SUMMARY OF SAFETY AND PROBABLE BENEFIT

I. GENERAL INFORMATION

Device Generic Name:	Ventricular Assist Device (VAD)
Device Trade Name:	EXCOR® Pediatric Ventricular Assist Device (EXCOR)
Applicant's Name and Address:	Berlin Heart Inc. 200 Valleywood, Suite A500 The Woodlands, Texas 77380
Humanitarian Device Exemption (HDE) Number:	H100004
Humanitarian Use Device (HUD) Designation Number:	2000-0064
Date of HUD Designation:	January 3, 2001
Date of Panel Recommendation:	July 21, 2011
Date of Good Manufacturing Practice Inspection:	May 12, 2011
Date of Notice of Approval to Applicant:	December 16, 2011

II. INDICATIONS FOR USE

EXCOR® Pediatric Ventricular Assist Device (referred to as EXCOR) is intended to provide mechanical circulatory support as a bridge to cardiac transplantation for pediatric patients. Pediatric candidates with severe isolated left ventricular or biventricular dysfunction who are candidates for cardiac transplant and require circulatory support may be treated using the EXCOR.

The indications for use statement is identical to that which was granted for the HUD designation.

III. CONTRAINDICATIONS

Patients unable to tolerate systemic anticoagulation therapy should not be implanted. Magnetic Resonance Imaging (MRI) is contraindicated in patients after being implanted with the EXCOR.

IV. WARNINGS AND PRECAUTIONS

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

V. DEVICE DESCRIPTION

EXCOR is an extracorporeal, pneumatically driven, pulsatile ventricular assist device. It is designed to support the right and/or left ventricle when the natural heart is unable to maintain normal blood flows, and/or pressures even with help of drug therapy and intraaortic balloon counterpulsation. The device is designed for mid to long term mechanical support.

The EXCOR consists of one or two extracorporeal pneumatically driven blood pumps, cannulae which connect the blood pump(s) to the atrium or ventricle and to the great arteries. The IKUS electro-pneumatic driver provides alternating air pressure to the blood pumps through driving tubes. The blood pump interior is divided into an air chamber and a blood chamber by a multi-layer, flexible polyurethane membrane. The alternating air pressure pulse moves the membrane, thus filling and emptying the chambers, respectively. Both the blood chamber and the polyurethane connectors are transparent to allow for detection of thrombotic deposits and for monitoring the filling and emptying of the blood pump. Valves (three-leaflet polyurethane valves) are located at the inlet and outlet positions of the blood pump connection stubs, thus ensuring unidirectional blood flow. The blood pumps are available in five different sizes with stroke volumes of 10 ml, 25 ml, 30 ml, 50 ml, and 60 ml according to their maximum blood chamber volume as shown in Figure 1, below.

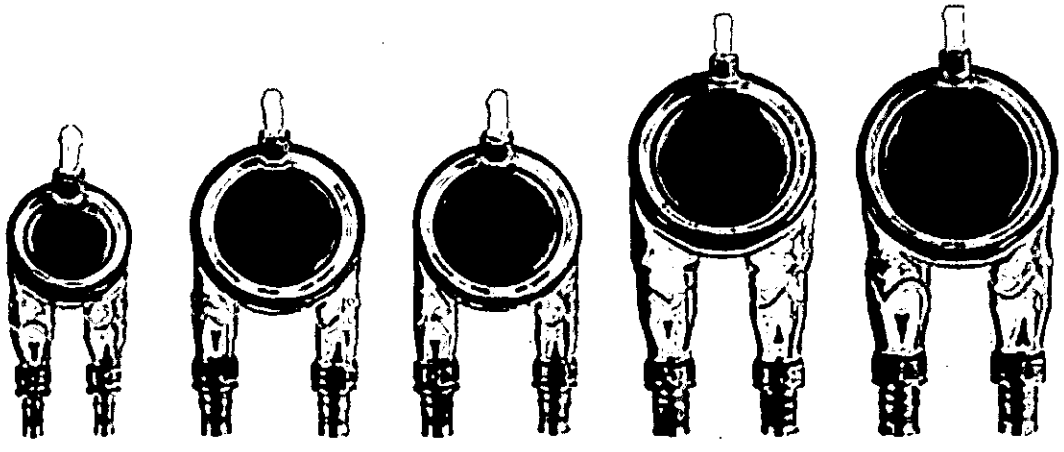

Figure 1: EXCOR Pumps shown in all five available sizes

Pulse rate, systolic drive pressure, diastolic suction pressure and the relative systolic duration can all be monitored and adjusted on the IKUS driving unit. The complete system is depicted in Figures 2 and 3:

Figure 2: Biventricular system shown in model

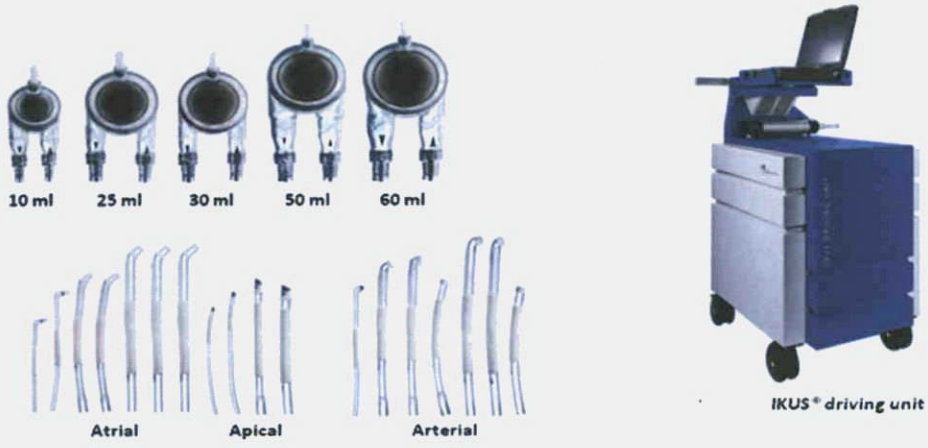

Figure 3: Blood pumps, Cannula and the Ikus Driving Unit

VI. ALTERNATIVE PRACTICES OR PROCEDURES

Procedures used in the treatment of pediatric patients with severe, isolated left ventricular or biventricular dysfunction include extracorporeal membrane oxygenation (ECMO) and other commercially available VADs. However, ECMO is not FDA-approved or cleared for this indication.

VII. MARKETING HISTORY

EXCOR was approved in Europe and obtained CE marking in 1996. Since that authorization, the EXCOR has been marketed in the following countries:

Germany, Austria, Belgium, Bulgaria, Estonia, Switzerland, Denmark, Spain, Finland, France, Great Britain, Greece, Hungary, Italy, Lithuania, Netherlands, Poland, Portugal, Romania, Sweden, Slovakia, Turkey, Argentina, Australia, Azerbaijan, Brazil, Canada, Chile, Taiwan, China, Hong Kong, Israel, Iran, New Zealand, Serbia, Russia, Saudi Arabia, and South Africa.

The EXCOR has not been withdrawn from marketing for any reason related to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Adverse events that may be associated with the use of the EXCOR are listed below. Other than death, adverse events are listed in decreasing order of frequency observed in the clinical study. For additional information on adverse events that occurred in the clinical study, please see Section X below.

- Death
- Pump change due to thrombus
- Major infection
- Major bleeding
- Hypertension
- Neurological dysfunction
- Respiratory failure
- Renal dysfunction
- Pericardial fluid collection
- Right heart failure
- Cardiac arrhythmia
- Psychiatric episode
- Hemolysis
- Hepatic dysfunction
- Arterial Non-Central Nervous System Thromboembolism
- Venous Thromboembolism

IX. SUMMARY OF PRE-CLINICAL STUDIES

A. Biocompatibility/Sterilization

The blood pumps and cannulae were extracted and tested in accordance with ISO 10993 (Biological Evaluation of Medical Devices) as shown in Table 1:

Subject	Standard/Method
Cytotoxicity	ISO 10993-5 L-929 mouse fibroblast elusion test
Sensitization	ISO 10993-10
Irritation/intracutaneous toxicity	ISO 10993-10
Systemic toxicity	ISO 10993-11
Gene mutation	ISO 10993-3 Reverse mutation assay using *Salmonella typhimurium*
Chromosome aberration	ISO 10993-3 *in-vitro* mammalian chromosome aberration test in Chinese hamster V79 cells
Implantation	ISO 10993-6 *in-vivo* implantation in the rabbit with histopathology; 90-days
Hemolysis	ISO 10993-4 *in-vitro* hemolysis
Thrombogenicity	ISO 10993-4 partial thromboplastin time (PTT) and activated PTT (aPTT)
Pyrogenicity	EP/USP Endotoxin
Pyrogenicity	*in-vivo* rabbit pyrogenicity

Table 1: Summary of Biocompatibility/Sterilization Testing

All tests passed. The blood pumps, cannulae and the sterile accessories of the EXCOR system were sterilized by the validated ethylene oxide (EtO) sterilization cycle.

B. *In-vitro* Characterization and Structural Integrity

In vitro characterization on a mock circulatory loop demonstrated the performance of the EXCOR system under hypotensive (80 mmHg) and hypertensive (120 mmHg) simulated pediatric operating conditions. All recommended combinations of blood pump sizes and cannulae sizes were tested. The pumps demonstrated complete filling and ejection in each pump cycle at the rates given in Table 2.

Cannulation		Blood Pump Size				
ø inflow cannula	ø outflow cannula	10 ml	25 ml	30 ml	50 ml	60 ml
5 mm	5-3 mm	90 bpm				
5 mm	5 mm	130 bpm				
6 mm	5 mm	130 bpm				
6 mm	6 mm	130 bpm	80 bpm	65 bpm		
9 mm	6 mm		80 bpm	65 bpm		
9 mm	9 mm		130 bpm	130 bpm	130 bpm	105 bpm
12 mm	9 mm				130 bpm	105 bpm
12 mm	12 mm				130 bpm	125 bpm

Table 2: Pump Flow and Rates

The following tests were conducted in order to determine the structural integrity of the pumps and cannulae.

- Resistance to kinking
- Expected flex and bending life
- Tensile strength
- Torque load limits
- Pressurization limits
- Resistance to leakage
- Resistance to occlusion
- Adhesion strength of velour wrapping

Results of these tests demonstrated that both the pumps and cannulae are sufficiently durable under the normal operating conditions of the device. The test acceptance criteria were met and the pumps and cannulae demonstrated stable, predictable operation under normal operating conditions.

C. System Reliability

Reliability testing of the main components of the device (pump, stationary driving unit Ikus, and Ikus batteries), was performed with 10 devices. Test results were collected on the electrical reliability of the Ikus system as well as the pneumatic subsystems of the pump-Ikus interface. Test results demonstrated that over a full service interval of 2000 hours, no failures occurred. Therefore, the pump and IKUS unit are 100% reliable for at least approximately 83 days.

