SUMMARY OF SAFETY AND PROBABLE BENEFIT

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1. General Information

Device Generic Name:	Ventricular Bypass (Assist) Device (21 CFR 870.3545)
Device Trade Name:	CentriMag® Right Ventricular Assist System (RVAS) for Humanitarian Use in Patients in Right Heart Failure
Applicant's Name and Address:	Levitronix LLC 45 First Avenue Waltham, MA 02451
Humanitarian Device Exemption (HDE) Number:	H070004
Humanitarian Use Device (HUD) Number:	06-0174
Date of Humanitarian Use Device Designation:	January 29, 2007
Date(s) of Panel Recommendation:	None
Date of Good Manufacturing Practices Inspection:	5/26/2008 – 06/05/2008
Date of Notice of Approval to Applicant:	October 7, 2008

2. Indications for Use

The Levitronix CentriMag RVAS is intended to provide temporary circulatory support for up to 14 days for patients in cardiogenic shock due to acute right ventricular failure.

The indications for use statement has been modified from that granted for the HUD designation. The HUD designation was granted for the indication to provide temporary circulatory support for patients in cardiogenic shock due to potentially reversible causes of acute right heart failure for up to 14 days. It was modified for the HDE approval because it is not possible to predict potentially reversible causes of acute right heart failure prior to treatment.

3. Contraindications

This CentriMag RVAS is contraindicated for use as a cardiotomy suction device. It is also contraindicated for patients who are unable or unwilling to be treated with heparin or an appropriate alternative anticoagulation.

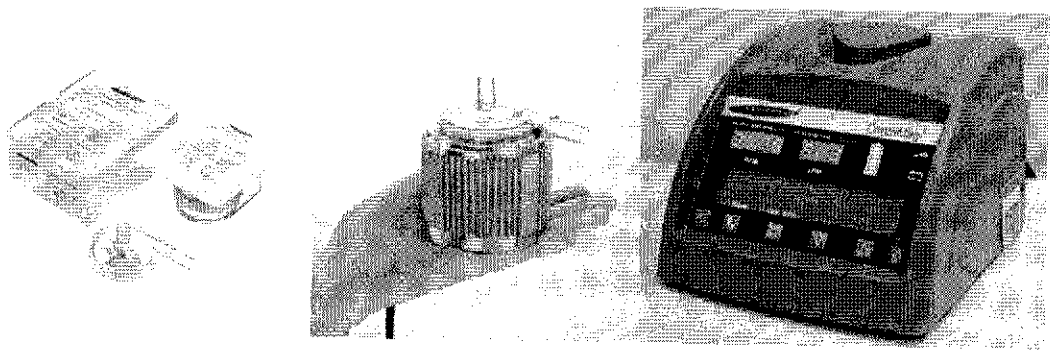
4. Warnings and Precautions

See Warnings and Precautions in the final labeling (Directions for Use).

5. Device Description

The Levitronix CentriMag Ventricular Assist System (VAS) is comprised of a single-use centrifugal blood pump, a primary motor, a primary drive console, a back up motor, a back up drive console and cannulae (see Figure 1). The Levitronix CentriMag VAS is designed to operate without mechanical bearings or seals. This is possible because the motor levitates the rotor (the spinning component of the device) magnetically so that rotation may be achieved without friction, regions of stasis, or component wear during operation.

Figure 1: Levitronix CentriMag blood pump, motor and primary console



Pump **Motor** **Primary Console**

The Levitronix CentriMag VAS is a continuous flow, centrifugal-type rotary blood pump. When used as a right ventricular support system, blood from the failing right heart is directed from the right ventricle or atrium to the inlet of the pump via an inlet cannula. Blood exits through the outlet of the pump, through the outlet cannula, and ultimately to the pulmonary circulation.

The design is based on "bearingless motor" technology, which combines drive, magnetic bearing, and pump rotor functions into a single unit that has no valves, seals, mechanical bearings, or moving parts aside from the magnetically levitated rotor. The bearingless motor is based on the principle of magnetic support of the rotor. The bearing forces in the bearingless motor are not generated by separate mechanical or magnetic bearings positioned on the sides of the motor block, but in the motor itself. Thus, the active motor generates not only the torque, but also the radial magnetic bearing force, which is needed for the suspension of the rotor.

The disposable, single-use pump is independent of the motor unit. The pump is comprised of a rotor and an outer two-piece shell. The rotor is directly integrated into the pump head eliminating the need for seals and bearings.

Under normal operating conditions, the electromotive force produced by the motor windings drives the levitated rotor. Rotation of the rotor with integral vanes creates a vortex that accelerates the blood using axial and centrifugal force. The energy imparted by the rotor serves to increase the velocity of blood along the direction of the axis of rotation through the pump outlet. The system is capable of operating over a range of speeds up to 5,500 revolutions per minute (RPM), theoretically generating flows up to 9.9 liters per minute (LPM).

Safety Elements

A number of safety elements are incorporated into the CentriMag System including:

- Audible and visual alarms indicating blood flow, excess current and battery status;
- Complete backup system including console, motor and batteries;
- Battery for alarms in the event that both primary power and batteries fail;
- Keyed connectors for all cable and console connections;
- 24 hour, 365 days per year technical support;
- Detailed Directions For Use; and
- Device/system training.

All system components, with the exception of the single-use, disposable pump, are intended for use on multiple patients. These components can be used for multiple patients but only on one patient at a time. The CentriMag System is intended for use in the inpatient setting and to provide mechanical circulatory support during patient transport.

6. Alternative Practices and Procedures

The methods currently available to treat right ventricular failure are limited, and include:

- Medical management with pharmacological agents to improve cardiovascular function;
- Mechanical circulatory support with commercially available blood pumps and/or extracorporeal membrane oxygenation (ECMO); and
- Cardiac transplantation.

Pumps used for ECMO and cardiopulmonary bypass are currently approved for up to six hours. The CentriMag RVAS is approved for up to 14 days use.

7. Worldwide Commercial and Marketing History

The CentriMag VAD has been marketed in Turkey and in the European Community in Austria, Belgium, Czech Republic, England, France, Germany, Ireland, Italy, Slovenia, Switzerland, Sweden, and Austria. The CentriMag VAD is also commercially available in Argentina and Panama. The CentriMag VAD received the CE mark for marketing in Europe in 2002. The CentriMag RVAD has been limited to clinical trials in the United States. The device has not been withdrawn from the market in any country for any reason related to the safety or effectiveness of the device or for any other reason.

8. Potential Adverse Effects of the Device on Health

Based on a review of the published literature on other ventricular assist devices, the risks usually associated with use of these devices and from a review of the data obtained from the CentriMag VAD worldwide experience, potential medical risks associated with use of the CentriMag VAD include:

- Death
- Stroke
- Bleeding
- Reoperation
- Hemolysis
- Infection (all cause)
- Thromboembolism
- Renal failure or dysfunction
- Respiratory dysfunction
- Hepatic Dysfunction
- Cardiac arrhythmias (atrial or ventricular)
- Limb ischemia or loss of limb
- Myocardial Infarction
- Neurological dysfunction
- Mechanical or electrical malfunction or possible failure
- Psychiatric events
- Hypotension
- Hypertension

In addition, risks due to the implantation procedure or anesthesia may also occur. For the specific adverse events that occurred in the clinical studies, please see Section 10.4.6 below.

