SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Ventricular Assist Device (VAD)
Device Trade Name:	EXCOR® Pediatric Ventricular Assist Device
Device Procode:	DSQ
Applicant's Name and Address:	Berlin Heart Inc. 200 Valleywood, Suite B100 The Woodlands, Texas 77380
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P160035
Date of FDA Notice of Approval:	June 6, 2017

The EXCOR® Pediatric Ventricular Assist Device was originally approved under Humanitarian Device Exemption (HDE), H100004, on December 16, 2011. The Summary of Safety and Probable Benefit (SSPB) to support the HDE approval is available on the CDRH website (https://www.accessdata.fda.gov/cdrh_docs/pdf10/H100004B.pdf) and is incorporated by reference here. The current PMA application is a conversion from the original HDE.

II. INDICATIONS FOR USE

EXCOR® Pediatric Ventricular Assist Device (referred to as EXCOR Pediatric) 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 Pediatric.

III. CONTRAINDICATIONS

Patients unable to tolerate systemic anticoagulation therapy should not be implanted with EXCOR Pediatric components.

Magnetic Resonance Imaging (MRI) is contraindicated in patients after being implanted with EXCOR Pediatric.

Patients with aortic valve regurgitation that is more than moderate that cannot be repaired at the time of implantation should not be implanted with EXCOR Pediatric. If repair of

the aortic valve regurgitation requires surgical closure of the aortic valve, EXCOR Pediatric should not be implanted. EXCOR Pediatic is not intended to be used as a total artificial heart and should not be used in this configuration.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the EXCOR Pediatric labeling.

V. DEVICE DESCRIPTION

EXCOR Pediatric 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 intra-aortic balloon counterpulsation. The device is designed for mid- to long-term mechanical support.

The EXCOR Pediatric 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, and the IKUS driving unit. 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 silicone cannulas 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 six different sizes with stroke volumes of 10 ml, 15 ml, 25 ml, 30 ml, 50 ml, and 60 ml according to their maximum blood chamber volume as shown in Figure 1.

Figure 1. EXCOR Pediatric Pumps shown in all six 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. EXCOR Pediatric Biventricular system

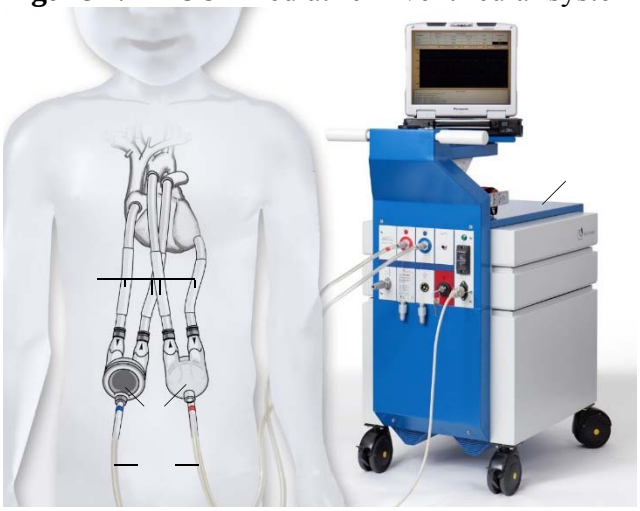
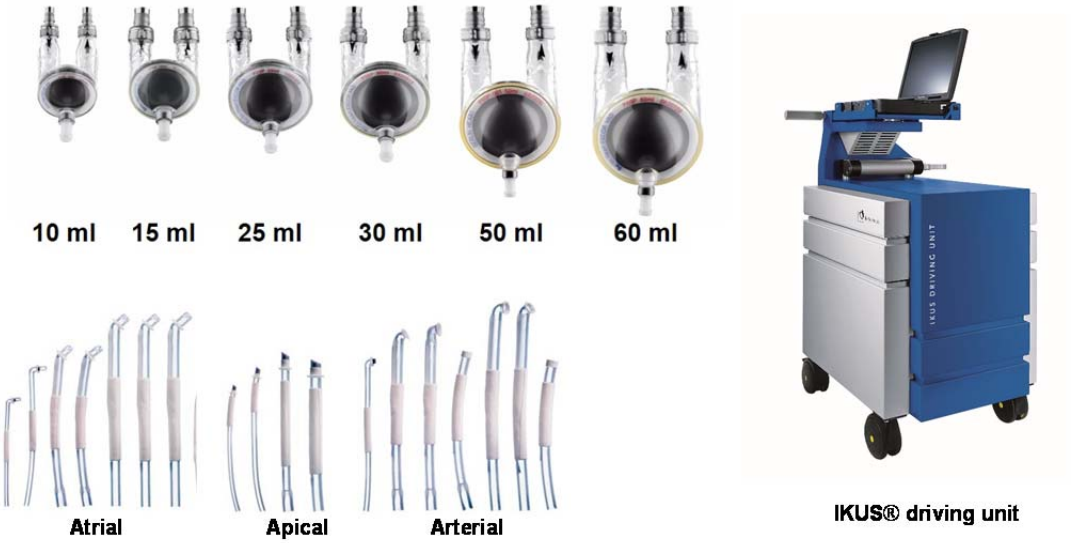