D. Fluid Characterization

In order to demonstrate fluid characterization, the sponsor conducted particle image velocimetry and mock-flow loop tests. The results of these tests adequately demonstrated no

areas of high shear or stagnant fluid flow under normal operating conditions. The pre-specified performance criteria were met.

E. Electromagnetic Compatibility & Electrical Safety

The EXCOR was tested for compliance with the FDA-recognized standards for electrical compatibility and electrical safety (IEC 60601-1 and IEC 60601-2, respectively). Test results demonstrated adequate electromagnetic compatibility and electrical safety of the entire system in the hospital environment. All of these bench tests supported the anticipated and intended performance of the device in the clinical/hospital environment. The device has not been subjected to tests for any external transport situation or the home environment.

F. Software Verification & Validation

Software verification and validation test results provided reasonable assurance that the software in the IKUS driving unit can consistently meet the specified requirements as intended.

G. *In-vivo* Testing

Animal study data were not provided for FDA review. The implantation of this device in greater than 100 outside-of-US (OUS) patients and several patients in the US under the CU/EU provisions was sufficient to initiate the IDE study for this device. Safety data for these subjects in the US provided sufficient evidence to support approval of an IDE study. OUS data do not generally mitigate the need to demonstrate safety via an animal study prior to beginning a clinical trial on a new device. In this case, however, FDA believed that the animal study data would not provide new information beyond the vast dataset that existed from OUS studies.

X. SUMMARY OF CLINICAL STUDIES

A. IDE Clinical Study Summary

Berlin Heart Inc. conducted a prospective, multi-center, single arm study to assess the safety and probable benefit of the Berlin Heart EXCOR® Pediatric Ventricular Assist Device (EXCOR). This was conducted under Investigational Device Exemption (IDE) number G050262.

The purpose of the study was to determine whether use of the EXCOR for bridge-to-transplantation is associated with reasonable assurance of safety and probable benefit such that the EXCOR merits approval by the Food and Drug Administration (FDA) under a Humanitarian Device Exemption (HDE).

B. Study Cohorts

The primary study population of 48 subjects aged 30 days-16 years consisted of two cohorts: 24 subjects in Cohort 1 (BSA <0.7 m^2)and 24 subjects in Cohort 2 (0.7 ≤ BSA < 1.5 m^2).
A third cohort of subjects was enrolled under CU/EU provisions and is classified as Cohort 3. The expanded access provision of the Food, Drug, and Cosmetic Act allows FDA to approve CU of a device to provide access for patients who do not meet the requirements for inclusion in a clinical investigation but for whom the treating physician believes the device may provide a benefit in treating and/or diagnosing their disease or condition and for whom no other medical device treatment is available. Furthermore, a patient may be implanted with a device under these provisions if the implanting site is not an investigational site for the clinical study. Patients who are emergently implanted are considered to have a life-threatening or serious disease or condition with no other clinical alternative. These patients are implanted "emergently" if there is not enough time to obtain prior FDA approval for "compassionate" use.

These Cohort 3 subjects followed the study protocol unless otherwise noted within the approval documentation for the subject. This cohort is further divided into groups based on the subject's BSA similar to Cohorts 1 and 2 and is labeled Cohort 3A (BSA is < 0.7 m^2) and Cohort 3B (0.7 ≤ BSA < 1.5 m^2).

C. Study Endpoints

1. Primary Effectiveness Endpoint

The primary effectiveness endpoint for the study was to demonstrate that the survival rate in subjects treated with EXCOR was different from the survival rate in the historical control of subjects treated with ECMO as a bridge-to-cardiac transplant. The historical ECMO control group was compiled from the Extracorporeal Life Support Organization (ELSO) registry, the most extensive registry of patients treated with ECMO in North America. The database was filtered to best match the EXCOR IDE study population. Each of the statistical analyses were performed separately for each cohort (Cohort 1 or Cohort 2) after 24 subjects reached an endpoint including cardiac transplantation, death or recovery (defined as survival at 30 days post-explant or discharge with acceptable neurologic outcome, whichever is longer).

Patients included for comparison to the EXCOR cohorts included patients from both genders, age 0-16 years, with weight greater than 3 kilograms (kg), cardiac only ECMO support, and support initiation from 2000 onward who met critical eligibility criteria. The dataset for the ELSO registry included baseline and outcomes data comparable to the EXCOR dataset. The control group was then created by matching the EXCOR subjects to the patients in the subset using a propensity score analysis (PSA) based on age, weight, primary diagnosis, ventilator status, inotrope use, and prior cardiac arrest.

2. Primary Safety Endpoint

The objective of the primary safety endpoint was to compare the serious adverse event (SAE) rate to a performance goal of 0.25 serious adverse events per patient-day of support. The adverse event performance goal number was determined based upon literature review and experience with this patient population. Adverse event definitions were based upon established definitions from INTERMACS. Currently used in adult VAD trials, these definitions were standardized by a committee of several members of the VAD community (including clinical, industry, government, and academic) and were modified as necessary to accommodate pediatric adverse events (AEs). The safety endpoint for the primary study cohorts was selected based solely on ensuring that the level of safety for EXCOR would meet the selected performance goal (SAEs per patient-day of support).

3. Secondary Effectiveness Endpoints

The pre-specified secondary effectiveness endpoints (which were evaluated via descriptive statistics only) were:

1. Days of transplant-eligible support; and
2. Ability to de-intensify concomitant hemodynamic support by analyzing the subjects status with respect to whether the subject is:
    a. Awake;
    b. Ambulating;
    c. Sedated;
    d. Intubated;
    e. On ECMO or another assist device; and
    f. Eating.

4. Supportive Analyses

In addition to the pre-specified primary and secondary endpoints, there were also four other analyses used to support the primary safety and probable benefit analyses.

1. Neurological Status - assessed using the Pediatric Stroke Outcomes Measure (PSOM).
2. Quality of Life / Neurodevelopmental Assessment - assessed with the Pediatric Quality of Life Generic Module (PedsQL).
3. Transfusion Requirements – evaluation of the number and amount of transfusions that a subject received between follow-ups was captured at each follow-up visit.
4. EXCOR Performance - all implanting sites were trained to record the system parameters including the rate, systolic pressure, diastolic pressure, and systolic percent. They were also trained to visually assess and record the filling and emptying of the blood pumps according to defined states (complete/almost complete, incomplete, poor, or unknown) on a regular basis.

D. Inclusion/Exclusion Criteria

Subjects of both genders who satisfy all inclusion and exclusion criteria were eligible for entrance into the primary cohorts of the clinical study.

Inclusion Criteria
Subjects of the study must have met the following criteria:

1. Severe New York Heart Association (NYHA) Functional Class IV (or Ross Functional Class IV for subjects ≤6 years) heart failure refractory to optimal medical therapy, and has met at least one of the following criteria:
   a. Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile status 1 or 1A, i.e. critical cardiogenic shock (low blood pressure [BP] unresponsive to support, compromised end organ perfusion, < 24 hour survival expected without mechanical support; may be due to VT/VF (1A)
   b. INTERMACS profile status 2 or 2A (i.e. progressive decline): not in imminent danger, but worsening despite optimal inotropic therapy; may be due to ventricular tachycardia/ventricular fibrillation (2A) AND at least one of the following criteria
      i. Decline in renal function as defined by a 50% reduction in estimated GFR despite optimization of subject volume status
      ii. Decline in nutritional status as defined by a sustained (≥7 days) inability to tolerate an enteral nutritional intake sufficient to provide at least 75% of the prescribed caloric needs for the subject, or signs of nutritional compromise (cachexia, nutritional weight loss) despite appropriate intervention
      iii. Decline in mobility/ambulation as defined by sustained bed confinement (≥7 days without prospect for improvement) attributable to heart failure symptoms or its treatment (e.g. intubation for pulmonary edema)
   c. Support with extra-corporeal membrane oxygenation (ECMO) or other mechanical circulatory support device

      OR

   d. Unable to separate from cardiopulmonary bypass (must be listed for heart transplantation at time of transfer to the operating room)
2. Listed (United Network for Organ Sharing [UNOS] status 1A or equivalent) for cardiac transplantation
3. Two-ventricle circulation, including cardiomyopathy, repaired structural heart disease (e.g. anomalous left coronary artery from the pulmonary artery [ALCAPA], aortic stenosis) or acquired heart disease (e.g. myocarditis, Kawasaki disease)
4. Age 0 to 16 years; corrected gestational (CGA) at least 37 weeks

5. Weight ≥ 3 kg and ≤ 60 kg
6. Legal guardian (and subject if age-appropriate) understands the nature of the procedure, are willing to comply with associated follow-up evaluations, and provide written informed consent and assent prior to the procedure

Exclusion Criteria

1. Support on ECMO for ≥10 days
2. Cardiopulmonary resuscitation (CPR) duration ≥30 minutes within 48 hours prior to device implantation
3. Body weight < 3.0 kg or BSA > 1.5 m^2
4. Presence of mechanical aortic valve
5. Unfavorable or technically-challenging cardiac anatomy including single ventricle lesions, complex heterotaxy, and restrictive cardiomyopathy
6. Evidence of intrinsic hepatic disease as defined by a total bilirubin level or aspartate aminotransferase/alanine aminotransferase (AST/ALT) greater than five times the upper limit of normal for age, except in association with acute heart failure as determined by the principal investigator
7. Evidence of intrinsic renal disease as defined by a serum creatinine greater than 3 times the upper limit of normal for age, except in association with acute heart failure as determined by the principal investigator
8. Hemodialysis or peritoneal dialysis (not including dialysis or Continuous Veno-Venous Hemofiltration [CVVH] for volume removal)
9. Evidence of intrinsic pulmonary disease (e.g. chronic lung disease, respiratory distress syndrome [RDS]) as defined by need for chronic mechanical ventilation, except in association with acute heart failure as determined by the principal investigator
10. Moderate or severe aortic and/or pulmonic valve insufficiency considered technically challenging to repair at the time of the device implantation as determined by the principal investigator
11. Apical ventricular septal defect [VSD] or other hemodynamically-significant lesion considered technically challenging to repair at the time of device implantation as determined by the principal investigator
12. Documented heparin induced thrombocytopenia (HIT) or idiopathic thrombocytopenia purpura (ITP) or other contraindication to anticoagulant/antiplatelet therapy
13. Documented coagulopathy (e.g. Factor VIII deficiency, disseminated intravascular coagulation) or thrombophilic disorder (e.g. Factor V Leiden mutation)
14. Hematologic disorder causing fragility of blood cells or hemolysis (e.g. sickle cell disease)
15. Active infection within 48 hours of implant demonstrated by:
    a. Positive blood culture

       OR

b. Temperature >38 degrees C and white blood cell (WBC) >15, 000/ ml

16. Documented human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS)
17. Evidence of recent or life-limiting malignant disease
18. Stroke within past 30 days prior to enrollment, or congenital central nervous system (CNS) malformation syndrome associated with increased risk of bleeding (e.g. arteriovenous malformation, moya moya)
19. Psychiatric or behavioral disease (e.g. antisocial disorder) with a high likelihood for non-compliance
20. Currently participating in another investigational device or drug trial and has not completed the required follow-up period for that study
21. Subject is pregnant or nursing

Subjects who did not meet the eligibility criteria were enrolled into Cohort 3.