9. Summary of Preclinical Studies

9.1. *In Vitro* Testing

Extensive laboratory testing was performed on each component of the CentriMag System to demonstrate that each component, as well as the integrated system, meets the intended functional requirements as defined in the product specifications and risk analyses. All requirements of the device design were tested and verified. All system components and the integrated system met all performance requirements and specifications. Major areas of testing included: 1) design and construction features (major components, physical characteristics, cannulae, biocompatibility, sterilization and particulates), 2) performance requirements (pump output, service life, flow probe and device measurement methods, ranges and accuracy), and 3) operational requirements (temperature, defibrillation, high power electrical fields, electromagnetic susceptibility, electrostatic discharge, vibration, humidity and ultrasonic energy).

9.1.1. Biocompatibility

Biocompatibility testing of the CentriMag Blood Pump was performed in accordance with the FDA Blue Book Memorandum - #G95-1 and Biological Evaluation of Medical Devices Guidance – International Standard ISO 10993-1, and in accordance with United States Pharmacopoeia – XXIII. The Blood Pump was subjected to tests required for "External Communicating Devices, Circulating Blood, Contact Duration Prolonged (24h to 30 days)". These specific tests included: cytotoxicity, sensitization, intracutaneous irritation, systemic toxicity, genotoxicity, hemocompatibility and sub-chronic toxicity. Based on the results of the biocompatibility testing performed, the CentriMag Blood Pump was determined to be biocompatible and non-toxic and, therefore, safe for its intended use.

9.1.2. Sterilization Validation

The CentriMag Blood Pump is a single-use device, which is provided pre-sterilized to the user. This device is sterilized using an ethylene oxide (EtO) cycle. The sterilization cycle was validated to ensure successful sterilization to a Sterility Assurance Level (SAL) of 10^{-6}, in accordance with the American National Standards Institute, Inc. (ANSI) standard ANSI/AAMI/ISO 11135 (Medical Devices – Validation and Routine Control of Ethylene Oxide Sterilization).

9.1.3. Hemolysis Testing

Hemolysis testing was performed in accordance with ASTM F1841. The test results demonstrated that when compared to a commercially-available centrifugal blood pump (Medtronic Biomedicus BPX-80 Bio-Pump), the hemolysis associated with the CentriMag Blood Pump did not exceed the level of hemolysis associated with the control device.

9.1.4. Software Verification & Validation

Software on-board the CentriMag Primary and Back-Up Consoles was verified & validated in accordance with the FDA Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices.

9.1.5. Shelf Life Studies

Accelerated aging study of the CentriMag Blood Pump was performed in accordance with ASTM F1980. These studies demonstrated that sterility, package integrity, and product functionality could be maintained for 36 months. Based upon these results, a shelf life of three years has been established for this device.

9.1.6. Shipping and Transportation Tests

Shipping and transportation tests of the CentriMag System were conducted per the requirements of ISTA Test Procedure 2A. The results have validated the integrity of the packaging and the functionality of the devices after testing.

9.1.7. System Reliability

Twelve CentriMag Systems were tested for 60 days for a mission time of 30 days. The CentriMag System achieved 90% reliability at 90% confidence level for the stated mission time. The test loop was maintained at 37°C in 0.9% normal saline. The systems were operated under worst case conditions with the pump speed at 5,500 RPM and flow rate of 0.5 LPM. Each system was tested for 1,440 hours without failure. All systems met the success criteria which required freedom from fluid leakage out of the pump, air ingress into the pump, cessation of pumping, inability to maintain flow, and ingress of fluid into the impeller.

9.1.8. Electrical Safety Testing

An independent laboratory has evaluated the electrical safety of the CentriMag VAS. The test results demonstrate that the CentriMag VAS meets the applicable requirements of the 2001 version of IEC 60601-1, the European standard for general safety requirements for medical electrical equipment.

9.1.9. Electromagnetic Compatibility (EMC) Testing

The CentriMag VAS was tested by an independent laboratory to demonstrate that it meets the requirements for conducted and radiated emissions; electrostatic discharge immunity; radiated electromagnetic immunity; electrical fast transient/burst immunity; and conducted disturbance induced by RF fields. The test results demonstrate that the CentriMag VAS meets the applicable requirements of the 2001 version of IEC 60601-1-2, the European standard for electromagnetic compatibility (EMC) for medical electrical equipment.

9.2. Laboratory Testing

9.2.1. Animal Studies

A series of *in* vivo animal studies were performed on the CentriMag System to assess system reliability, pump operation, hemodynamic stability, organ function and pathology, and to demonstrate the safety and readiness of the CentriMag System for clinical implantation

Twenty-three animals were studied in five different investigations to verify and validate that the Levitronix CentriMag VAS performs as intended. The bovine animal model was used in each study. The location of each investigation along with a brief description of each study may be seen below:

1. Six-Hour *In Vivo* Studies (N=6) – University of Zurich, Switzerland
2. 28-Day Veno-Venous Studies (N=7) – University of Zurich, Switzerland
3. Acute VAD Studies (N=3) – Texas Heart Institute, Houston Texas
4. 28-Day VAD Studies (N=5) – Texas Heart Institute, Houston Texas
5. Acute BVAD Studies (N=2) – St. Luke's Medical Center, Milwaukee, Wisconsin

The first study at the University of Zurich served as the initial test to evaluate the basic biocompatibility of the system for up to six hours of use. The CentriMag VAS successfully supported all six animals during the test with no device-related adverse events.

The second study was also performed at the University of Zurich to evaluate the system using a veno-venous shunt to assess hemocompatibility, including the risk of thrombus formation, for 28 days or twice the intended duration of use. Four of the 7 animals were successfully supported for the 28-day period. The remaining three animal studies were non-electively terminated due to bleeding, a torn cannula (due to excessive animal movement) and pneumonia following 3, 9 and 24 days of support, respectively. No

thrombus was seen in the pumps at device retrieval, and no pathologic findings such as thrombus or infarcts were seen at necropsy. Basic hemocompatibility was demonstrated.

Recognizing the target indication for use is for ventricular assistance, the third study at the Texas Heart Institute was designed to evaluate the surgical implantation technique as well as candidate cannulae for the procedure. These studies were carried out for less than a day to establish the methods to be used in the chronic studies, and to verify that the system performs as intended as a ventricular assist system. All three studies were successfully completed and the surgical technique defined. In addition, these studies served to verify that the system operates as designed for the intended indication for use as a VAS.

Having completed the acute studies, the fourth study was conducted at the Texas Heart Institute to validate that the system operates safely and effectively for 28 days in the bovine animal model as a functional ventricular assist system in anticipation of submitting an IDE to FDA to begin human clinical studies. All five studies that were performed were successfully completed.

The CentriMag VAS was tested in the RVAD configuration in two acute animals. The primary objectives of the studies were to validate the cannulation scheme, biocompatibility, and to verify that the devices provided satisfactory hemodynamic support when the system was operated in the RVAD configuration. Satisfactory hemodynamic support and biocompatibility were demonstrated and both studies were electively terminated following the intended duration of the studies (<24 hours).