Figure 3. top left: Blood pumps, bottom left: Cannulas and right: IKUS Driving Unit



VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are alternatives to provide mechanical circulatory support for pediatrics. If the patient is eligible, heart transplantation can be used to replace the heart. Additionally, FDA approved durable ventricular assist devices can be implanted for appropriately sized patients, but are limited based on patients' body surface area (BSA). While not FDA approved or cleared, extracorporeal membrane oxygenation (ECMO) can be utilized as an alternative. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The EXCOR Pediatric is commercially available in the following countries and has not been withdrawn from marketing for any reason related to its safety or effectiveness:

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

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- Arterial non-central nervous system thromboembolism
- Cardiac arrhythmia
- Death
- Device malfunction
- Hemolysis
- Hepatic dysfunction
- Hypertension
- Major bleeding
- Major infection
- Neurological dysfunction
- Pericardial fluid collection
- Psychiatric episode
- Renal dysfunction
- Respiratory failure
- Right heart failure
- Venous thromboembolism event
- Wound dehiscence

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

A summary of previously reported preclinical studies can be found in the Summary of Safety and Probable Benefit (SSPB) for the original HDE (https://www.accessdata.fda.gov/cdrh_docs/pdf10/H100004B.pdf)

X. SUMMARY OF PRIMARY CLINICAL STUDY

Berlin Heart has performed two clinical studies to establish a reasonable assurance of safety and effectiveness of mechanical circulatory support with EXCOR Pediatric Ventricular Device in the US under IDE #G050262 and the post approval study for HDE # H100004. Data from these clinical studies were the basis for the PMA approval decision. Summaries of the IDE clinical study and HDE post approval study (PAS) are presented below.

IDE Clinical Study

A. Study Design

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 ($0.7 \leq$ BSA <1.5 m^2). A third cohort of subjects was enrolled under Compassionate Use (CU) and Emergency Use (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 1and 2and is labeled Cohort 3A (BSA is <0.7 m^2) and Cohort 3B ($0.7 \leq$ 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 1or 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 1or 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 (lA)
    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 glomerular filtration rate (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 3times 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 noncompliance
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 l 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 1 and 2 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.

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

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

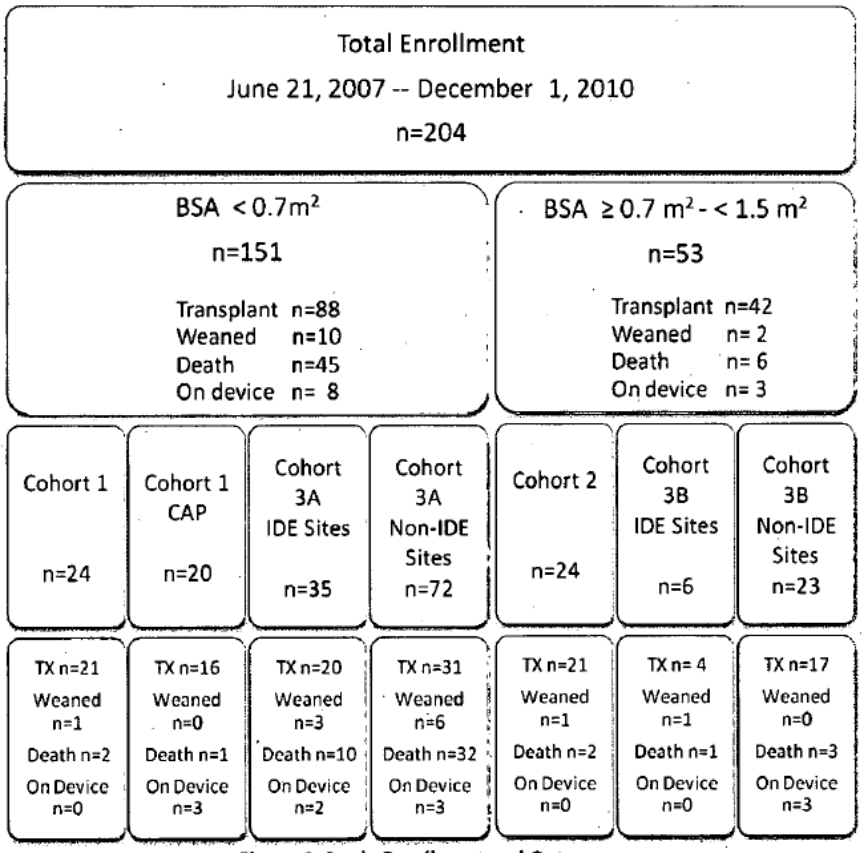
Table 2. PSA Variable Data Summary for Cohort 2 and Matched Control Group

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

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 ($0.7 \leq BSA < 1.5\ m^2$) 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. IDE Study Enrollment and Outcomes



G. Subject Demographics

Table 3 summarizes the demographic data for Cohorts 1 and 2. The most predominant cardiac diagnosis for Cohort 1was dilated cardiomyopathy (79.2%) and the majority of this group, 54.2%, presented with progressive decline. The most predominant cardiac diagnosis for Cohort 2was also dilated cardiomyopathy (70.8%) and most (54.2%) were listed in critical cardiogenic shock.