E. Historical Control Group

The historical ECMO control dataset was collected from the Extracorporeal Life Support Organization (ELSO) registry.

A propensity score analysis (PSA) was performed to match EXCOR subjects to two control patients from the ELSO database. The propensity score for each subject was the conditional probability of receiving an EXCOR instead of ECMO given age, weight, diagnosis, ventilator status, inotrope use, and prior cardiac arrest.

This analysis was completed for both of the primary cohorts. The ELSO dataset was separated into patients younger than 4 years and older than 4 years to ensure that there would not be a chance of a control patient being matched to a subject in both Cohort 1 and Cohort 2. Furthermore, BSA measurements were not available in the ELSO registry, so the patients could not be separated in this way. In the following summary, the results using the pre-specified analysis are presented. As planned in the original PSA, the new PSA resulted in 48 ELSO subjects being matched to 24 EXCOR subjects for each cohort.

Tables 3 and 4 demonstrate how well the propensity score analysis matched the respective control groups to the study cohorts. There were no statistically significant differences between the 2 groups of subjects for each of the variables used for the matching.

Variable	Category	Cohort 1 n=24	ELSO matches n=48	p-value*
Age Group	0 - 30 days	0 (0%)	0 (0%)	0.1035
	30 days – 2 Years	20 (83%)	30 (62.5%)	
	2 to 10 years	4 (17%)	18 (37.5%)	
	10 to 16 years	0 (0%)	0 (0%)	
Age (months)	Mean ± Std Median Min – Max	15.4 ± 12.4 11.7 2.6 - 45.6	18.5 ± 11.5 16.1 1.8 – 43.7	0.2869
Weight Group	3 – 10 kg	16 (67%)	28 (58.3%)	0.6105
	10 – 30 kg	8 (33%)	20 (41.7%)	
	30 – 60 kg	0 (0%)	0 (0%)	
Weight (kg)	Mean ± Std Median Min - Max	9.1 ± 2.7 9.2 3.6 - 13.6	9.4 ± 2.4 9.9 4.0 - 13.9	0.6442
Primary Diagnosis	Cancer	0 (0.0%)	0 (0.0%)	0.3139
	Congenital Heart Disease	3 (12.5%)	9 (18.8%)	
	Coronary Artery Disease	0 (0.0%)	0 (0.0%)	
	Dilated Myopathy	19 (79.2%)	38 (79.2%)	
	Hypertrophic Cardiomyopathy	1 (4.2%)	0 (0.0%)	
	Restrictive Myopathy	1 (4.2%)	0 (0.0%)	
	Valvular Heart Disease	0 (0.0%)	1 (2.1%)	
Ventilator Use (pre-implant)	Yes	20 (83.3%)	42 (87.5%)	0.7221
Inotrope Use (pre-implant)	Yes	22 (91.7%)	45 (93.8%)	1.0000
Cardiac Arrest (pre-implant)	Yes	7 (29.2%)	15 (31.3%)	1.0000

Table 3: PSA Variable Data Summary for Cohort 1 and Matched Control Group

Variable	Category	Cohort 2 n=24	ELSO matches n=48	p-value*
Age Group	0 - 30 days	0 (0%)	0 (0%)	0.6184
	30 days – 2 Years	0 (0%)	0 (0%)	
	2 to 10 years	14 (58%)	24 (50.0%)	
	10 to 16 years	10 (42%)	24 (50.0%)	
Age (months)	Mean ± Std Median Min – Max	113.2 ± 37.6 111.2 50.8 - 191.8	117.0 ± 44.3 118.5 50.2 – 188.6	0.7225
Weight Group	3 – 10 kg	0 (0%)	0 (0%)	0.6267
	10 – 30 kg	12 (50%)	27 (56.3%)	
	30 – 60 kg	12 (50%)	21 (43.8%)	
Weight (kg)	Mean ± Std Median Min - Max	32.2 ± 12.5 30.7 16.0 – 58.1	31.7 ± 13.3 27.0 13.0 – 59.0	0.8776
Primary Diagnosis	Cancer	0 (0.0%)	0 (0.0%)	0.5016
	Congenital Heart Disease	6 (25.0%)	17 (35.4%)	
	Coronary Artery Disease	0 (0.0%)	1 (2.1%)	
	Dilated Myopathy	17 (70.8%)	29 (60.4%)	
	Hypertrophic Cardiomyopathy	0 (0.0%)	0 (0.0%)	
	Restrictive Myopathy	1 (4.2%)	0 (0.0%)	
	Valvular Heart Disease	0 (0.0%)	0 (0.0%)	
Ventilator Use (pre-implant)	Yes	12 (50.0%)	30 (62.5%)	0.3247
Inotrope Use (pre-implant)	Yes	21 (87.5%)	44 (91.7%)	0.6792
Cardiac Arrest (pre-implant)	Yes	5 (20.8%)	15 (31.3%)	0.4138

Table 4: PSA Variable Data Summary for Cohort 2 and Matched Control Group

F. Study Enrollment

Figure 4 summarizes the complete enrollment (including the subjects enrolled at non-IDE sites) by subject's BSA. As of the data cutoff for the updated HDE report (February 2011 report with January 17, 2011 data cutoff), there were 151 smaller sized subjects (BSA < 0.7m^2) enrolled and 53 larger sized subjects (0.7 ≤ BSA < 1.5 m^2) enrolled. This figure also provides the overall study results for all 204 patients implanted with the device and accounted for in Cohorts 1, 2, and 3 and at all sites.

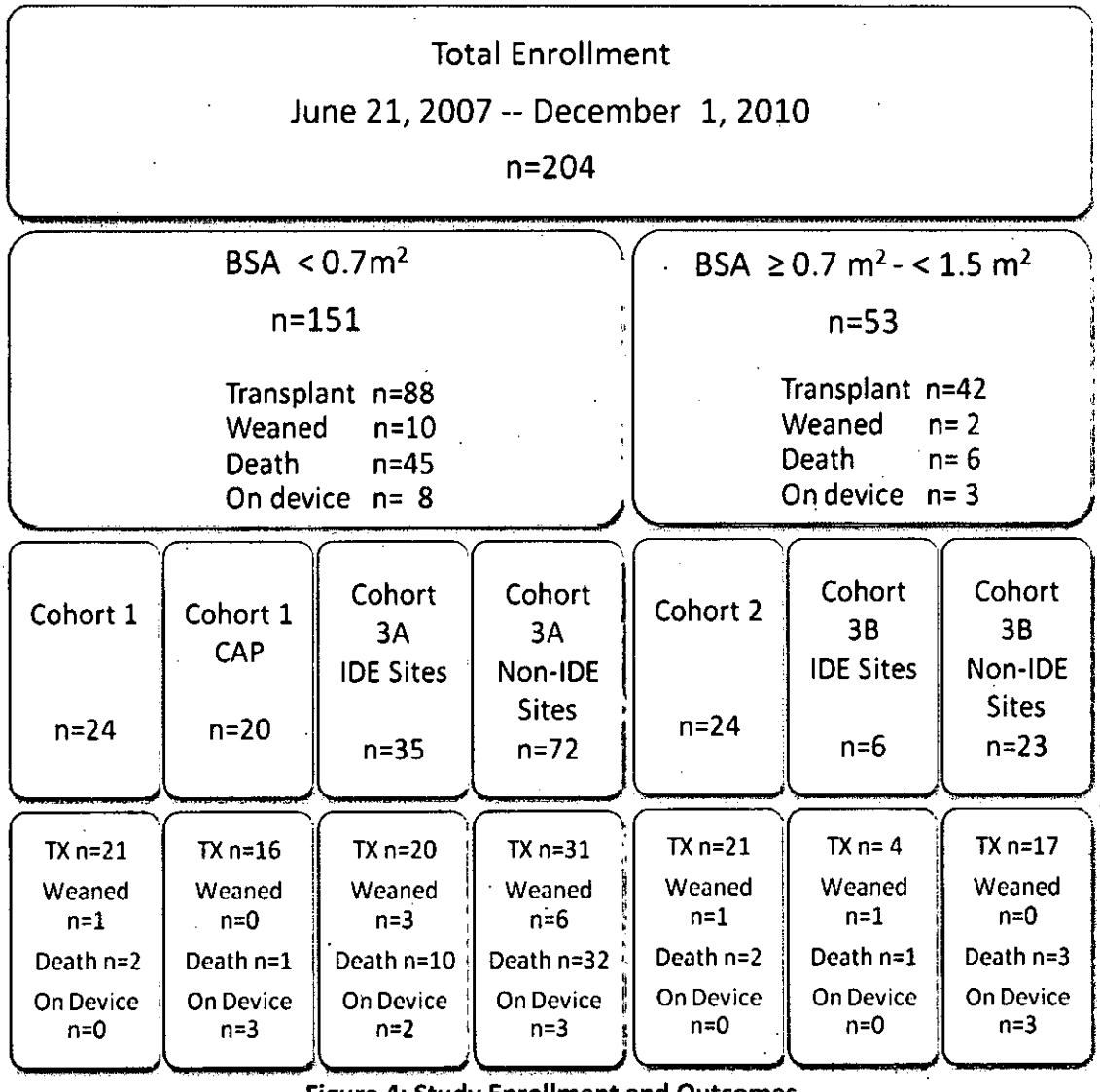

Figure 4: Study Enrollment and Outcomes

Enrollment in Cohorts 1 CAP, 3A, 3B (IDE and non-IDE) are supportive data and are only included in the safety summary tables.

G. Subject Demographics

Table 5 summarizes the demographic data for Cohorts 1 and 2. The most predominant cardiac diagnosis for Cohort 1 was dilated cardiomyopathy (79.2%) and the majority of this group, 54.2%, presented with progressive decline. The most predominant cardiac diagnosis for Cohort 2 was also dilated cardiomyopathy (70.8%) and most (54.2%) were listed in critical cardiogenic shock.