In general, the animals demonstrated no clinical signs indicative of device failures or other device-related abnormalities. The overall rate of thromboembolism was 14% in animals and there were no incidences of infection at any site. There were minimal changes in end organ function as measured by creatinine, blood urea nitrogen and total bilirubin. There were no incidences of mechanical failure. Specific analyses related to device performance indicated that the device performed as intended in the animal recipients.

10. Summary of U.S. Clinical Studies

Data from two pilot trials in the United States were considered to support safety and probable benefit of the CentriMag VAS when used for short-term support until the patient recovered, underwent transplantation or was weaned onto a long-term ventricular assist system. A total of 32 patients were enrolled in these trials with 24 of these 32 patients treated with a CentriMag RVAD. A summary of each trial is provided below.

10.1. Cardiogenic Shock Pilot Trial (N=22)

This trial was an open-label, non-randomized, multi-center pilot study to evaluate the use of the CentriMag System for up to 14 days when used as either an LVAS or a BVAS to treat patients in cardiogenic shock. Two distinct groups were evaluated: 1) patients suffering from cardiogenic shock postcardiotomy, and 2) patients suffering from cardiogenic shock post acute myocardial infarction. No control population was used. The intent was to maintain each patient on mechanical circulatory support until the

patient recovered, underwent transplantation or was weaned onto a long-term ventricular assist system. All surviving patients were monitored for up to six months after weaning. To be considered a success, patients must have survived to 30 days after weaning, transplant, or being placed on a long-term VAD.

The objectives of the trial were to evaluate:

- The percentage of patients weaned to recovery, a long-term device or transplant;
- 30-day survival after device removal;
- Improvement in hemodynamics; and
- Device-related adverse effects.

Detailed data collection occurred for 30 days post-explant or until discharge (whichever was longest). A six-month follow-up evaluation was performed by phone or by review of the patient's medical record.

Twenty-two patients were enrolled into the Cardiogenic Shock Pilot Trial. Ten subjects were enrolled in the postcardiotomy cardiogenic shock (PCCS) arm and twelve subjects were enrolled in the post acute myocardial infarction (Post-MI) arm.

Eight of the twenty-two patients were treated with a CentriMag for left-sided support only. The remaining fourteen patients were implanted with a CentriMag RVAD as part of a biventricular configuration, with a CentriMag device also serving as an LVAD.

10.2. Use as an RVAS after Implantation of a Commercial LVAD (N=10)

This trial was an open-label, nonrandomized, multi-center pilot study to evaluate the use of the CentriMag System for up to 14 days as an RVAS following implantation of a commercially available LVAD. Patients were enrolled into this study either intraoperatively following one or more unsuccessful attempts at weaning from cardiopulmonary bypass, or postoperatively for hemodynamic decompensation following weaning from cardiopulmonary bypass, or postoperatively for hemodynamic decompensation following procedures without cardiopulmonary bypass. For those patients enrolled postoperatively, enrollment must have occurred within 24 hours of the original surgery. No control group was used. Similar to the cardiogenic shock trial, the intent was to maintain the patient on mechanical circulatory support until the patient recovered, underwent transplantation or was weaned onto a long-term RVAD. To be considered a success, patients must have survived to 30 days after weaning or after heart transplantation or after being placed on a long-term RVAD.

The objectives of the trial were to evaluate:

- 30 day survival after device removal for patients that are weaned and do not go on to long-term biventricular support or transplant.

- 30 day survival after device removal for patients bridged to a long-term biventricular device or heart transplant.

- Improved hemodynamics during support and after device removal for patients that are

weaned and do not go on to a long-term biventricular device or transplant.

- Improved hemodynamics during support for patients that are bridged to a long-term biventricular device or heart transplant.

- An acceptable level of device-related adverse effects

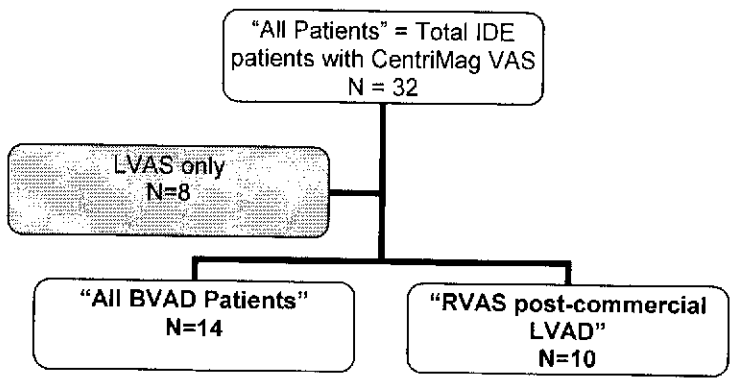
Ten patients were enrolled into this study. In one case, an inclusion exception was granted by the sponsor. The patient was implanted with the investigational device 4 days after implantation of the LVAD, three days beyond that allowed by the protocol.

10.3. Patient Population

As noted above, patients enrolled into the study presented in cardiogenic shock post-cardiotomy or post myocardial infarction. All patients required immediate mechanical circulatory support until they recovered, were transplanted or underwent implantation with a long-term ventricular assist device. Patients enrolled into the RVAD trial suffered right ventricular failure after placement of a commercially available left ventricular assist device. These patients were enrolled either intraoperatively or postoperatively. As with the cardiogenic shock study, patients in the RVAD trial were supported with the CentriMag until recovery, transplantation or implantation with a long term device.

10.4. Results

The chart below illustrates the patient populations included in the clinical assessment for this submission:



For the purposes of this report, clinical data are analyzed in three different groups. The following terminology is followed throughout:

- **All Patients, N=32** – This represents all patients enrolled in both the Cardiogenic Shock Pilot trial (n=22) and the RVAS after Implantation of a Commercial LVAD trial (n=10). This is the entire combined clinical group evaluated in support of this submission, which is shown in the top row of the chart shown above.

- **All BVAD Patients, N=24** – This represents all patients enrolled in both pilot trials

who required biventricular support (patients with only left-sided support were censored). This includes the bottom row of the chart shown above. Fourteen patients enrolled in the Cardiogenic Shock trial received a Levitronix CentriMag pump for both left and right-sided support. The ten patients enrolled in the RVAS after Implantation of a Commercial LVAD trial received a Levitronix CentriMag pump for right-sided support after implantation of a commercial LVAD.

- **RVAS Post Commercial LVAD, N=10** – This represents all patients enrolled in the RVAS after Implantation of a Commercial LVAD trial. These patients received the Levitronix CentriMag pump for right-sided support after implantation of a commercial LVAD.

Table 1 summarizes baseline demographics in both trials. Table 2 summarizes baseline parameters. Table 3 summarizes the type of LVAD implanted in those patients receiving biventricular support in both the BVAD and RVAD trials (N=24).