Table 3. IDE Demographic Data Summary

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)	15.4 ± 12.4 (24)	113.2 ± 37.6 (24)
	Median	11.7	111.2
	Min - Max	2.6 – 45.6	50.8 – 191.8
BSA (m^2)	Mean ± Std (N)	0.43 ± 0.10 (24)	1.09 ± 0.29 (24)
	Median	0.44	1.08
	Min - Max	0.23 – 0.62	0.71 – 1.66[1]
Weight (kg)	Mean ± Std (N)	9.1 ± 2.7 (24)	32.2 ± 12.5 (24)
	Median	9.2	30.7

	Min - Max	3.6 – 13.6	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	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%)
	Dilated cardiomyopathy: Myocarditis	0 (0.0%)	2 (8.3%)
	Dilated cardiomyopathy: Viral	1 (4.2%)	0 (0.0%)
	Dilated cardiomyopathy:	1 (4.2%)	2 (8.3%)

	Other		
	Restrictive Cardiomyopathy : Secondary to Radiation/Chemotherapy	0 (0.0%)	1 (4.2%)
	Valvular Heart Disease	0 (0.0%)	1 (4.2%)
	Congential Heart Disease (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 (33.33%)

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

Table 4. IDE Pre-Implant Support

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%)

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.

$$H_o: HR \geq 1$$
$$H_\lambda: HR < 1$$

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 1was 0.04 (p-value=0.004); the adjusted hazard ratio for Cohort 1was 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 5 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 1subjects (12.5%) failed (2 deaths and 1weaned 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 1who 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.

Table 5. IDE Primary Efficacy Study and Control Groups (Updated Control Group Data)

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

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 1and 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

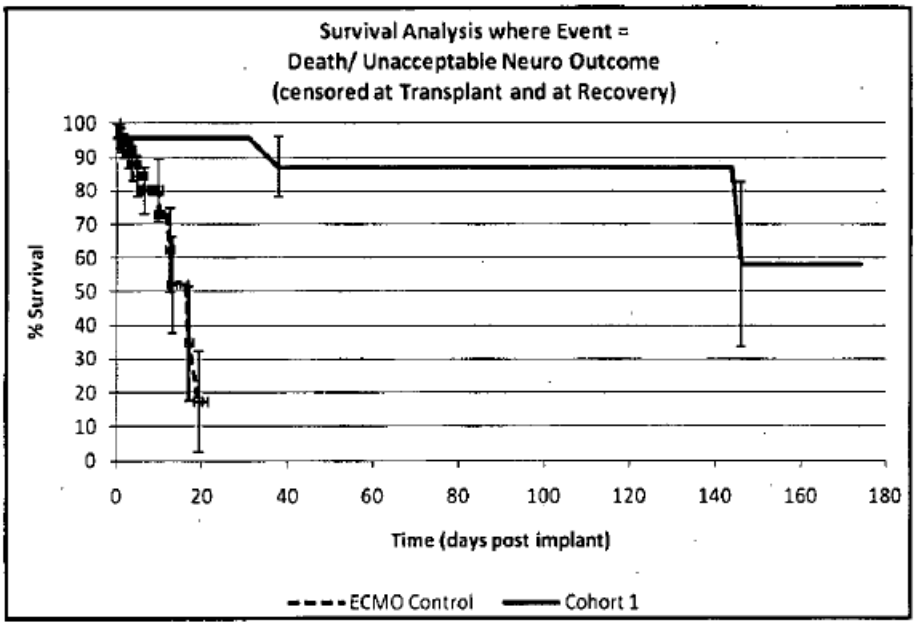
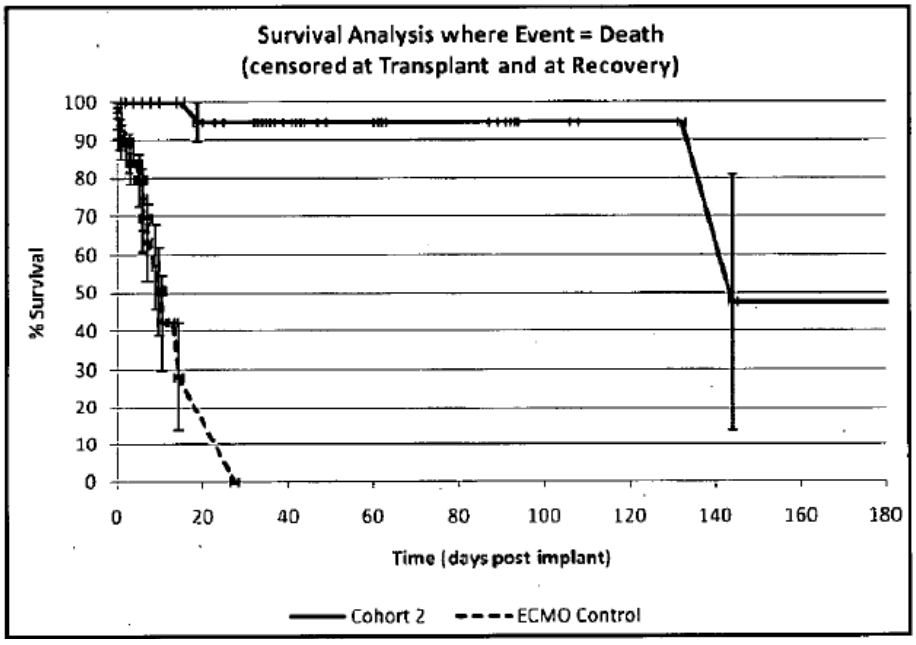