Variable	Category	Cohort 1 n=24	Cohort 2 n=24
Gender	Female	12 (50.0%)	11 (45.8%)
	Male	12 (50.0%)	13 (54.2%)
Age (months)	Mean ± Std (N) Median Min – Max	15.4 ± 12.4 (24) 11.7 2.6 - 45.6	113.2 ± 37.6 (24) 111.2 50.8 - 191.8
BSA (m^2)	Mean ± Std (N) Median Min – Max	0.43 ± 0.10 (24) 0.44 0.23 - 0.62	1.09 ± 0.29 (24) 1.08 0.71 - 1.66[1]
Weight (kg)	Mean ± Std (N) Median Min – Max	9.1 ± 2.7 (24) 9.2 3.6 - 13.6	32.2 ± 12.5 (24) 30.7 16.0 – 58.1
Race	African-American	7 (29.2%)	6 (25.0%)
	American Indian/Alaska Native	1 (4.2%)	0 (0.0%)
	Asian	0 (0.0%)	1 (4.2%)
	Hawaiian/other Pacific Islander	0 (0.0%)	1 (4.2%)
	White	13 (54.2%)	15 (62.5%)
	Other/none of the above	3 (12.5%)	1 (4.2%)
	Unknown/Undisclosed	0 (0.0%)	0 (0.0%)
Ethnicity: Hispanic or Latino:	Yes	7 (29.2%)	1 (4.2%)
Patient Profile/Status	1 Critical Cardiogenic Shock	11 (45.8%)	13 (54.2%)
	2 Progressive decline	13 (54.2%)	11 (45.8%)
	3 Stable but Inotrope dependent	0 (0.0%)	0 (0.0%)
Primary Cardiac Diagnosis	Congenital Heart Disease (CHD)	3 (12.5%)	6 (25.0%)
	Dilated cardiomyopathy	19 (79.2%)	17 (70.8%)
	Hypertrophic cardiomyopathy	1 (4.2%)	0 (0.0%)
	Restrictive cardiomyopathy	1 (4.2%)	1 (4.2%)
Secondary Cardiac Diagnosis (multiple Choices)	Congenital Heart Disease	2 (8.3%)	3 (12.5%)
	Coronary Artery Disease	0 (0.0%)	2 (8.3%)
	Dilated cardiomyopathy: Familial	1 (4.2%)	0 (0.0%)
	Dilated cardiomyopathy: Idiopathic	0 (0.0%)	2 (8.3%)
	Dilated cardiomyopathy: Ischemic	0 (0.0%)	1 (4.2%)

[1] One patient had a BSA of 1.66 m^2 which is outside entrance criteria; a protocol deviation was documented for this occurrence and this subject is omitted from the "Per Protocol" analysis group

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Variable	Category	Cohort 1 n=24	Cohort 2 n=24
	Dilated cardiomyopathy: Myocarditis	0 (0.0%)	2 (8.3%)
	Dilated cardiomyopathy: Viral	1 (4.2%)	0 (0.0%)
	Dilated cardiomyopathy: Other	1 (4.2%)	2 (8.3%)
	Restrictive cardiomyopathy: Secondary to Radiation/Chemotherapy	0 (0.0%)	1 (4.2%)
	Valvular Heart Disease	0 (0.0%)	1 (4.2%)
	CHD/Dilated cardiomyopathy: Familial	1 (4.2%)	0 (0.0%)
	None	18 (75.0%)	10 (41.7%)
Heart Rate	Mean ± Std (N) Min – Max	126.3 ± 25.5 (24) 91.0 - 175.0	117.9 ± 21.1 (24) 85.0 - 168.0
Systolic Blood Pressure	Mean ± Std (N) Min – Max	85.3 ± 16.0 (24) 45.0 - 110.0	95.2 ± 13.5 (24) 60.0 - 112.0
Diastolic Blood Pressure	Mean ± Std (N) Min – Max	56.0 ± 14.1 (24) 38.0 - 89.0	65.9 ± 14.8 (24) 46.0 - 100.0
Previous Cardiac operations	(# Yes)	5 (20.8%)	8 (33.3%)

Table 5: Demographic Data Summary

Table 6 summarizes the pre-implant support for the subjects.

Variable	Category	Cohort 1 n=24	Cohort 2 n=24
Prior support within 48 hours	No support	0 (0.0%)	0 (0.0%)
	Ventilator	20 (83.3%)	12 (50.0%)
	ECMO	6 (25.0%)	8 (33.3%)
	Ultrafiltration	3 (12.5%)	1 (4.2%)
	VAD	2 (8.3%)	0 (0.0%)
	Dialysis	0 (0.0%)	0 (0.0%)
	Feeding Tube	10 (41.7%)	7 (29.2%)
	IABP	0 (0.0%)	0 (0.0%)
	Inotropes	22 (91.7%)	21 (87.5%)

Table 6: Pre-Implant Support

H. Results

1. Primary Effectiveness Endpoint Results

Effectiveness for the IDE trial was assessed by comparing hazard rates of EXCOR and the historical ECMO control. Subjects who were transplanted were censored at the time of explant. Subjects who were explanted due to recovery of their ventricular function and survived to 30 days or discharged with acceptable neurologic status or those who had unacceptable neurological outcome at 30 days were censored at the time of explant. Subjects who were explanted due to recovery of their ventricular function and died within 30 days or discharge (whichever was longer) were counted as a failure with time to failure being the explant date.

The hypothesis for the primary effectiveness was to test the hazard ratio of EXCOR relative to ECMO control using the Cox proportional hazards regression tested at two-sided significance level of 0.05.

$$H_0 : HR \geq 1$$
$$H_A : HR < 1$$

where HR is the true hazard ratio of EXCOR group relative to the ECMO control group.

The unadjusted hazard ratio, which ignored the correlation among the matched triplets (2 matched-control ECMO patients to each 1 EXCOR patient), for Cohort 1 was 0.04 (*p*-value=0.004); the adjusted hazard ratio for Cohort 1 was 0.10 (*p*-value=0.03). This means that the data show that the ECMO patients are 10 times more likely to die on the device compared to the EXCOR patients, after adjusting for the observed differential characteristics between the two treatment groups and potential selection biases. For Cohort 2, the unadjusted hazard ratio was 0.02 (*p*-value=0.0003); the ECMO patients are 50 times more likely to die than the EXCOR patients, after adjusting for the observed differential characteristics. However, the statistical significance for the adjusted hazard ratio for Cohort 2 varied depending on the implemented statistical method since there seems to be wide variation between the matched triplets.

Table 7 summarizes the survival to transplant/successful recovery for each primary Cohort intent-to-treat (ITT) and per protocol (PP) group as well as their matched ECMO control groups.

Three (3) of the Cohort 1 subjects (12.5%) failed (2 deaths and 1 weaned subject with unacceptable neurological outcome at 30 days post-explantation) compared to 14 of the 48 (29.2%) patients in the matched ECMO control group. The 3 subjects from Cohort 1 who died or were considered failures were all supported with ECMO at the time of implant. The failures occurred at day 0 (death), day 38 (death) and day 146 (weaned-failure).

The control group for Cohort 1 was on ECMO for a median of 4.7 days and a maximum of 30 days compared to the primary cohort subjects who were supported a median of 27.5 days and

maximum of 174 days. Half of the Cohort 1 subjects were supported longer than the entire ECMO control group (i.e. longer than 30 days).

Two of the Cohort 2 subjects (8.3%) failed due to death compared to 19 of the 48 (39.6%) patients in the matched ECMO control group. One of the subjects who died in Cohort 2 was supported with ECMO at the time of implant. These deaths occurred at day 19 and day 144.

The control group for Cohort 2 was on ECMO for a median of 5.2 days and a maximum of 48 days compared to the primary cohort subjects who were supported a median of 42.5 days and a maximum of 192 days. Nine (9) of the 24 (37%) subjects in Cohort 2 were supported longer than the entire ECMO control group (i.e. longer than 48.2 days) and 75% (18 of 24) were supported longer than 21 days, the length of the second longest ECMO supported patient.

Group	Total	Max Time on Device (days)	# Successes	# Failures	Survival Time		
					30 Days	60 days	90 days
Cohort 1 ITT	24	174	21 (87.5%)	3 (12.5%)	95.8%	87.1%	87.1%
Cohort 1 Per-Protocol	22	174	19 (86.4%)	3 (13.6%)	95.5%	86.8%	86.8%
ECMO Control Group	48	30	34 (70.8%)	14 (29.2%)	0.0%	N/A	N/A
Cohort 2 ITT	24	192	22 (91.7%)	2 (8.3%)	94.7%	94.7%	94.7%
Cohort 2 Per-Protocol	22	144	20 (90.9%)	2 (9.1%)	94.1%	94.1%	94.1%
ECMO Control Group	48	48.2	29 (60.4%)	19 (39.6%)	18.3%	N/A	N/A

Table 7: Primary Efficacy Study and Control Groups (Updated Control Group Data)

Comparison of the ITT groups to their respective matched ECMO control group survival rates were both statistically significant (log-rank p value <0.0001). Therefore, there is a significantly higher survival rate of Cohort 1 and 2 subjects as compared to their respective ECMO control group.

Figures 5 and 6 display the Kaplan-Meier curves for the endpoint of death/weaned with unacceptable outcome for both Cohort 1 ITT and Cohort 2 ITT and their respective ECMO control groups.

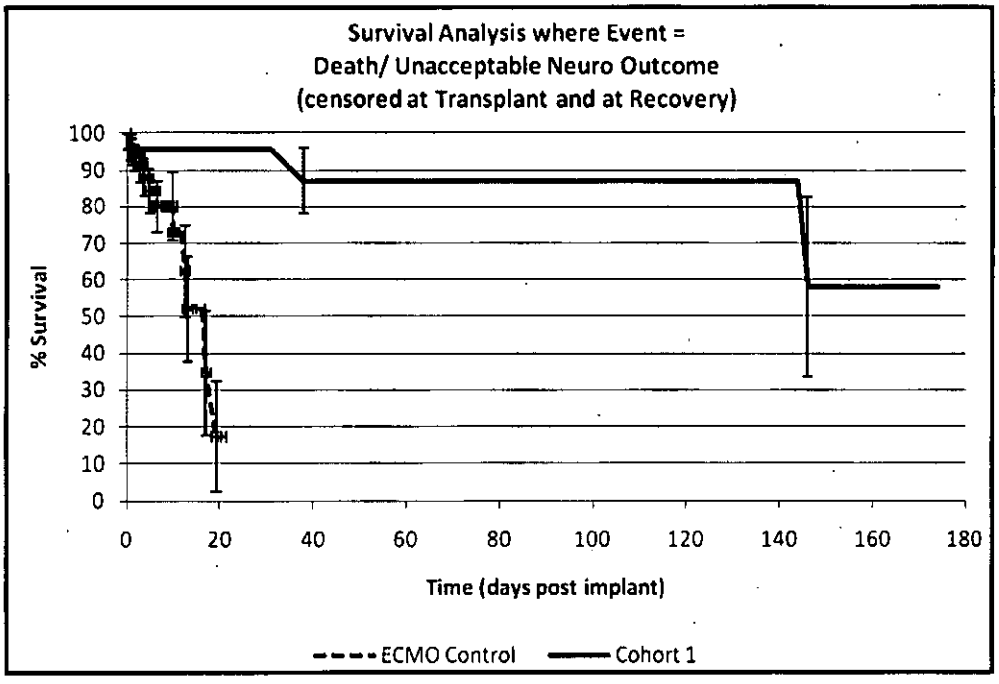

Figure 5: Survival to Death/Weaned with Unacceptable Neurological Outcome - Cohort 1 versus ECMO

