfusion: Any after 7 days	77	1.36	37 (26.4)	31	2.77	25 (17.9)	46	1.01	20 (14.3)
Other	6	0.11	5 (3.6)	3	0.27	3 (2.1)	3	0.07	2 (1.4)
Cardiac Arrhythmia	63	1.11	46 (32.9)	42	3.76	35 (25.0)	21	0.46	14 (10.0)
Ventricular	29	0.51	25 (17.9)	15	1.34	14 (10.0)	14	0.31	11 (7.9)
Supraventricular	32	0.56	25 (17.9)	25	2.24	21 (15.0)	7	0.15	6 (4.3)
Not Specified	2	0.04	2 (1.4)	2	0.18	2 (1.4)	0	0	0
Hemolysis	4	0.07	4 (2.9)	2	0.18	2 (1.4)	2	0.04	2 (1.4)
Hepatic Dysfunction	4	0.07	4 (2.9)	3	0.27	3 (2.1)	1	0.02	1 (0.7)
Infection	102	1.80	53 (37.9)	49	4.38	35 (25.0)	53	1.17	32 (22.9)
Sepsis	11	0.19	10 (7.1)	3	0.27	3 (2.1)	8	0.18	7 (5.0)
Driveline Exit Site	19	0.34	14 (10.0)	5	0.45	5 (3.6)	14	0.31	11 (7.9)
Localized Non-device	37	0.65	33 (23.6)	20	1.79	20 (14.3)	17	0.37	17 (12.1)
Other	35	0.62	24 (17.1)	21	1.88	16 (11.4)	14	0.31	11 (7.9)
Myocardial Infarction	1	0.02	1 (0.7)	0	0	0	1	0.02	1 (0.7)
Peri-operative	0	0	0	0	0	0	0	0	0
Non-perioperative	1	0.02	1 (0.7)	0	0	0	1	0.02	1 (0.7)

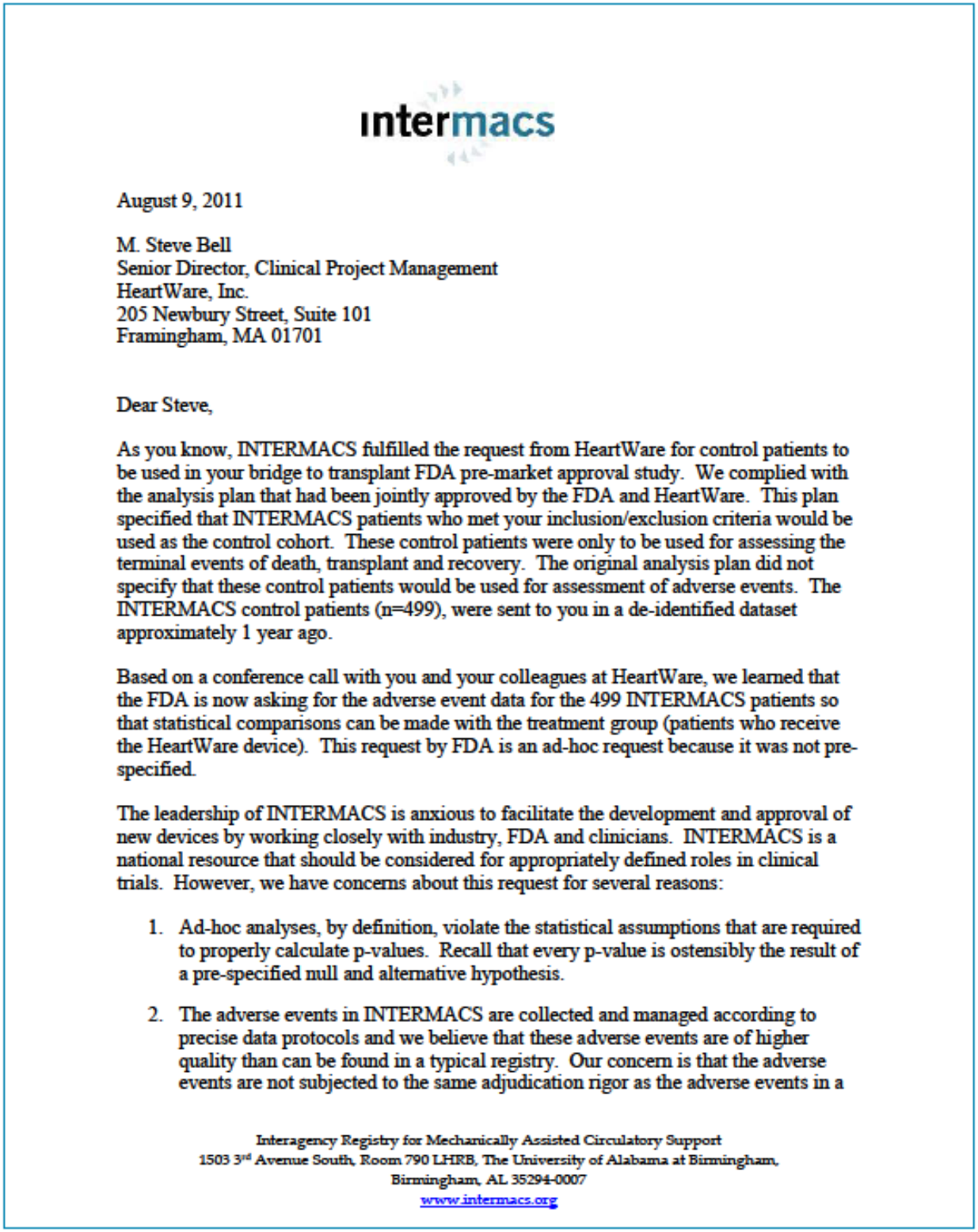
Note: Includes INTERMACS events with onset time on or post skin incision for implantation. All summarized events have been adjudicated.
[1] Subject Years calculated as sum of all subject post-implant follow-up in days divided by 365.24.
[2] Subjects with multiple events of the same type or subcategory are counted only once per row and column combination.