Figure 6. Survival to Death/Weaned with Unacceptable Neurological Outcome - Cohort 2 versus ECMO



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

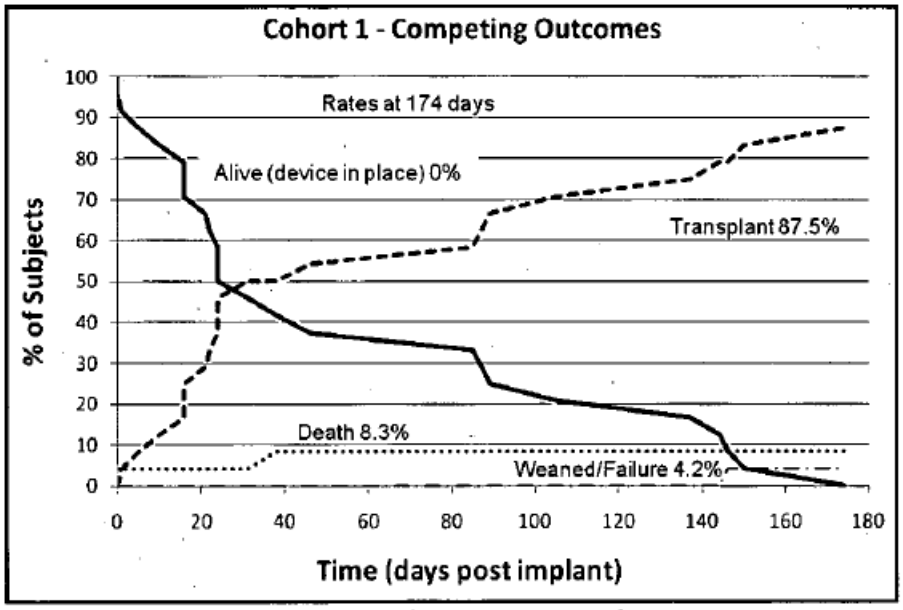


Figure 8 shows the "Competing Outcomes" for the ECMO control group for Cohort 1. The longest support time was 30 days at which time 71% were weaned from ECMO for recovery or transplant.

Figure 8. Competing Outcomes – ECMO Control Group for Cohort 1

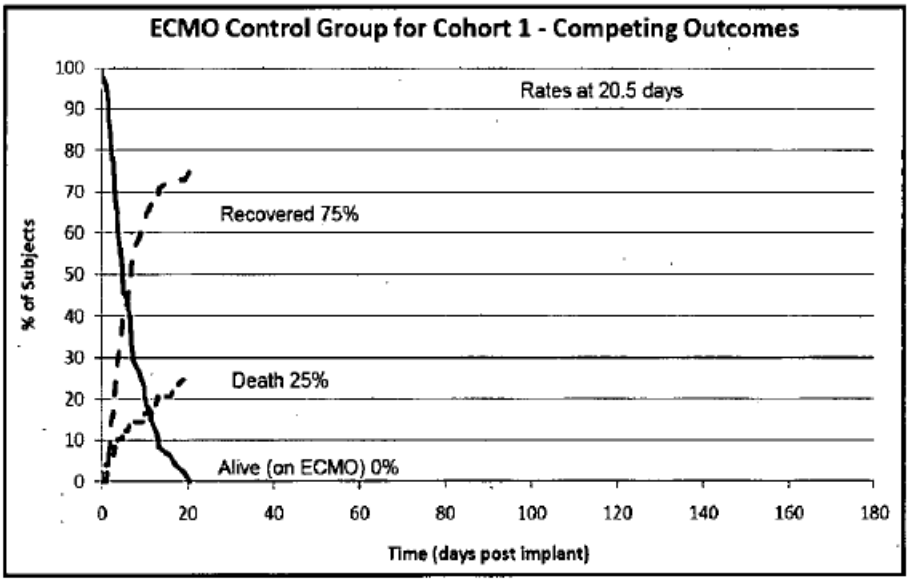


Figure 9 shows the "Competing Outcomes" for Cohort 2. Of the 24 Cohort 2 subjects, 21 were transplanted between 3 to 192 days of support. The 2 deaths in this Cohort occurred at 19 and 144 days post implant. One subject was successfully weaned to recovery after 9 days.