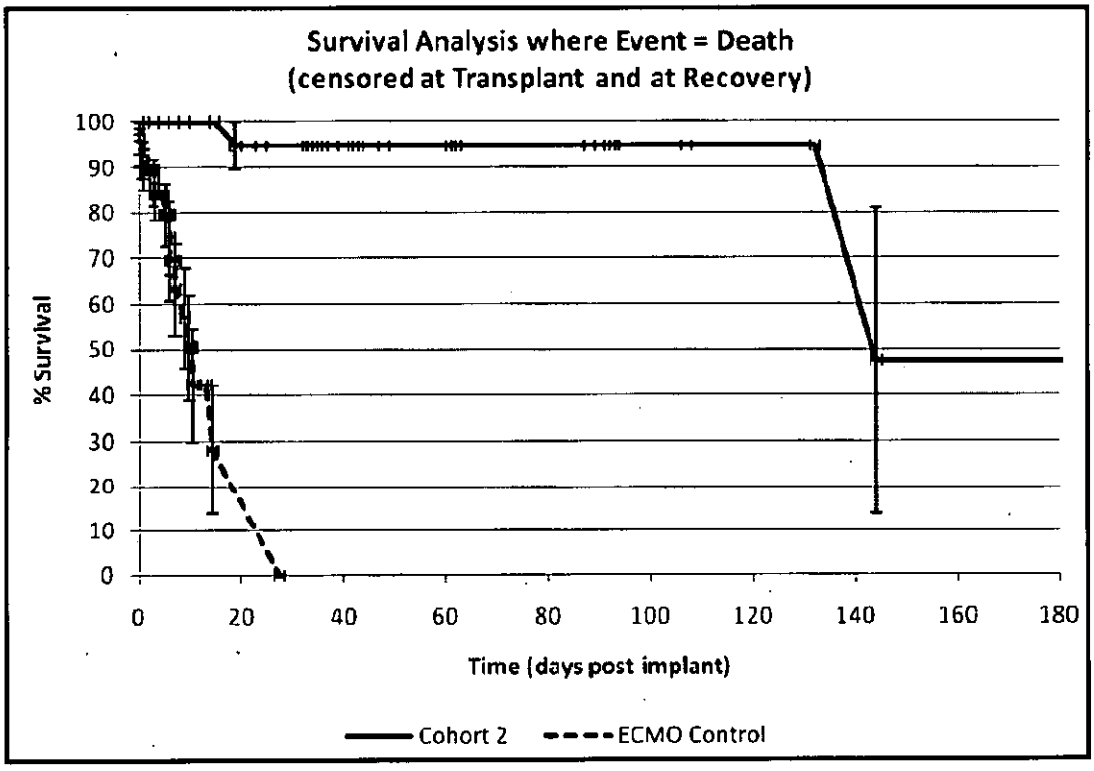

Figure 6: Survival to Death/Weaned with Unacceptable Neurological Outcome - Cohort 2 versus ECMO

Because the Kaplan-Meier analysis censors subjects at time of transplant, "Competing Outcomes" curves were constructed to show a more complete picture of the endpoints.

Figure 7 shows the "Competing Outcomes" for Cohort 1. The curves represent each of the outcomes and at any time point the sum of the proportions of outcomes equals 100%.

Of the 24 Cohort 1 subjects, 21 were transplanted between 1 to 174 days of support. The 2 deaths in this Cohort occurred at 0 and 38 days post implant. One subject was weaned after 146 days due to poor prognosis.

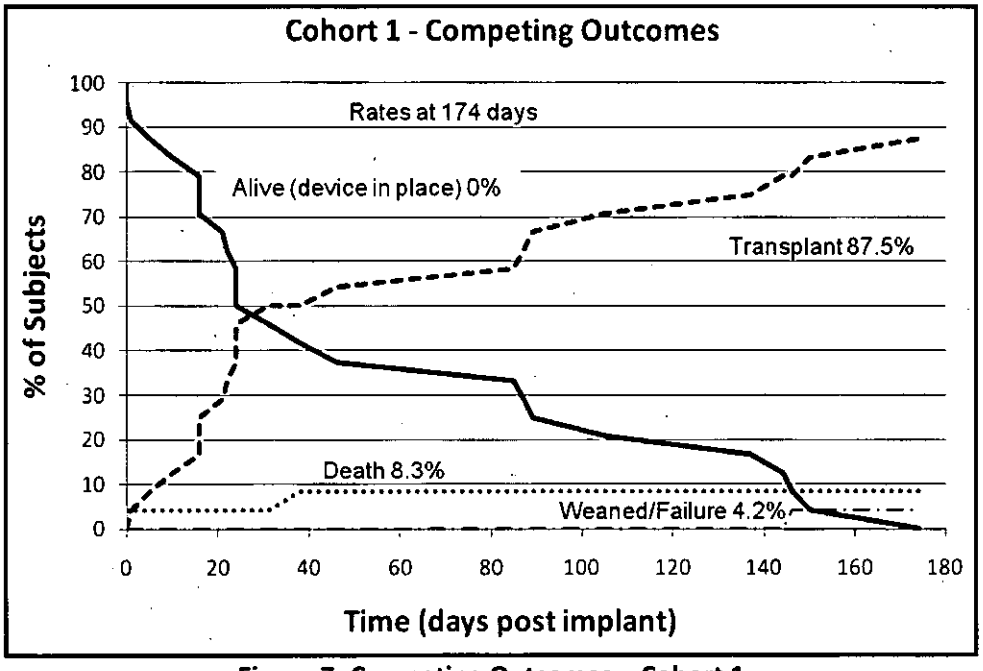

Figure 7: Competing Outcomes – Cohort 1

Figure 8 shows the "Competing Outcomes" for the ECMO control group for Cohort 1. The longest support time was 30 days at which time 71% were weaned from ECMO for recovery or transplant.

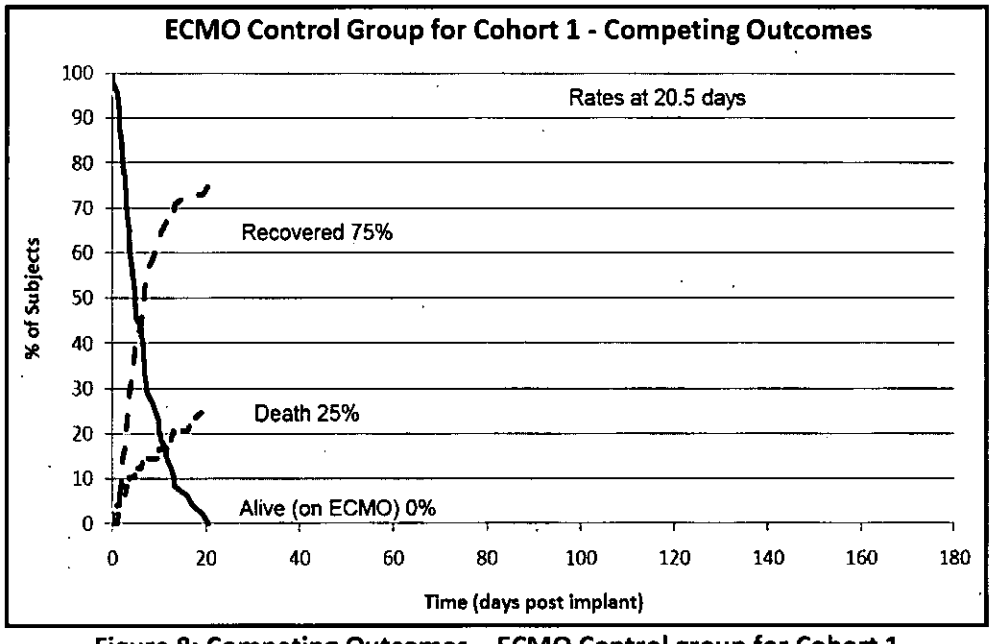

Figure 8: Competing Outcomes – ECMO Control group for Cohort 1

Figure 9 shows the "Competing Outcomes" for Cohort 2. Of the 24 Cohort 2 subjects, 21 were transplanted between 3 to 192 days of support. The 2 deaths in this Cohort occurred at 19 and 144 days post implant. One subject was successfully weaned to recovery after 9 days.

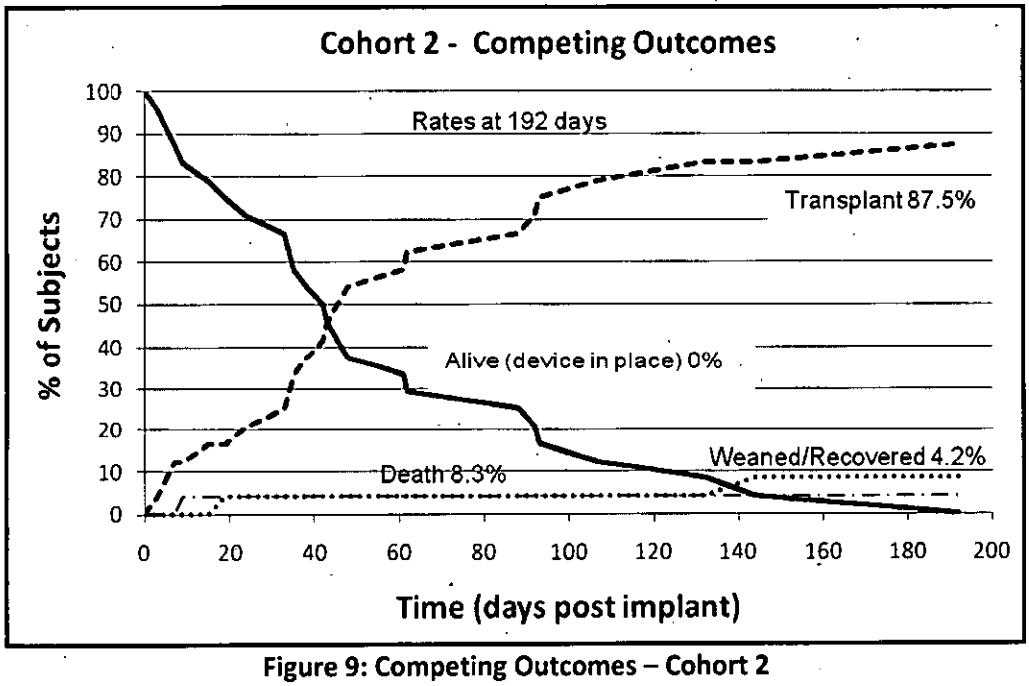

Figure 9: Competing Outcomes – Cohort 2

Figure 10 shows the "Competing Outcomes" for the ECMO control group for Cohort 2. The longest support time was 48.2 days at which time 60% were weaned from ECMO for recovery or transplant.