Table 1: Baseline Demographics

	Cardiogenic Shock		RVAS Following Commercial LVAD N=10	Combined Cohort N=32
	Postcardiotomy N=10	Post-acute MI N=12		
Age (years)				
Mean (SD)	61 (10.2)	61 (7.7)	57 (14.8)	60 (10.8)
Range	43 - 73	51 - 72	32 - 75	32 - 75
Gender				
Male	4 (40%)	8 (67%)	7 (70%)	19 (59%)
Female	6 (60%)	4 (33%)	3 (30%)	13 (41%)
Height (cm)				
Mean/SD	165 (10.4)	172 (11.4)	173 (12.4)	170 (11.6)
Range	152 - 182	147 - 185	155 - 192	147 - 192
Weight (kg)				
Mean (SD)	79 (13.4)	88 (20.4)	89 (21.3)	85 (18.8)
Range	60 - 99	48 - 117	68 - 128	48 - 128
Body Surface Area (m^2)				
Mean (SD)	1.88 (0.2)	2.00 (0.3)	2.10 (0.3)	1.99 (0.3)
Range	1.60 – 2.12	1.40 – 2.30	1.70 – 2.55	1.40 – 2.55
Indication				
Idiopathic Dilated Cardiomyopathy	NA	NA	3 (30%)	
Ischemic Heart Disease			5 (50%)	
CHF/Cardiogenic Shock			1 (10%)	
Postcardiotomy Cardiogenic Shock			1 (10%)	

Table 2: Baseline Parameters*

	Cardiogenic Shock Protocol		RVAS Following Commercial LVAD Protocol N=10	Combined Cohort N=32
	Postcardiotomy N=10	Post-acute MI N=12		
Pulmonary Capillary Wedge Pressure (PCWP) (mmHg) Mean (SD)	22 (2.1)	25 (9.5)	16 (9.8)	22 (9.3)
Central Venous Pressure (CVP) (mmHg) Mean (SD)	19 (3.8)	20 (8.1)	17 (3.6)	19 (6.1)
Mean Arterial Pressure (MAP) (mmHg) Mean (SD)	69 (26.3)	72 (13.2)	64 (14.1)	73 (20.2)
Cardiac Index (CI) Mean (SD) (L/min/m^2)	1.4 (0.3)	1.5 (0.3)	2.1 (0.6)	1.7 (0.6)
Surgery Type Pre-CentriMag Placement**				
CABG	7	3	N/A	10
Valve	2	1		3
VSD repair	1	1		2

* not all patients had parameters recorded at baseline
** patients may have had more than one surgery type

Table 3: All BVAD Patients N=24

Type of LVAD Implanted

LVAD Type	Number of Subjects
CentriMag	14 (59%)
Thoratec XVE	8 (33%)
Thoratec PVAD	1 (4%)
Novacor	1 (4%)

10.4.1. Patient Disposition

Patient disposition in both trials is outlined in Table 4. In the cohort of 24 patients who received support with the BVAD, 50% survived to 30 days after device removal. In the combined cohort of all 32 patients, 15 patients survived to 30 days following device removal for an overall survival rate of 47%. In the RVAS-only cohort, six of the 10 patients (60%) survived to 30 days after device removal. In the post-cardiotomy cohort of the cardiogenic shock trial, three patients (30%) attained 30 day survival after device removal; in the post-myocardial infarction cohort, six patients (50%) survived to 30 days after device removal.

Table 4: Patient Disposition

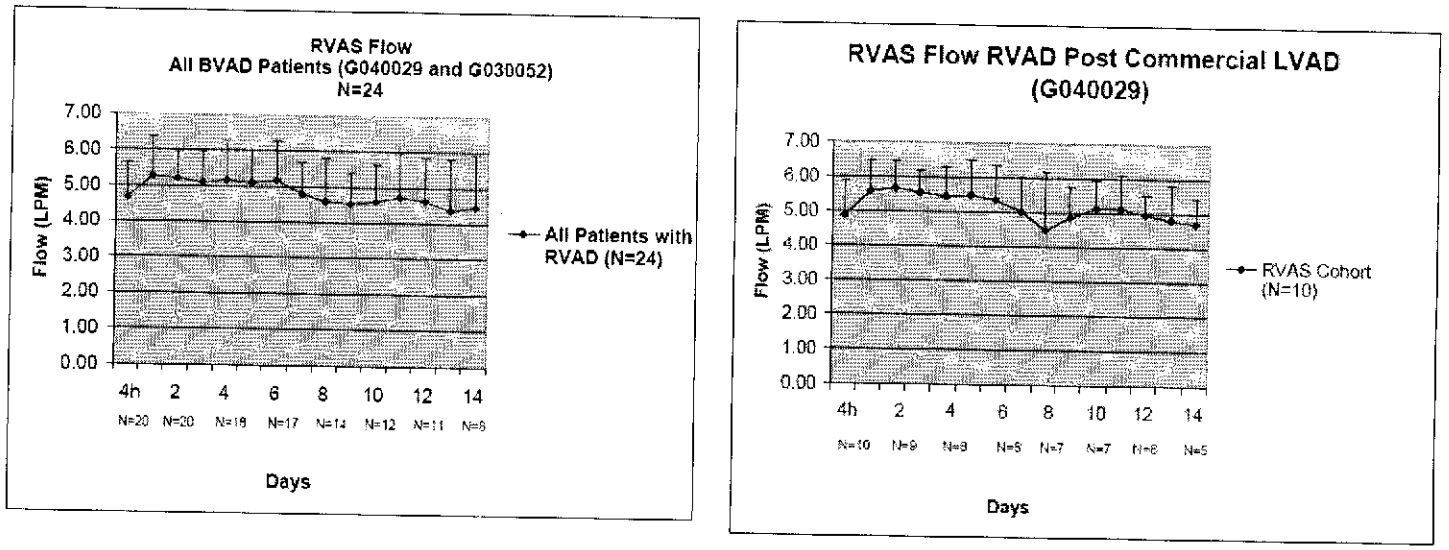
	Cardiogenic Shock Protocol		**RVAS Following Commercial LVAD Protocol**	**Combined Cohort**
	Postcardiotomy N=10	**Post-acute MI N=12**	**N=10**	**N=32**
Duration of Support (days) Mean/SD Range	7.6 (8.4) 1 - 29	15.9 (16.3) 1 - 60	14.0 (9.2) 1 - 29	12.7 (12.3) 1 - 60
Patients Alive at 30 days	3 (30%)	6 (50%)	6 (60%)	15 (47%)
Patients Discharged	3 (30%)	6 (50%)	4 (40%)	13 (41%)

The following figures detailing pump flow, hemodynamics and laboratory data are analyzed in three different groups. The terminology previously outlined in Section 10.4, regarding the different patient cohorts is used for these figures as well.

10.4.2. Pump Flows

The average right-sided flows for the 10 RVAD patients may be seen in Figure 2 (Right). Also shown are the flows for the BVAS cohort (Left). The flows remained stable throughout support for both cohorts of patients.