Figure 9. Competing Outcomes – Cohort 2

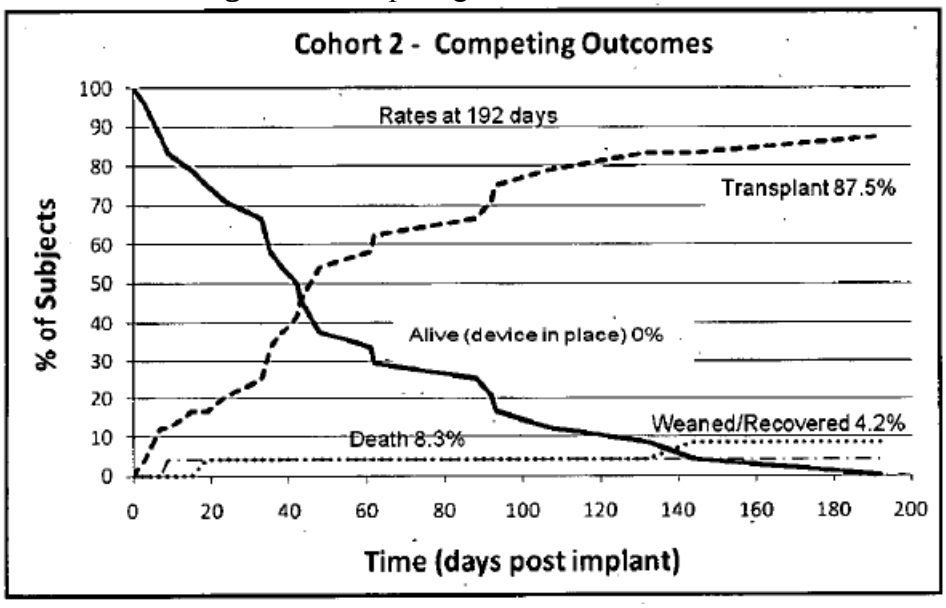
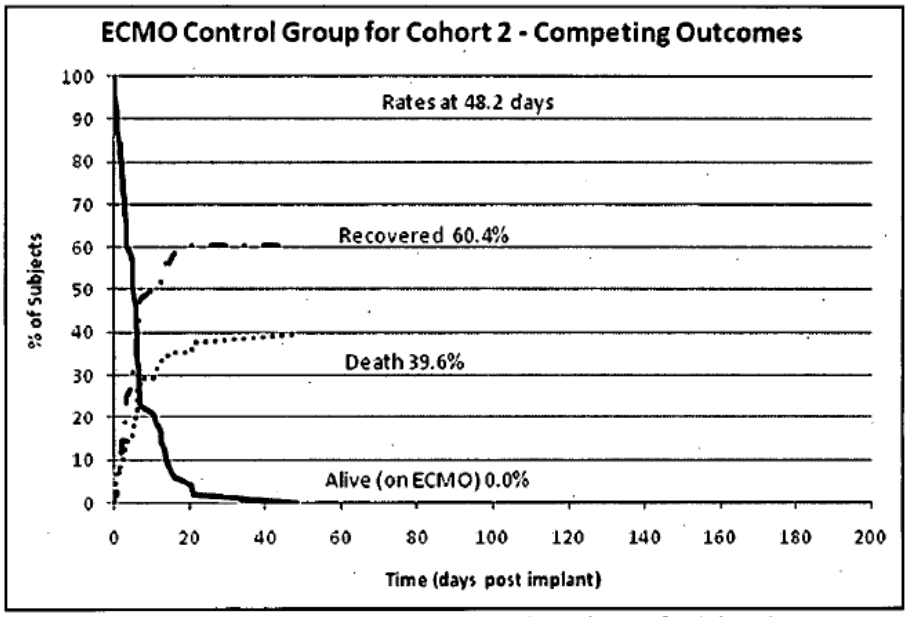


Figure 10 shows the "Competing Outcomes" for the ECMO control group for Cohort 2.The longest support time was 48.2 days at which time 60% were weaned from ECMO for recovery or transplant.

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 6. These data do not account for organs that were offered, but refused due to temporary conditions such as stroke and bleeding.