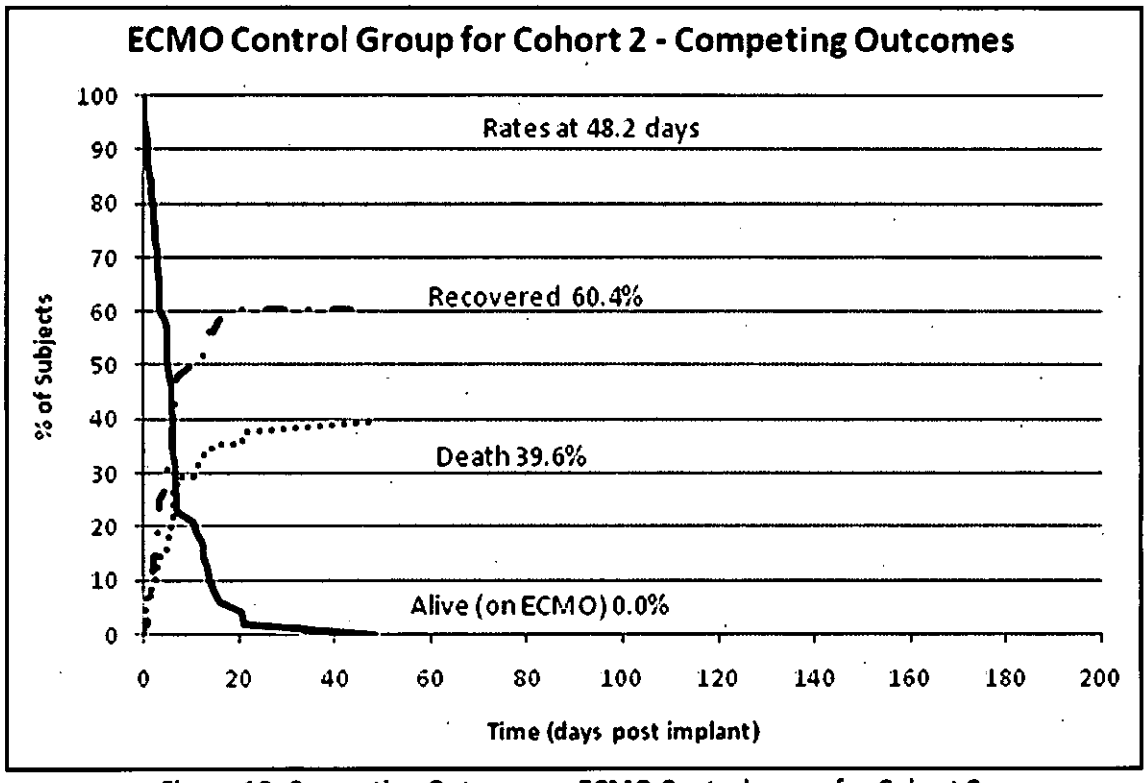

Figure 10: Competing Outcomes – ECMO Control group for Cohort 2

a) Secondary Effectiveness Endpoint Results

There were two secondary effectiveness objectives of the study. The first was to summarize the days of transplant eligible support.

Only one subject was removed from the transplantation listing at any point during their support. The subject (in Cohort 2) was first listed on day 3 of support (10/03/09) and then was delisted from 01/15/10 to 02/22/10 due to a neurological event. The subject was successfully transplanted on 04/10/10. The summary statistics of time of eligible support are detailed in Table 8. These data do not account for organs that were offered, but refused due to temporary conditions such as stroke and bleeding.

Cohort	N	Median	Mean ± Std	Range
Cohort 1	24	27.5	58.8 ± 56.1	0 – 174
Cohort 2	24	42.5	55.6 ± 44.3	3 – 151

Table 8: Days of Transplant Eligible Support

The second objective was to show the ability to de-intensify concomitant hemodynamic support. At each visit, the subject's status was recorded with the following choices: sedated, intubated, on ECMO, awake, ambulating or eating. Table 9 summarizes those choices pre-implant, and at 2 weeks and 1 month post-implant. A subject could have more than one status subcategory checked.

Prior to implant, 22 of the 24 Cohort 1 subjects (92%) and 16 of 24 Cohort 2 subjects (67%) were sedated and/or intubated and over 30% were supported by ECMO immediately prior to device implant.

In Cohort 1 there were 7 subjects (7/20=35%) who were sedated and intubated at 2 weeks with 1 sedated and awake (1/20=5%). The other 12 (12/20=60%) were awake with some of those also ambulating and eating.

In Cohort 2, 6 subjects (6/20=30%) were still sedated and intubated at 2 weeks with 1 awake and intubated (1/20=5%) and the remaining 13 awake (13/20=65%). At 1 month post-implant, those numbers drop to only 3 of the Cohort 1 and 4 of the Cohort 2 subjects remaining sedated and intubated.

Time Point	**Status** (more than 1 could be checked)	**Cohort 1** **n=24**	**Cohort 2** **n=24**
Pre-implant	Sedated	21 (87.5%)	16 (66.7%)
	Intubated	21 (87.5%)	14 (58.3%)
N=24	On ECMO/other	8 (33.3%)	9 (37.5%)
In each cohort	Awake	3 (12.5%)	12 (50.0%)
	Ambulating	0 (0.0%)	5 (20.8%)
	Eating	0 (0.0%)	8 (33.3%)
2 Weeks	Sedated	8 (40.0%)	6 (30.0%)
	Intubated	7 (35.0%)	6 (30.0%)
N=20	Awake	13 (65.0%)	14 (70.0%)
In each cohort	Ambulating	3 (15.0%)	4 (20.0%)
	Eating	6 (30.0%)	12 (60.0%)
1 Month	Sedated	4 (33.3%)	5 (29.4%)
	Intubated	3 (25.0%)	5 (29.4%)
N=12 Cohort 1	Awake	9 (75.0%)	13 (76.5%)
N=17 Cohort 2	Ambulating	3 (25.0%)	8 (47.1%)
	Eating	4 (33.3%)	9 (52.9%)

Table 9: Support Status at each Follow-up Visit

2. Sex/Gender Differences

In the EXCOR group, of the 24 subjects in Cohort 1, 12 were female (50%) and 12 were male (50%). Of the 24 subjects in Cohort 2, 11 (45.8%) were female and 13 (54.2%) were male.

FDA typically encourages analysis of study data for sex-specific differences in baseline characteristics or clinical outcomes. In this study, the sample size available for each sex is quite small and biological differences between sexes would also differ by age which further limits the ability to perform any meaningful analysis. Ultimately, FDA determined that any analysis of sex-specific differences (while interesting for hypothesis-generating purposes) would not be expected to impact the overall treatment decision due to the limited therapy options available for this patient population.

3. Primary Safety Endpoint Results

The hypothesis for the primary safety endpoint was to show that the serious adverse event rate is no greater than 0.25 events per patient-day tested at one-sided significance level of 0.025 using the Poisson exact method.

$$H_0 : \lambda \geq 0.25$$
$$H_A : \lambda < 0.25$$

where λ is the true SAE rate per patient-day.

The total time on device of the Cohort 1 subjects was 1,411 days. There were 96 serious adverse events (SAEs) for this cohort yielding a rate of ***0.068 events per patient-day***. The 95% Poisson confidence interval was calculated as: [0.055, 0.083]. The total time on device for Cohort 2 was 1,376 days. There were 109 SAEs for this cohort yielding a rate of ***0.079 events per patient-day*** with the confidence interval as [0.065, 0.096].

Serious adverse events for all primary cohort patients were reported in the primary study analysis as events per patient-day. These events were calculated based upon a total time on device for all patients. Calculation for Cohort 1 subjects (who were supported a total of 1411 days), yielded a rate of 0.068 SAEs per patient-day. Calculation for Cohort 2 subjects (who were supported a total of 1376 days), yielded a rate of 0.079 SAEs per patient-day.

The rates of SAEs per patient-day were separated based upon support with or without ECMO pre-implant and are summarized in the following table. In Cohort 1, those supported with ECMO pre-implant had twice as many events per patient-day of support. For Cohort 2, those supported with ECMO pre-implant had 1.5 times as many events per patient-day of support.

Group	ECMO Pre-Implant	# Events	Total Time on Support (Days)	Rates[2] Success Criterion <0.25	
				Events per Patient-Day	Upper bound of CI
Cohort 1	Yes	38	345	0.110	0.151
	No	58	1066	0.054	0.070
Cohort 2	Yes	43	450	0.096	0.129
	No	64	926	0.069	0.088

Table 10: SAEs per Patient-day by Pre-Implant ECMO

The following table details each SAE with the number of events experienced and the number and percent of subjects experiencing each SAE. Some of the SAEs have subcategories (see indented descriptions) which provide additional detail regarding the type of SAE.

Rates for subjects enrolled in the Cohorts 1 CAP (Continued Access Protocol which allowed continued access to the device following the conclusion of enrollment in the primary cohorts) and Compassionate Use (CU) and Emergency Use (EU) Cohorts 3A and 3B are also included. These cohorts are further described below.

[2] Confidence Interval calculated with Poisson distribution

Table 11. SAE Summary per Cohort

SAE	COHORT									
	BSA <0.7 m^2						0.7 ≤ BSA < 1.5 m^2			
	1 Total	Per Subject (% of 24)	1 CAP Total	Per Subject (% of 20)	3A Total	Per Subject (% of 35)	2 Total	Per Subject (% of 24)	3B Total	Per Subject (% of 6)
Major Bleeding	**15**	**10 (41.7%)**	**12**	**7 (35.0%)**	**25**	**18 (51.4%)**	**22**	**12 (50.0%)**	**3**	**3 (50.0%)**
Cardiac Arrhythmia	**1**	**1 (4.2%)**	**2**	**2 (10.0%)**	**3**	**3 (8.6%)**	**6**	**4 (16.7%)**	**2**	**1 (16.7%)**
Cardiac Arrhythmia-Sustained Ventricular Tachycardia	1	1 (4.2%)	0	0 (0.0%)	2	2 (5.7%)	2	2 (8.3%)	2	1 (16.7%)
Cardiac Arrhythmia-Sustained Supraventricular Tachycardia	0	0 (0.0%)	2	2 (10.0%)	1	1 (2.9%)	4	3 (12.5%)	0	0 (0.0%)
Pericardial Fluid Collection	**3**	**3 (12.5%)**	**5**	**5 (25.0%)**	**4**	**4 (11.4%)**	**4**	**3 (12.5%)**	**1**	**1 (16.7%)**
Pericardial Fluid Collection-With Tamponade	1	1 (4.2%)	3	3 (15.0%)	2	2 (5.7%)	2	2 (8.3%)	0	0 (0.0%)
Pericardial Fluid Collection-Without Tamponade	2	2 (8.3%)	2	2 (10.0%)	2	2 (5.7%)	2	2 (8.3%)	1	1 (16.7%)
Hemolysis	**1**	**1 (4.2%)**	**1**	**1 (5.0%)**	**1**	**1 (2.9%)**	**1**	**1 (4.2%)**	**1**	**1 (16.7%)**
Hemolysis-Early	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	1	1 (16.7%)
Hemolysis-Late	1	1 (4.2%)	1	1 (5.0%)	1	1 (2.9%)	1	1 (4.2%)	0	0 (0.0%)
Hepatic Dysfunction	1	1 (4.2%)	0	0 (0.0%)	6	5 (14.3%)	1	1 (4.2%)	3	2 (33.3%)
Hypertension	12	12 (50.0%)	15	13 (65.0%)	9	9 (25.7%)	8	8 (33.3%)	1	1 (16.7%)
Major Infection	**35**	**15 (62.5%)**	**15**	**7 (35.0%)**	**39**	**16 (45.7%)**	**24**	**12 (50.0%)**	**8**	**4 (66.7%)**
Major Infection-Localized Non-Device	25	12 (50.0%)	10	6 (30.0%)	20	11 (31.4%)	18	10 (41.7%)	7	3 (50.0%)
Major Infection-Percutaneous Site or Pocket	4	4 (16.7%)	1	1 (5.0%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
Major Infection-Sepsis	6	5 (20.8%)	4	2 (10.0%)	19	9 (25.7%)	6	6 (25.0%)	1	1 (16.7%)