Figure 2: RVAS Flow



10.4.3. Hemodynamics

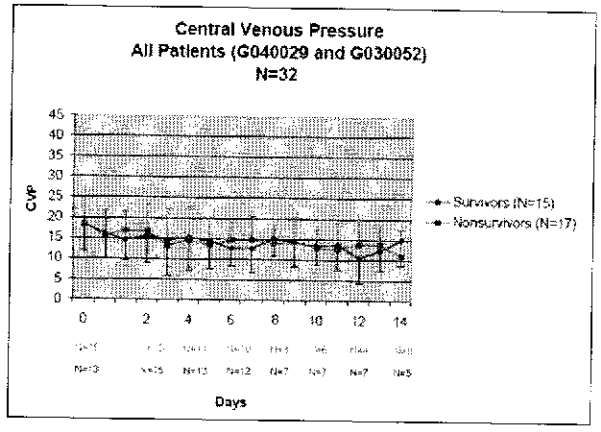
In the RVAS study, patients were required to meet two of the following three hemodynamic parameters for inclusion into the trial: 1) CVP or RAP ≥ 15 mmHg, 2) right ventricular stroke work index ≤ 4.1 gm/m^2/beat, and 3) Change (decrease) in mean pulmonary artery pressure (PAPm) ≤ 10 mmHg, following the initiation of LVAS support.

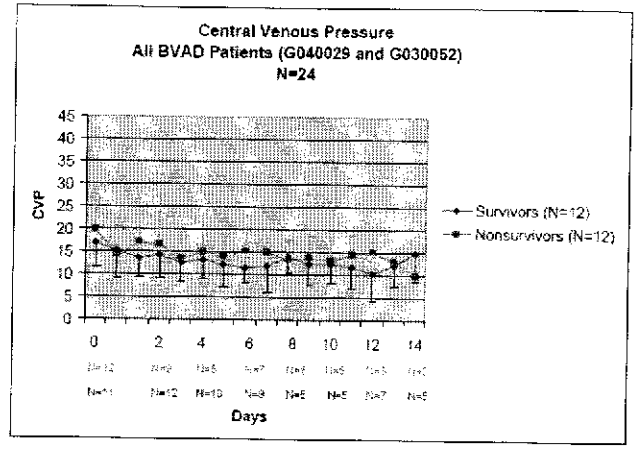
In the cardiogenic shock trial, patients were required to meet the following hemodynamic parameters for entry: 1) pulmonary capillary wedge pressure (PCWP) or pulmonary artery diastolic pressure ≥ 18 mmHg, and 2) a cardiac index of 2.0 L/min/m^2 or less. In both studies, patients who were unweanable from cardiopulmonary bypass could be enrolled without meeting hemodynamic inclusion criteria.

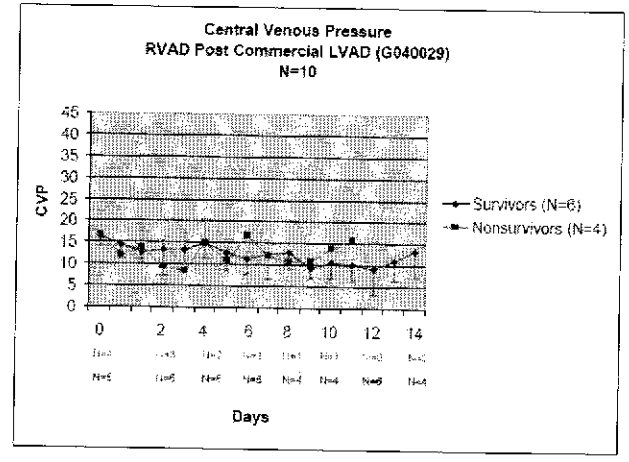
Figures 3 and 4 illustrate CVP and MAP, respectively, over a 14 day time period. Data are presented in three ways: the "All Patients" cohort from both trials (N=32), the "All BVAD Patients" cohort that received a BVAD in both trials (N=24), and the cohort of patients enrolled in the "RVAD Post Commercial LVAD" trial only. Data have also been presented as a function of survivors and non-survivors. In general, the CVP reduced over time during VAD support across all groups while MAP remained stable.[1]

[1] Note: There are missing data for many of the parameters at baseline. In the majority of cases this was due to patients being hemodynamically unstable and unable to be weaned from bypass. These patients were emergently enrolled into the trial without obtaining the baseline data which was permitted by the protocol.

Figure 3: Central Venous Pressure*

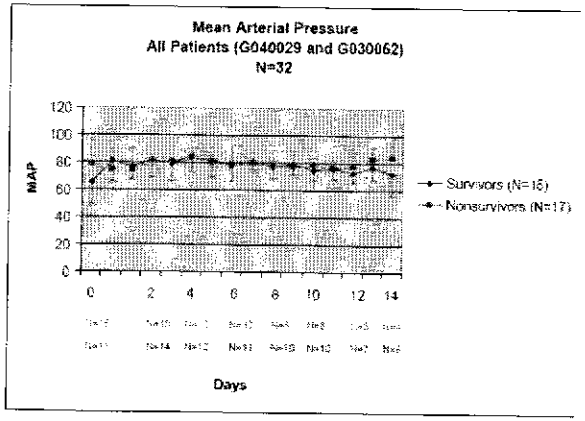


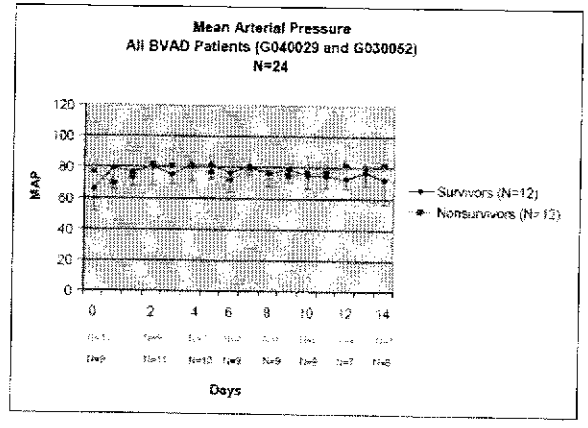


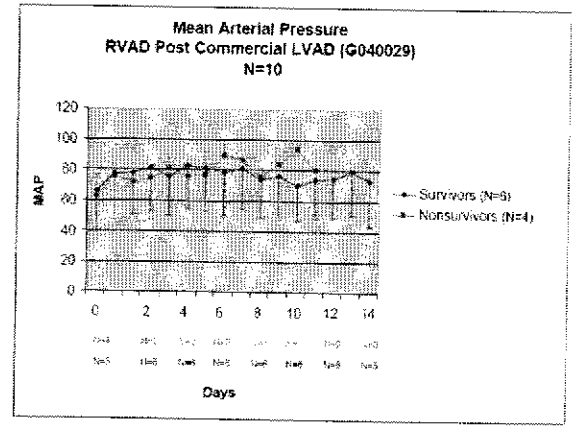


* Not all patients had measurements at baseline; the majority due to hemodynamic instability.