Table 6. Days of Transplant Eligible Support

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

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 7 summarizes those choices pre-implant, and at 2weeks and 1 month post-implant. A subject could have more than one status subcategory checked.

Prior to implant, 22 of the 24 Cohort 1subjects (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 2weeks with 1 awake and intubated (1/20=5%) and the remaining 13 awake (13/20=65%). At 1month post-implant, those numbers drop to only 3of the Cohort 1 and 4 of the Cohort 2 subjects remaining sedated and intubated.

Table 7. IDE Support Status at each follow-up visit

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

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.

$$H_O: \lambda \geq 0.25$$
$$H_{\lambda:} \lambda < 0.25$$

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

The total time on device of the Cohort 1subjects 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 1subjects (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.

Table 8. IDE SAEs per Patient day by Pre-Implant ECMO

Group	ECMO Pre – Implant	# Events	Total Time on Support (Days)	Rates[1] 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

[1]Confidence Interval calculated with Poisson distribution

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 1CAP (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.

Table 9. IDE 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 9 cont. IDE 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 over dispersion, 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 1occurred in subjects less than 2 years old. Five of the 10 subjects in Cohort 1with 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 red blood cell (RBC) production (due to nutritional deficits, inflammatory processes or low erythropoietin levels) and increased RBC turnover due to hemolysis. Cohort 1subjects 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 left ventricular assist device (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 l and 2 subjects experienced a neurological dysfunction with long term severe results (Pediatric Stroke Outcome Measure [PSOM] scores 22) 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 10 summarizes this information.

Table 10. IDE Summary of Neurological Event Status – All Subjects

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 $\geq$ 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%)

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 l 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.

Table 11. Pump Change Due to Thrombus

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	2787	0.02 ± 0.03	24.1 ± 19.7
				0 - 4		0.00 – 0.13	4 - 105
IDE Cohorts	109	57 (52.3%)	114	1.1 ± 1.4	6350	0.02 ± 0.03	19.1 ± 16.9
				0 – 6		0.00 – 0.18	2 - 105
Non-IDE Cohorts	95	36 (37.9%)	58	0.6 ± 1.0	7240	0.01 ± 0.03	41.9 ± 44.6
				0 - 4		0.00 – 0.27	2 - 198
Total	204	93 (45.6%)	172	0.8 ± 1.2	13590	0.02 ± 0.03	27.8 ± 32.3
				0 - 6		0.00 – 0.27	2 - 198

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 12.

Table 12. IDE Primary and Secondary Cause of Death

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 1 (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

The following table (Table 13) demonstrates a comparison of mortality between the primary cohorts (Cohorts 1and 2) and continued access protocol (CAP) and compassionate/emergency use (CU/EU) patients (Cohorts 3A and 3B).

Table 13. IDE Summary of Mortality Rates for Each Cohort

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%)

HDE Post Approval Study

A. Study Design

The study was an "all comers" prospective study consisting of pediatric patients aged 0 to 21 years implanted according to the Instructions for Use (IFU) with the EXCOR Pediatric who were transplant eligible children in need of mechanical circulatory support and who consented to be enrolled into the study. Patients were treated between January 2013 and March 2014. The post approval study enrolled 39 patients at 19 investigational sites. IRB approval was obtained at 26 sites who agreed to participate.

1. Clinical Inclusion and Exclusion Criteria
   Enrollment in the HDE Post Approval study was an all comers registry.

2. Follow-up Schedule
   All patients were scheduled to return for follow-up examinations at 3 weeks, 6 weeks, 3 months after the procedure and every 3 months thereafter while on device. After the device was explanted, follow-up examinations were performed at hospital discharge, 12 months, and 24 months (post device explant).

3. Clinical Endpoints
   With regards to safety, the primary endpoint was the serious adverse event (SAE) rate, which was calculated as the total number of SAEs divided by the sum of days all subjects were supported on the EXCOR Pediatric device.

   With regards to effectiveness, the endpoint was defined as transplant, recovery of left ventricular function, or death.

Secondary endpoints include:

- Device Malfunction
- Site evaluation of explanted pumps for suspected thrombus
- Assessment of the learning curve

The primary endpoints were summarized by stratifying the subjects into two groups based on BSA (cutoff of 0.7 m^2) and again by age (cutoff of 4 years of age). The cutoff for BSA was chosen to match that of the pre-market study and the cutoff of age was chosen based on supplementary analysis performed during the pre-market study to evaluate outcome differences between younger and older subjects.

B. Accountability of PMA Cohort

At the time of database lock, of 565 patients within the available datasets, 100 % patient data were available for analysis as demonstrated in Figure 11.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a pediatric population undergoing LVAD Support in the US.