Table 11. SAE Summary per Cohort

SAE	COHORT									
	BSA <0.7 m^2						0.7 ≤ BSA < 1.5 m^2			
	1 Total	Per Subject (% of 24)	1 CAP Total	Per Subject (% of 20)	3A Total	Per Subject (% of 35)	2 Total	Per Subject (% of 24)	3B Total	Per Subject (% of 6)
Psychiatric Episode	**0**	**0 (0.0%)**	**0**	**0 (0.0%)**	**0**	**0 (0.0%)**	**1**	**1 (4.2%)**	**0**	**0 (0.0%)**
Neurological Dysfunction	8	7 (29.2%)	6	5 (25.0%)	6	6 (17.1%)	9	7 (29.2%)	4	3 (50.0%)
Neurological Dysfunction- Transient Ischemic Attack	0	0 (0.0%)	1	1 (5.0%)	0	0 (0.0%)	0	0 (0.0%)	1	1 (16.7%)
Neurological Dysfunction-Ischemic Cerebrovascular (CVA)	8	7 (29.2%)	5	5 (25.0%)	4	4 (11.4%)	7	7 (29.2%)	3	3 (50.0%)
Neurological Dysfunction-Hemorrhagic CVA	0	0 (0.0%)	0	0 (0.0%)	2	2 (5.7%)	2	2 (8.3%)	0	0 (0.0%)
Renal Dysfunction	**3**	**2 (8.3%)**	**0**	**0 (0.0%)**	**7**	**7 (20.0%)**	**4**	**3 (12.5%)**	**2**	**1 (16.7%)**
Renal Dysfunction-Acute	3	2 (8.3%)	0	0 (0.0%)	7	7 (20.0%)	2	2 (8.3%)	2	1 (16.7%)
Renal Dysfunction-Chronic	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)	2	2 (8.3%)	0	0 (0.0%)
Respiratory Failure	**3**	**3 (12.5%)**	**8**	**8 (40.0%)**	**6**	**5 (14.3%)**	**9**	**6 (25.0%)**	**6**	**5 (83.3%)**
Right Heart Failure	**2**	**2 (8.3%)**	**2**	**2 (10.0%)**	**8**	**7 (20.0%)**	**3**	**3 (12.5%)**	**1**	**1 (16.7%)**
Arterial Non-CNS Thromboembolism	**1**	**1 (4.2%)**	**1**	**1 (5.0%)**	**2**	**2 (5.7%)**	**0**	**0 (0.0%)**	**0**	**0 (0.0%)**
Venous Thromboembolism Event	**1**	**1 (4.2%)**	**1**	**1 (5.0%)**	**0**	**0 (0.0%)**	**0**	**0 (0.0%)**	**0**	**0 (0.0%)**
Wound Dehiscence	**0**	**0 (0.0%)**	**0**	**0 (0.0%)**	**1**	**1 (2.9%)**	**0**	**0 (0.0%)**	**0**	**0 (0.0%)**
Other	**10**	**6 (25.0%)**	**6**	**5 (25.0%)**	**17**	**12 (34.3%)**	**15**	**6 (25.0%)**	**7**	**4 (66.7%)**
Other Ischemic w/o symptoms	**0**	**0 (0.0%)**	**0**	**0 (0.0%)**	**1**	**1 (2.9%)**	**0**	**0 (0.0%)**	**0**	**0 (0.0%)**
Other Covert Stroke	**0**	**0 (0.0%)**	**0**	**0 (0.0%)**	**0**	**0 (0.0%)**	**0**	**0 (0.0%)**	**1**	**1 (16.7%)**

Note that the rates of SAEs per patient-day were calculated under the Poisson distribution, which assumes a constant rate over time for each patient. Due to significant overdispersion, additional analyses using a negative binomial model and a nonparametric (bootstrap) method were performed to adjust for the additional variation. However, the upper 95% confidence intervals of the rates of SAEs per patient-day using the negative binomial and the bootstrap methods were also lower than the performance goal of 0.25 SAEs per patient-day for both Cohort 1 and Cohort 2.

a) Infection Serious Adverse Events

Major Infection events were reported according to the Investigational Plan definition (which is the same as the INTERMACS definition). Any time an additional medication was added for treating a different or new infection a new SAE was reported (or adjudicated as an event). The study definition was intentionally broad with regard to setting a low threshold for calling an event an infection: Fever was defined at 38 degrees Celsius, WBC > 15,000, positive cultures from any source, or decision to start antibiotics with or without positive cultures were listed as an SAE and subsequently adjudicated. Each infection was counted as a separate event even when occurring concurrently in one patient, ensuring that the infection rate would not be under-reported.

In Cohort 1, 15 subjects had 35 total infectious events reported. In Cohort 1, a majority of subjects had pre-existing risks for infection including ventilation (83%), pre-implant ECMO support (33%), and previous cardiac surgery (21%).

In the larger subjects (Cohort 2) there were fewer events (12 subjects with 24 events) which is expected based on age and body size.

Outcomes of any of the subjects did not appear to be affected by infections as the deaths that occurred were not solely related to infection, even when one was present. These cases tended to have multi-factorial contributors such as stroke, end-organ failure, arrhythmias, or thromboembolism. All other subjects with a noted infectious SAE were transplanted or weaned. Infection had little impact on the transplant wait time since 99.3% of the total time the subjects were on support was considered transplant eligible time.

b) Major Bleeding Serious Adverse Events

Major bleeding was the third most frequently reported SAE in Cohort 1 (10 subjects with at least one event). All bleeding events for Cohort 1 occurred in subjects less than 2 years old. Five of the 10 subjects in Cohort 1 with bleeding events were younger than 9 months old. Anemia in acute or critical illness may be exacerbated by numerous factors including blood loss (due to hemorrhage or sampling), reduced RBC production (due to nutritional deficits, inflammatory processes or low erythropoietin levels) and increased RBC turnover due to hemolysis. Cohort 1 subjects had a pre-implant history of transfusion in 92% (22/24), history of ECMO or previous VAD in 33% (8/24), and 21% (5/24) of subjects had previous cardiac surgeries. These

factors along with the strict Major Bleeding definition could have contributed to the percentage of events reported.

Major bleeding was one of most prevalent events in Cohort 2 with 12 of 24 (50%) subjects experiencing a bleeding event.

c) Hypertension Serious Adverse Events

Hypertension was reported per the protocol definition (consistent with the INTERMACS definition). An event was logged each time a subject's blood pressure reached the 95th percentile for age and was treated with an IV agent. Several hypertension events were reported in the early post-op periods. However, 75% (15/20) of the hypertension events were in Cohort 1 and 2 subjects who only received LVAD support. This is not surprising as it is common for patients supported only with left sided devices to require pharmacological support in order to optimize right ventricular function with agents that can cause hypertension, resulting in the concomitant need for agents to lower the blood pressure in the early post-operative period. Additionally, hypertension is one of the leading post operative cardiac surgical events for children, especially the younger children, possibly due to their reactive vasculature. Per the definition, hypertension events were reported when the values met the definition even if the subject was also on a pressor or in a period where the site was trying to optimize the overall hemodynamic status of the subject in the early post-op period. There did not appear to be a correlation between hypertension and major bleeding.

d) Neurological Dysfunction Serious Adverse Events

Four of the 48 (8.3%) Cohort 1 and 2 subjects experienced a neurological dysfunction with long term severe results (Pediatric Stroke Outcome Measure [PSOM] scores ≥2) and another 2 (4.2%) were withdrawn from support due to the neurological injury.

In Cohort 1, 7 of the 24 subjects experienced a neurological event (29.2%). One subject experienced 2 ischemic events. Of the 7 subjects, 1 was withdrawn from support as a result of the neurological injury. Of the remaining 6 subjects, PSOM exams were performed post explant and 1 had no deficit (assessed 17 days post-explant); 2 had mild deficits (23 and 221 days post-explant), 1 had moderate deficit (82 days post-explant) and 2 had severe deficits (PSOM score of 3 at 34 days post-explant and score 4 at 54 days post-explant).

In Cohort 2, 7 of the 24 subjects experienced a neurological event (29.2%). Two of those subjects experienced both an ischemic and hemorrhagic event. Of the 7 subjects, 1 was withdrawn from support as a result of the neurological injury. Of the remaining 6 subjects, PSOM exams were performed post explant and 1 had no deficit (50 days post-explant); 2 had mild deficits (27 and 49 days post-explant), 1 had moderate deficit (357 days post-explant) and 2 had severe deficits (PSOM scores of 10 at 29 and 38 days post-explant).

Table 12 summarizes this information.

Long term Result	Cohort 1 N=24	Cohort 2 N=24	Total N=48
No Deficit (PSOM 0.0)	1 (4.2%)	1 (4.2%)	2 (4.2%)
Mild (PSOM 0.5-1.0)	2 (8.3%)	2 (8.3%)	4 (8.3%)
Moderate (PSOM 1.5-2.0)	1 (4.2%)	1 (4.2%)	2 (4.2%)
Severe (PSOM ≥ 2.5)	2 (8.3%)	2 (8.3%)	4 (8.3%)
Support withdrawn	1 (4.2%)	1 (4.2%)	2 (4.2%)
TOTAL	7 (29.2%)	7 (29.2%)	14 (29.2%)

Table 12: Summary of Neurological Event Status – All Subjects

e) Pump Replacement Due to Thrombus

During the course of the support, a clinician may have identified that a pump required replacement due to visualized thrombus within the blood pump. These replacements were not considered adverse events. However, these were nonetheless regarded as sentinel events due to their frequency and association with thromboemboli.