Table 2. INTERMACS Events through August 23, 2010

	HeartWare LVAD (N=140)								
				Onset Day of Event					
	Overall			Day 1-30			> Day 30		
Subject Years (Cumulative) [1]:	84.9			11.2			73.7		
INTERMACS Event Type [2]	Events n	Events/ Subject Year	Subjects n (%)	Events n	Events/ Subject Year	Subjects n (%)	Events n	Events/ Subject Year	Subjects n (%)
Total Events	501	5.90	121 (86.4)	249	22.26	100 (71.4)	252	3.42	79 (56.4)
Bleeding	133	1.57	60 (42.9)	68	6.08	49 (35.0)	65	0.88	28 (20.0)
Re-operation	28	0.33	24 (17.1)	23	2.06	20 (14.3)	5	0.07	5 (3.6)
Transfusion: >=4 within 7 days	11	0.13	11 (7.9)	11	0.98	11 (7.9)	0	0	0
Transfusion: Any after 7 days	87	1.02	41 (29.3)	31	2.77	25 (17.9)	56	0.76	25 (17.9)
Other	7	0.08	6 (4.3)	3	0.27	3 (2.1)	4	0.05	3 (2.1)
Cardiac Arrhythmia	70	0.82	48 (34.3)	42	3.76	35 (25.0)	28	0.38	17 (12.1)
Ventricular	33	0.39	27 (19.3)	15	1.34	14 (10.0)	18	0.24	13 (9.3)
Supraventricular	35	0.41	27 (19.3)	25	2.24	21 (15.0)	10	0.14	9 (6.4)
Not Specified	2	0.02	2 (1.4)	2	0.18	2 (1.4)	0	0	0
Hemolysis	5	0.06	5 (3.6)	2	0.18	2 (1.4)	3	0.04	3 (2.1)
Hepatic Dysfunction	4	0.05	4 (2.9)	3	0.27	3 (2.1)	1	0.01	1 (0.7)
Infection	124	1.46	61 (43.6)	50	4.47	36 (25.7)	74	1.00	42 (30.0)
Sepsis	19	0.22	16 (11.4)	3	0.27	3 (2.1)	16	0.22	13 (9.3)
Driveline Exit Site	26	0.31	17 (12.1)	5	0.45	5 (3.6)	21	0.28	14 (10.0)
Localized Non-device	40	0.47	35 (25.0)	21	1.88	21 (15.0)	19	0.26	19 (13.6)
Other	39	0.46	26 (18.6)	21	1.88	16 (11.4)	18	0.24	13 (9.3)
Myocardial Infarction	1	0.01	1 (0.7)	0	0	0	1	0.01	1 (0.7)
Peri-operative	0	0	0	0	0	0	0	0	0
Non-perioperative	1	0.01	1 (0.7)	0	0	0	1	0.01	1 (0.7)