Table 14. PAS Study Demographics

Variable	**Category**	**N (% of 39)**
Age (years)	Median	1.9
	Q1 – Q3	0.7 -11.5
	Min – Max	0.0 -16.3
Weight (kg)	Median	10.6
	Q1 – Q3	7.8 -30.3
	Min – Max	3.4-70.0
Height (cm)	Median	85.0
	Q1 – Q3	69.0-130.0
	Min – Max	50.0-169.8
BSA (m2)	Median	0.49
	Q1 – Q3	0.39-1.01
	Min – Max	0.23-1.76
Gender	Male	19 (48.7%)
	Female	20 (51.3%)
Primary Diagnosis	Dilated cardiomyopathy	25 (64.1%)
	Congenital Heart Disease	5 (12.8%)
	Post open heart transplant	4 (10.2%)
	Restrictive cardiomyopathy (RCMP)	3 (7.7%)
	Left ventricular non-compaction cardiomyopathy (LVNC)	1(2.6%)
	Left ventricular aneurysm	1 (2.6%)

INTERMACS® Profile	1 "Critical Cardiogenic Shock"	16 (41.0%)
	2 "Progressive Decline"	21 (53.9%)
	3 "Stable by Inotrope dependent"	2 (5.1%)
Ventricle Type	Single Ventricle	2 (5.1%)
	2- Ventricle	37 (94.9%)

D. Safety and Effectiveness Results

The safety and effectiveness results are summarized in the section below titled, Summary of Supplemental Clinical Information since the review team evaluated the totality of the data for the PMA.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical and HDE PAS studies included 136 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

In March 2012, FDA requested that Berlin Heart gather information for patients implanted with the EXCOR Pediatric in the United States following HDE approval (December 16, 2011) who were not enrolled in the post approval study. Berlin Heart receives basic patient, device and mechanism of implantation information through the device ordering and return processes. Additionally Berlin Heart receives verbally-reported information regarding patient status and outcome through routine site communication.

A total of 245 patients have been implanted with the EXCOR Pediatric at 45 hospitals following approval (outside the post approval study) through December 31, 2015. The available data yields a total of 565 implants from June 21, 2007 to December 31, 2015 which is made up of: 187 implants under the IDE and PAS study protocols, 133 implants at sites following the IDE protocol but not participating in the IDE study, and 245 implants occurring post approval outside a study.

Table 15 summarizes the implants for each time period.