In primary Cohorts 1 and 2, 24 (50%) of the subjects had at least one pump replacement due to suspected thrombus (n=11, Cohort 1; n=13, Cohort 2). The number of pump replacements ranged from 0 to 4 per subject. The average number of replacements per subject was 0.9 ± 1.2. However, subjects were supported on the device for varying lengths of time therefore it may be more informative to consider the replacements per length of time on device. The average replacements-per-day on device was 0.02 ± 0.03 per day.

At all of the IDE sites, 57 (52.3%) of the 109 subjects had at least one pump replacement due to thrombus (n=11, Cohort 1; n=14, Cohort 1 CAP; n=13, Cohort 2; and n=19, Cohort 3). The number of pump replacements ranged from 0 to 6 per subject. The average number of replacements per subject was 1.1 ± 1.4 and the average replacements-per-day on device was 0.02 ± 0.03 per day.

Of the 204 total subjects, 93 (45.6%) subjects had at least one pump replacement due to thrombus (n=11, Cohort 1; n=14, Cohort 1 CAP; n=13, Cohort 2; and n=19, Cohort 3; n=36, Cohort 3). The number of pump replacements ranged from 0 to 6 per subject. The average number of replacements per subject was 1.1 ± 1.4 and the average replacements-per-day on device was 0.02 ± 0.03 per day.

Cohort	N	# Subjects With at least 1 replacement	Total number of replacements	Replacements per Subject	Total Days on Device	Replacements per Days on Support	Time to first replacement (days)
Primary Cohorts 1 and 2*	48	24 (50.0%)	43	0.9 ± 1.2 0 - 4	2787	0.02 ± 0.03 0.00 - 0.13	24.1 ± 19.7 4 - 105
IDE Cohorts	109	57 (52.3%)	114	1.1 ± 1.4 0 – 6	6350	0.02 ± 0.03 0.00 – 0.18	19.1 ± 16.9 2 - 105
Non-IDE Cohorts	95	36 (37.9%)	58	0.6 ± 1.0 0 – 4	7240	0.01 ± 0.03 0.00 – 0.27	41.9 ± 44.6 2 - 198
Total	204	93 (45.6%)	172	0.8 ± 1.2 0 – 6	13590	0.02 ± 0.03 0.00 – 0.27	27.8 ± 32.3 2 - 198

**Note: the 48 subjects in the "Primary Cohorts" group are a subset of the "IDE Cohorts" group (n=109)*

Table 13: Pump Change Due to Thrombus

4. Death Information

Two subjects in each of the primary cohorts died after support was withdrawn. The 4 subjects were supported for a median time of 28.5 days ranging from 0 to 144 days (mean ± std: 50.3 ± 64.4 days). Of the 4 subjects who died, 75% (3/4) were supported with ECMO at the time of EXCOR implant.

The clinical events committee (CEC) reviewed all deaths at the IDE sites and assigned primary and secondary causes of death. These causes are summarized by subject in Table 14.

Patient	Days On Device	Primary Cause	Secondary Cause(s)
COHORT 1		**(2 deaths/24 subjects)**	
#1	0	Pulmonary Respiratory Failure	Cardiovascular: Left A-V valve regurgitation
#2	38	CNS: Multiple ischemic strokes	None
COHORT 2		**(2 deaths/24 subjects)**	
#3	144	Other: Arterial CNS and non-CNS Thromboembolism	Infection
#4	19	CNS: Large ischemic strokes with hemorrhagic conversion	Other: Tonsillar herniation

Table 14: Primary and Secondary Cause of Death

The following table (Table 15) demonstrates a comparison of mortality between the primary cohorts (Cohorts 1 and 2) and continued access protocol (CAP) and compassionate/emergency use (CU/EU) patients (Cohorts 3A and 3B).

Group	Mortality		
	Met Protocol Eligibility Criteria n/N (%)	Did Not Meet Protocol Eligibility Criteria n/N (%)	Total n/N (%)
Cohorts 1, 1 CAP, 2	5/63 (7.9%)	0/5 (0.0%)	5/68 (7.4%)
IDE sites Cohort 3A, 3B	2/13 (15.4%)	9/28 (32.1%)	11/41 (26.8%)
Non-IDE sites Cohort 3A, 3B	16/48 (33.3%)	19/47 (40.4%)	35/95 (36.8%)
TOTAL	**23/124 (18.6%)**	**28/80 (35.0%)**	**51/204 (25.0%)**

Table 15: Summary of Mortality Rates for Each Cohort

XI. Risk-Probable Benefit Analysis

The Berlin Heart EXCOR device is intended to provide mechanical circulatory support for pediatric patients. These patients include those with severe isolated left ventricular or biventricular dysfunction and who are candidates for cardiac transplant. Comparable treatments for this disease condition include the use of ECMO (as is seen in the study control group) which is not FDA-approved as a bridge-to-transplant device and other commercially available VADs. The risks and benefits of these alternative treatments for the intended patient population are described here. ECMO is currently the most widely-used clinical alternative to the Berlin Heart EXCOR. However, as seen in the results of the IDE study and other literature studies, ECMO is generally utilized for a limited amount of time.

The results of the Berlin Heart EXCOR IDE demonstrated that a majority of primary study patients (73% from Cohorts 1 and 2) survived to successful weaning or cardiac transplantation with acceptable neurological status (PSOM < 1). However, the study also demonstrated that use of the Berlin Heart EXCOR device is accompanied by significant risks. FDA noticed a high rate of neurological events in the EXCOR primary study patients, where greater than 30% experienced an ischemic neurological event. Due to the lack of long-term neurological follow-up in the EXCOR patients during the post-explant phase, FDA cannot be confident in the device's long-term effects on these patients' neurological status. Also, there appeared to be a high incidence of pump thrombus, with pump changes due to visible thrombus being required in 52% of all primary study patients (an average of 1.1 pump changes per patient in Cohorts 1 and 2 combined). Furthermore, compared to the primary study and CAP cohorts who met all eligibility criteria (9% mortality and failed wean; 6/68), data from the study demonstrated higher failure in patients who did not meet the strict entrance criteria of the study (38% mortality and failed

wean; 33/88) and patients who were implanted at non-study centers (37% mortality and failed wean; 35/95). Finally, data from experienced IDE study centers showed that patients requiring support on ECMO prior to EXCOR insertion and children with single ventricle circulations were also at higher risk for mortality.

Data from the IDE trial demonstrate that the device is safe as defined by the safety endpoint. Furthermore, in light of the other clinically-available alternatives, the device provides probable benefit to this very limited patient population. FDA believes that the benefits of the device outweigh its known risks.

XII. Panel Recommendation

At an advisory meeting held on July 21, 2011, the Circulatory System Devices Panel recommended that Berlin Heart's HDE for the EXCOR be approved. Citing the limitations of other available options for this critically-ill and limited patient population (and voicing concern over the incidence of stroke), the panel unanimously agreed (16-0) that the device provided a reasonable assurance of safety and that the probable benefit of the device outweighed the known risks.

The Panel discussed the primary effectiveness endpoint results and noted the differences in survival rates between patients treated with the EXCOR and those in the control group who were treated with ECMO. Survival rates were in favor of the EXCOR and the panel specifically noted that observational data showed that patients could remain on this device for longer periods of time compared to the time patients were on ECMO. The panel believed that the device meets a critical need for patients with end stage heart failure who are awaiting a transplant.

The Panel also felt that the secondary effectiveness endpoint results were supportive of clinical conclusions resulting from the primary effectiveness endpoint. The data showed that transplant eligibility is maintained while the need for other supportive measures that require sedation and limit patient mobility are diminished.

The Panel commented on the primary safety endpoint and agreed that the overall rate of SAEs was less in the EXCOR patients compared to the ECMO patients. The panel specifically noted the clinical significance of the higher, acute stroke rates and neurologic outcomes that were observed in patients treated with the EXCOR. Despite a greater than 33% neurologic event rate, approximately 90% of pediatric patients were successfully transplanted. However, it was concluded that stroke rates and neurological outcomes are serious issues that need to be investigated further in the setting of a post-approval study. The panel also suggested that strokes and their outcomes must be better defined and that more data are necessary to understand the impact of pediatric antiplatelet therapy and drug efficacy for this patient population.

There was Panel agreement that the rate of pump changes could be independent of the stroke rate and does not seem to be a quality metric for strokes. Visible thrombus is an important clinical finding

and steps should be taken to prevent thrombus build up in the pump and to determine its cause. The Panel stated that the relationship between visible thrombus and stroke rate requires further study to better understand their effects on long term outcomes.

The Panel discussed the number of pediatric transplant centers and the number of patients that might be implanted in a given year. There was agreement that a precise and thorough training program should be required for site initiation.

The Panel concluded that all available clinical data for all patients in the study should be clearly summarized in a specific clinical section of the labeling, including survival data regarding patients with single ventricle circulation and those who have had use of pre-implant ECMO. The panel agreed that the labeling should not include contraindications and enough data should be included to allow physicians to make an informed decision based on patient selection factors that may lead to optimal success and outcomes in these complex patients. Specific inclusion of the eligibility criteria used for study patients in this trial should be included as a guide for optimal patient selection.

The Panel also discussed the post-approval study (PAS) design and considered 2 elements of the study: 1) follow-up of current IDE patients and 2) enrollment of a new cohort with important baseline data with follow-up beyond explant. They agreed that the overall EXCOR data from this trial would be an appropriate comparator for the PAS given the limitations of the ELSO registry and the lack of any other suitable comparators. The Panel felt that the overall AE rate used as a baseline for this PAS should be substantially less than the 0.25 per patient day on support, and that the proposal for future performance goals should be informed by the results of patients in the IDE. Participation in existing registries or design of a distinct registry for tracking of these patients for acute and long-term outcomes was also thought to be of critical importance. The Panel proposed that approximately 5 year data should be collected on stroke, pump thrombus and longer-term neurologic and quality of life outcomes to adequately assess the longer-term impact of device implantation.

XIII. CDRH Decision

CDRH issued an approval order on December 16, 2011. FDA believes that data from the IDE trial demonstrate that the benefits of the device outweigh its known risks. Although some concerns exist with regard to stroke and neurologic outcomes, the parents and patients will be adequately informed of the risks via labeling. Long-term outcomes as a result of neurologic events and strokes remain unknown. Therefore, such data will be garnered in the sponsor's post-approval study. The post-approval study will also help evaluate whether there is a learning curve associated with the device that contributed to the high mortality rate seen in non-IDE study patients, and help further understand thrombus formation by examination of explanted pumps.

XIV. Approval Specifications

Directions for use: See the Physician's Labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See Approval Order.