Figure 4: Mean Arterial Pressure*





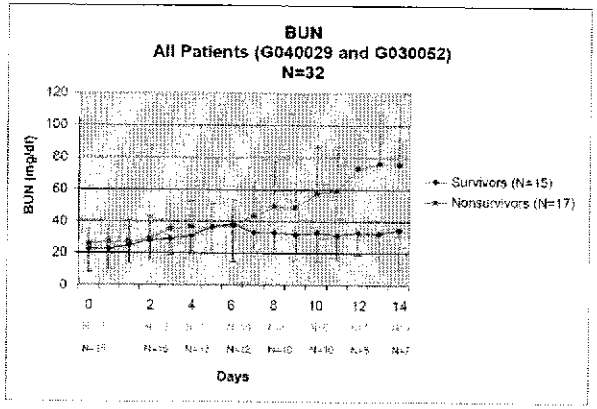


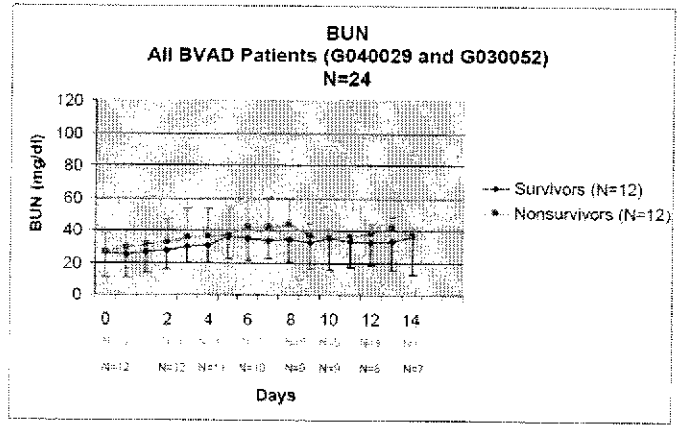
* Not all patients had measurements at baseline; the majority due to hemodynamic instability.

10.4.4. Laboratory Measurements

Laboratory measurements were obtained daily while patients were on VAD support. Figures 5, 6, and 7 illustrate blood urea nitrogen (BUN), creatinine and total bilirubin, respectively. Data are presented in three ways: the combined cohort from both trials (N=32) (left), the cohort of patients that received a BVAD in both trials (N=24) (middle), and the cohort of patients enrolled in the RVAD trial (N=10) only (right). Data have also been presented as a function of survivors and non-survivors. In general, renal function remained reasonably stable for the survivors. Hepatic function was also reasonably stable, and showed a slight trend toward improvement for the RVAS survivors during support. Non-survivors in the N=32 group demonstrated deteriorating end-organ function over time as evidenced by worsening renal (increasing BUN levels) and hepatic (increasing total bilirubin) laboratory measurements. While renal dysfunction appeared to deteriorate based on rising BUN levels for the nonsurvivors, creatinine levels appeared to remain stable over time for both nonsurvivors and survivors. All patients enrolled in the trials were in severe cardiogenic shock requiring urgent placement of a ventricular assist device. These patients underwent extensive surgical procedures resulting in significant fluid shifts, were aggressively diuresed, and often experienced significant bleeding. All of these events may cause disproportionate BUN/creatinine ratios which may have been indicative of pre-renal azotemia. Intravascular volume depletion and hypovolemia have been reported to be associated with high BUN/creatinine ratios. Previous studies of short-term ventricular assist devices have shown increases in BUN with stable creatinine, citing cardiogenic shock as a possible precursor to mild renal dysfunction. Pre-renal azotemia appears to be a syndrome associated with acute cardiogenic shock. This finding is contrary to what has been observed for congestive heart failure patients electively treated with a long-term VAD. Generally, creatinine and BUN levels decrease simultaneously in this population in response to circulatory support. These data underscore how different the acute cardiogenic shock population is from the congestive failure population. As with the hemodynamic measurements, a decrease in the number of patients was seen over time. The reduction in the number of patients was due to individuals coming off support.

Figure 5: Blood Urea Nitrogen





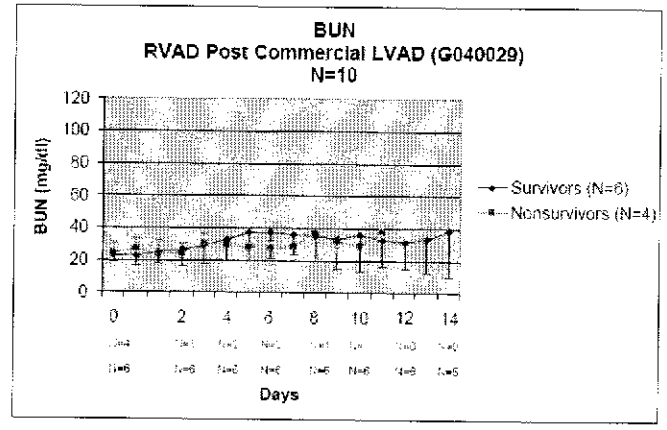
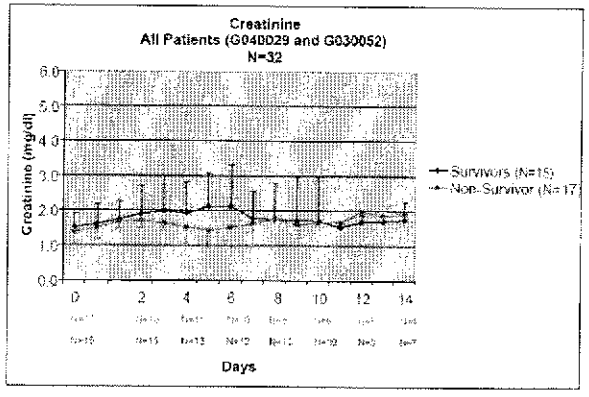
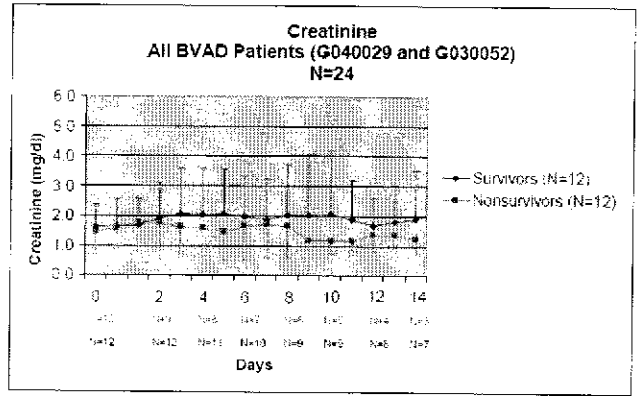