Note: Includes INTERMACS events with onset time on or post skin incision for implantation up to last subject last visit occurring on August 23, 2010. All summarized events have been adjudicated.
[1] Subject Years calculated as sum of all patient post-implant follow-up in days divided by 365.24.
[2] Subjects with multiple events of the same type or subcategory are counted only once per row and column combination.
[3] One case was misidentified as thrombus on the inflow cannula by TEE and is reported here as arterial. However, at transplant this was subsequently shown to be pannus (healing tissue) growing up the side of the inflow cannula.

APPENDIX B.



intermacs

August 9, 2011

M. Steve Bell
Senior Director, Clinical Project Management
HeartWare, Inc.
205 Newbury Street, Suite 101
Framingham, MA 01701

Dear Steve,

As you know, INTERMACS fulfilled the request from HeartWare for control patients to be used in your bridge to transplant FDA pre-market approval study. We complied with the analysis plan that had been jointly approved by the FDA and HeartWare. This plan specified that INTERMACS patients who met your inclusion/exclusion criteria would be used as the control cohort. These control patients were only to be used for assessing the terminal events of death, transplant and recovery. The original analysis plan did not specify that these control patients would be used for assessment of adverse events. The INTERMACS control patients (n=499), were sent to you in a de-identified dataset approximately 1 year ago.

Based on a conference call with you and your colleagues at HeartWare, we learned that the FDA is now asking for the adverse event data for the 499 INTERMACS patients so that statistical comparisons can be made with the treatment group (patients who receive the HeartWare device). This request by FDA is an ad-hoc request because it was not pre-specified.

The leadership of INTERMACS is anxious to facilitate the development and approval of new devices by working closely with industry, FDA and clinicians. INTERMACS is a national resource that should be considered for appropriately defined roles in clinical trials. However, we have concerns about this request for several reasons:

1. Ad-hoc analyses, by definition, violate the statistical assumptions that are required to properly calculate p-values. Recall that every p-value is ostensibly the result of a pre-specified null and alternative hypothesis.

2. The adverse events in INTERMACS are collected and managed according to precise data protocols and we believe that these adverse events are of higher quality than can be found in a typical registry. Our concern is that the adverse events are not subjected to the same adjudication rigor as the adverse events in a

Interagency Registry for Mechanically Assisted Circulatory Support
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Birmingham, AL 35294-0007
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clinical trial. The differing processes of managing adverse events could lead to biases in either direction.

3. We understand that the FDA is fully aware of the limitations inherent in comparing the adverse events from the two sources. We also trust that FDA has the ability to incorporate the limitations as they assess the adverse event comparisons. Our concern lies in how the information will be made publicly available. Certainly the public Summary of Safety and Effectiveness (SSE) will have to contain these comparisons. Even if the limitations are plainly stated, we are concerned that the numerical comparisons may be lifted and quoted without reference to the limitations.

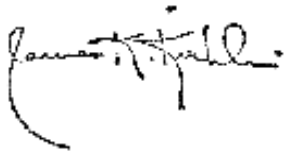
4. INTERMACS has published several papers containing analyses of adverse events. Perhaps HeartWare can refer to the published data and use this information to define a "reference group".

5. We would encourage both HeartWare and the FDA to revisit the original analysis plan and implement whatever the plan specified about assessing adverse events.

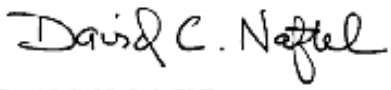
In consideration of these points, we regret that it is not possible to provide the narrowly restricted adverse event data that you have requested for the ancillary analyses that are beyond the original scope of the data sharing agreement. We would be pleased to share with you the aggregated adverse event data for the entire INTERMACS cohort.

In summary, we believe that the comparisons of adverse event rates as requested would have more potential for misinterpretation than the potential for informing your clinical trial. We would like to reiterate that we are very willing to discuss these issues with HeartWare and with the FDA.

Sincerely,



James K. Kirklin, MD
Principal Investigator for INTERMACS



David C. Naftel, PhD
Co-Principal Investigator for INTERMACS

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