Figure 6: Creatinine





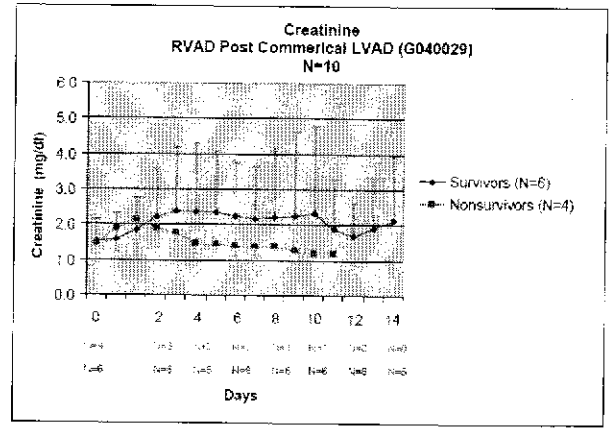
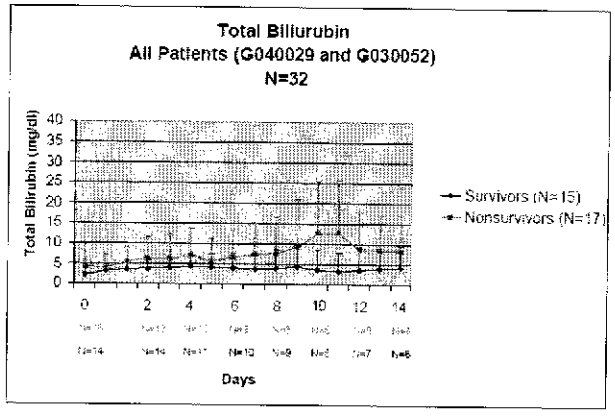
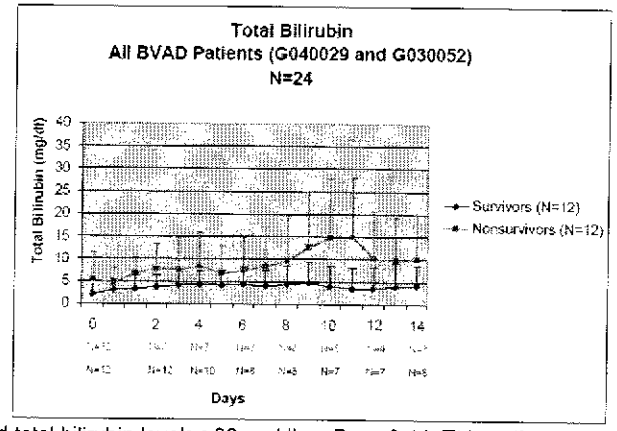
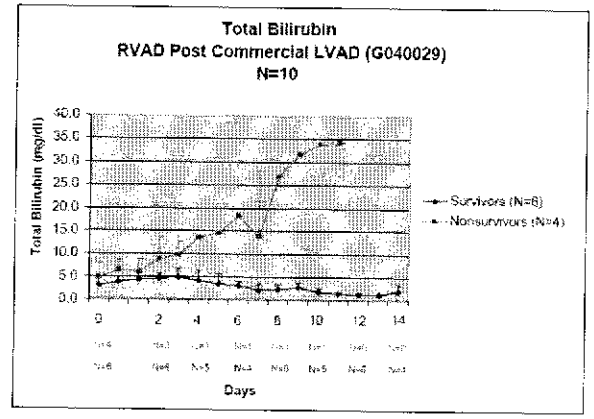


Figure 7: Total Bilirubin*







* In the "All Patients" figure, patient DDC of the RVAS cohort had total bilirubin levels >30 mg/dl on Days 9-11. This patient came off pump on Day 11 which accounts for the steep drop in overall average from Day 11 to Day 12. Two patients did not have total bilirubin levels drawn at baseline due to the emergent nature of those cases.

10.4.5. Pump Performance

There were no instances of device failures across all trials. In the RVAS trial, 10 pumps were utilized without failure. In the cardiogenic shock cohort, a total of 38 pumps were utilized without failure. Eight patients were implanted in a left ventricular configuration and fourteen patients required biventricular support. One patient in the BVAS cohort on biventricular support had both CentriMag pumps electively replaced at the midpoint of support. No pump malfunctions were noted; the treating physician felt it prudent to replace pumps as support was required beyond the intended duration of use.

10.4.6. Adverse Events

All adverse events were reported by the clinical centers, regardless of the relationship to the device. Investigators were required to classify the cause of each event as being device-related, patient-related, management-related or other-related. A summary of adverse events is listed in Table 5.

Table 5: Adverse Events/All Patients (N=32)

Adverse Event Type	Total Number of Events	Number of Device-Related Events	Number of Patients With Event
Infection[1]	54	18	17 (53%)
Bleeding[2]	58	2	27 (84%)
Respiratory Failure	21	1	21 (66%)
Cardiac Tamponade	4	1	4 (13%)
Reoperation	21	5	17 (53%)
Arrhythmias	23	0	9 (28%)
Hypotension	5	0	5 (16%)
Hypertension	0	0	0 (0%)
Hepatic Dysfunction	6	0	5 (16%)
Renal Failure	2	0	2 (6%)
Neurologic Dysfunction Stroke TIA Other (metabolic encephalopathy)	 6 0 2	2[3]	8 (25%)
Thrombotic Vascular	3	0	3 (9%)
Thrombotic Pulmonary	0	0	0 (0%)
Hemolysis	8	5	5 (16%)

Adverse Event Type	Total Number of Events	Number of Device-Related Events	Number of Patients With Event
Right Ventricular Dysfunction	11	0	14 (44%)
Limb Ischemia	2	0[4]	2 (6%)
Limb Loss	0	0	0 (0%)
Device Failure	0	0	0 (0%)
Aneurysm	1	0	1 (3%)
Death While on device support < 30 days post explant	17 10 7	0 0 0	17 (53%) 10 (31%) 7 (22%)

1. Infection was defined as any positive culture of body tissue or fluid requiring treatment with anti-microbial agents, or treatment of culture-negative symptoms, but excluding routine prophylactic treatments.
2. Bleeding was defined as blood loss requiring surgical exploration or transfusion of more than 3 units within a 24 hour period.
3. Both neurologic events were classified by the investigator as "questionable relationship to device".
4. One limb ischemia event was classified by the investigator as "unable to determine the cause".

Table 6: Adverse Events By Gender
(N=19 Males; N=13 Females)

Adverse Event Type	Total Number of Events	Number of Device-Related Events	Number (%) of Patients With Event	Number (%) of Males with Event	Number (%) of Females with Event
Infection[1]	54	18	17 (53%)	9 (47%)	8 (62%)
Bleeding[2]	58	2	27 (84%)	17 (89%)	10 (77%)
Respiratory Failure	21	1	21 (66%)	13 (68%)	8 (62%)
Cardiac Tamponade	4	1	4 (13%)	2 (11%)	2 (15%)
Reoperation	21	5	17 (53%)	10 (53%)	7 (54%)
Arrhythmias	23	0	9 (28%)	4 (21%)	5 (38%)
Hypotension	5	0	5 (16%)	4 (21%)	1 (8%)
Hypertension	0	0	0 (0%)	0 (0%)	0 (0%)
Hepatic Dysfunction	6	0	5 (16%)	2 (11%)	3 (23%)
Renal Failure	2	0	2 (6%)	2 (11%)	0 (0%)

Adverse Event Type	Total Number of Events	Number of Device-Related Events	Number (%) of Patients With Event	Number (%) of Males with Event	Number (%) of Females with Event
Neurologic Dysfunction Stroke TIA Other (metabolic encephalopathy)	 6 0 2	2[3]	8 (25%)	4 (21%)	4 (31%)
Thrombotic Vascular	3	0	3 (9%)	2 (11%)	1 (8%)
Thrombotic Pulmonary	0	0	0 (0%)	0 (0%)	0 (0%)
Hemolysis	8	5	5 (16%)	3 (16%)	2 (15%)
Right Ventricular Dysfunction	11	0	14 (44%)	8 (42%)	6 (46%)
Limb Ischemia	2	0[4]	2 (6%)	2 (11%)	0 (0%)
Limb Loss	0	0	0 (0%)	0 (0%)	0 (0%)
Device Failure	0	0	0 (0%)	0 (0%)	0 (0%)
Aneurysm	1	0	1 (3%)	1 (5%)	0 (0%)
Death While on device support < 30 days post explant	17 10 7	0 0 0	17 (53%) 10 (31%) 7 (22%)	9 (28%) 5 4	8 (25%) 5 3

1. Infection was defined as any positive culture of body tissue or fluid requiring treatment with anti-microbial agents, or treatment of culture-negative symptoms, but excluding routine prophylactic treatments.
2. Bleeding was defined as blood loss requiring surgical exploration or transfusion of more than 3 units within a 24 hour period.
3. Both neurologic events were classified by the investigator as "questionable relationship to device".
4. One limb ischemia event was classified by the investigator as "unable to determine the cause".

There was a potential trend toward higher rates of bleeding and limb ischemia in males, and a potential trend toward higher rates of infection, arrhythmias, and neurologic dysfunction in females. None of these potential trends were statistically significant. The small sample size and variability of patient population (as evidenced in baseline characteristics) makes it difficult to draw any conclusions

The studies were not powered for a specific analysis of adverse event rates. There were no new types of adverse events not usually seen in VAD studies. Rates of adverse events were within the expected range for patients with RV failure supported by a mechanical circulatory support device. As expected in this patient population, the rate of bleeding, infection and respiratory failure was high, although the number of these events which were directly attributable to the device was relatively low. In many instances, the patients' chests were not closed after the initial surgery, requiring a planned reoperation. In the case of infection, all infections diagnosed during the period of VAD support were classified as "device related", unless the infection had been diagnosed and the

organism(s) cultured prior to initiation of VAD support. In addition, some events were reported by the centers as multiple infections when, in actuality, they represented one continuous event. There were no instances of device failure.

10.4.6.1 Neurological Events

An attempt was made to correlate clinical course, pump retrieval findings and, when appropriate, autopsy findings to each neurological event. In only two patients was there a "questionable relationship" to the device. In the first case, the patient was diagnosed with neurological dysfunction two days after device removal, although the event may have occurred during the time of device support. A CT scan performed five days post device removal showed evidence of a cerebral infarction. The investigator reviewed the patient's records and found that anticoagulation levels while the device was implanted may have been inadequate or ineffective during periods of intentional low flow (2 lpm), possibly contributing to stasis in the system with eventual thrombus formation. Thrombus was noted in the left atrium and LVAS return cannula at the time of pump removal. Also observed at the time of removal was a 5 mm x 10 mm thrombus in the outflow cannula lumen. No pannus, thrombus or vegetation was noted in the remainder of the system.

The second case of questionable device-related neurologic dysfunction occurred in a patient with a diagnosis of post-myocardial infarction cardiogenic shock who was implanted with a LVAS. On Day 5 following implantation of the CentriMag LVAS, the patient underwent emergent surgical removal of an intra-aortic balloon pump (IABP) due to a gas leak. During this period, a decline in the patient's neurological status was observed. Examination of the pump post-explant revealed small fibrous deposits on the impeller blades and on the pump inflow port as well as fibrous formation on the connector to the arterial cannula. A CT scan performed 3 days post explant demonstrated evidence of a cerebral infarction. Although the neurologic deficit was first noted at the time of IABP removal, the investigator could not definitively state the exact time and cause of this event. Review of the patient's record found that heparin anticoagulation may have been ineffective due to an anti-thrombin III deficiency, contributing to the risk of thromboembolism.

10.4.7 Gender Analysis

Table 7 below summarizes the survival outcome by gender for each of the trial cohorts. In general, the survival outcome for both genders for the postcardiotomy and RVAS cohorts appeared comparable. Survival for the female gender appeared lower for the post-acute MI and combined cohorts but higher in the cohorts of patients receiving an RVAS after postcardiotomy or commercial LVAD. These data illustrate the difficulty in drawing conclusions based on the gender of the patient considering the limited clinical experience with the CentriMag RVAS.

Table 7: Survival Outcome as a Function of Gender

Gender	Cardiogenic Shock Protocol		RVAS Following Commercial LVAD Protocol	Combined Cohort
	Postcardiotomy	Post-acute MI		
Male	1/4 (25%)	5/8 (63%)	4/7 (57%)	10/19 (53%)
Female	2/6 (33%)	1/4 (25%)	2/3 (67%)	5/13 (38%)

11. Risk and Probable Benefit Analysis

The CentriMag VAS is expected to provide total right ventricular unloading and circulatory support for patients with right heart failure and cardiogenic shock with a low incidence of device malfunctions. The overall survival rate is anticipated to be consistent with that seen in the U.S. pilot trials. The 30-day survival in the twenty-four patients receiving RVAD support was 50%. The survival rate seen in the RVAS cohort being treated with the CentriMag solely for right-sided support was 60%.

Pump performance data for the CentriMag RVAS suggest flow rates sufficient to meet the patients' circulatory needs.

The probable benefits associated with the CentriMag RVAS are: 1) adequate ventricular unloading, 2) adequate circulatory support, 3) ease of implantation, 4) reliable device function, 5) a low incidence of device related complications, and 6) support conditions conducive to post-operative recovery and weaning.

Risks associated with the CentriMag RVAS are consistent with those associated with commercially approved devices and alternative treatment options. Currently available circulatory support options for patients in cardiogenic shock are limited by low survival rates and complications, such as infection, bleeding and neurologic events. ECMO, while suitable for respiratory support in addition to cardiac support, historically has a high rate of device related complications. Patients with ECMO and other centrifugal pumps are immobilized and these blood pumps are cleared for only 6 hours of use. Other commercially available extracorporeal devices have drawbacks due to the device design, priming volume, lack of portability, and device size.

The positive outcome data combined with the low incidence of device related adverse events suggest the benefits associated with use of the CentriMag RVAS VAD outweigh the risks. This risk-benefit ratio is highlighted when taking into account the risks and benefits associated from alternative methods of treatment, and from the morbidity and mortality associated with cardiogenic shock if left untreated.

Therefore, it is reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment when used as indicated in accordance with the directions for use.

12. Panel Recommendation

This HDE was not taken to a meeting of the Cardiovascular Devices Panel because other marketing applications for ventricular assist devices have been reviewed by the panel. This HDE does not raise any unanticipated safety issues. Therefore, it was determined that this application need not be submitted to the advisory panel.

13. CDRH Decision

CDRH has determined that, based on the data submitted in the HDE, that the CentriMag® Right Ventricular Assist System (RVAS) will not expose patients to an unreasonable or significant risk or illness or injury, and the probable benefit to health from using the device outweighs the risks of illness or injury, and issued an approval order on October 7, 2008.

14. Approval Specifications

14.1. Indications for Use

See the *Directions for Use*

14.2. Hazards to Health from use of the Device

See Contraindications, Warnings and Precautions, and Adverse Events in the *Directions for Use*

14.3. Post approval Requirements and Restrictions

See Approval Order