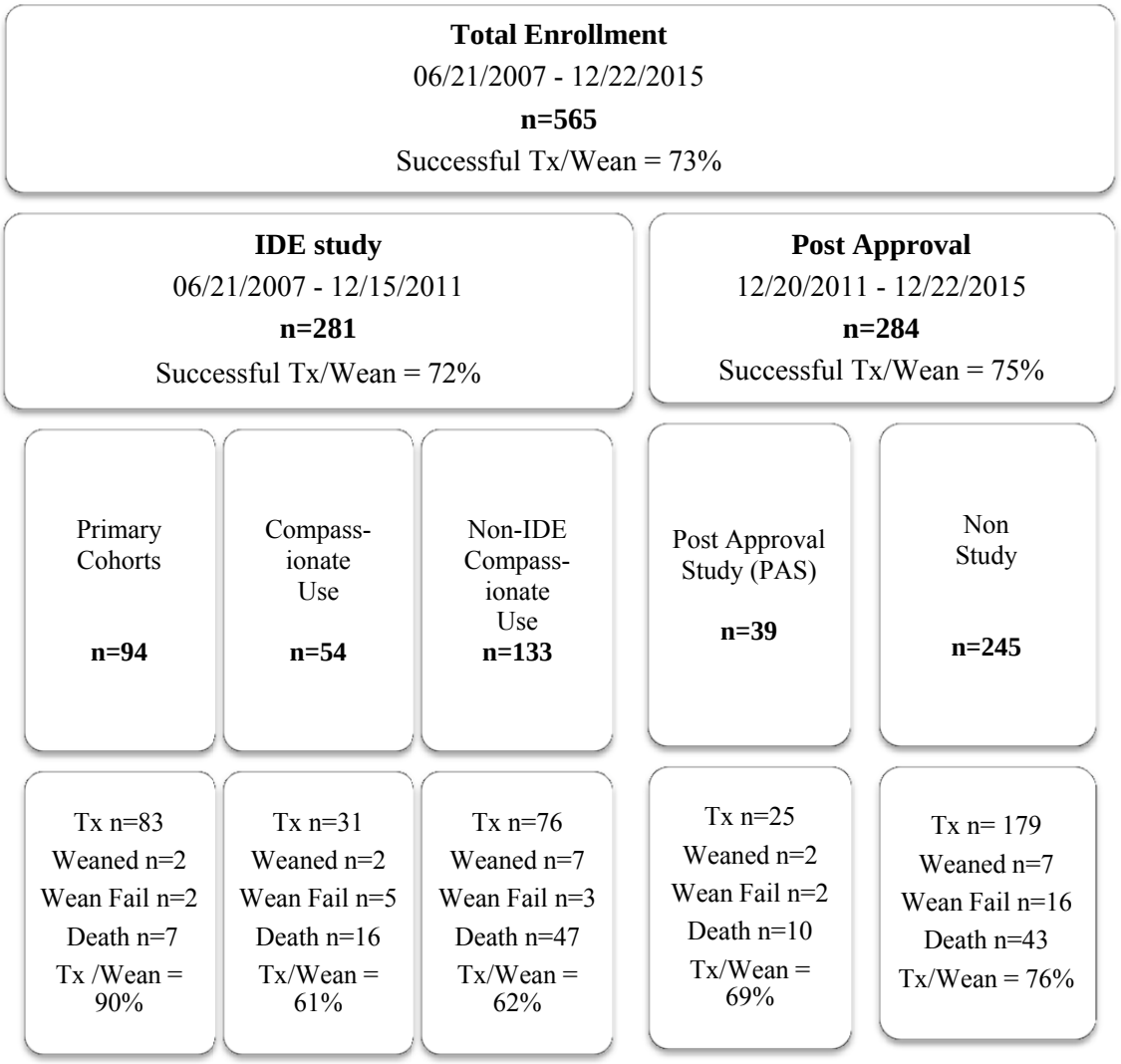
Table 15. Implants per Time Period

Study Group	Implant Period	N
IDE study Primary Cohorts	2007-2011	94

Study Group	Implant Period	N
IDE study Compassionate Use	2007-2011	54
Non-IDE site Compassionate Use	2007-2011	133
Post Approval Study	2013-2015	39
Post approval non study	2011-2015	245
TOTAL	**2007-2015**	**565**

Figure 11 details the complete implantations of EXCOR Pediatric since the initiation of the IDE.

Figure 11. IDE and PAS Studies Enrollment and Outcomes



Brief Summary of Results

Summary data is presented in three groups as shown in Table 16 and Figure 11. The Study Group (n=187) contains the IDE study data that was monitored and adjudicated (IDE Study Primary Cohorts, n=94; and IDE Compassionate Use, n=54) combined with the Post-approval Study data (n=39). The Database Group (n=320) contains the Study Group data from the 3 cohorts defined above (n =187) combined with the Compassionate Use data from non-IDE sites that agreed to enter data into the study database (n=133). The All Implant Group (n=565) is a comprehensive group containing all Database Group Patients (n=320) combined with all non-study patients implanted from the time of IDE approval in 2007 through 2015 (n=245).

Table 16. Basic Demographic Data

Variable	**Category**	**Study Group** (IDE + Comp Use[1] + PAS) **n=187**	**Database Group** (IDE + Non-IDE Comp Use[2] + PAS) **n=320**	**All Implant Group** **n=565**
Age (mo.)	Median [Range]	19.8 [0 – 194.7]	20.5 [0 – 239.3]	20.0 [0.0 – 389.3]
Weight (kg)	Median [Range]	10.6 [3.0 – 70.0]	10.7 [2.8 – 71.0]	10.7 [2.8 – 112.0]
Height (cm)	Median [Range]	82.0 [45.0 – 171.0]	82.0 [44.0 – 171.0]	81.0 [44.0 – 181.0]
BSA (m^2)	Median [Range]	0.50 [0.20 – 1.76]	0.50 [0.19 – 1.76]	0.49 [0.19 – 2.30]
Device Type	LVAD	118 (63.1%)	201 (62.8%)	382 (67.6%)
	BVAD	69 (36.9%)	119 (37.2%)	183 (32.4%)

[1] Compassionate use cases occurring at study sites
[2] Compassionate use cases occurring at both the study and non-study sites

Table 17 summarizes the basic demographic and pre-implant data that is available for all implants. Tables 18 and 19 summarize the demographic and pre-implant data that is available for the study and database groups. Overall, the patients ranged in age from 0 days to 389.3 months, the weight ranged from 2.8 to 112 kilograms and the BSA ranged from 0.13 to 2.3 m^2.

Approximately half of study subjects were female (51%) and slightly more than half presented with cardiomyopathy (53%). Other prevalent diagnoses were congenital heart disease (28%), and myocarditis (12%). Most of the subjects presented with either progressive decline (48%) or critical cardiogenic shock (48%) with the remaining presenting as stable but inotrope dependent (3%) or other (1%).

Prior to implantation, 90% of the subjects in the database groups were receiving inotrope therapy, 74% ventilatory support and over 41.8% were on ECMO or temporary VAD support. Additionally, 80% of subjects had a history of transfusion.

Table 17. Demographic Data for Study and Database Groups

Variable	**Category**	**Study Group** (IDE + PAS)	**Database Group** (IDE + Comp Use + PAS)
		n=187	**n=320**
Gender	Male	90 (48.1%)	158 (49.4%)
	Female	97 (51.9%)	162 (50.6%)
Device strategy	Bridge to Transplant (BTT)	176 (94.1%)	298 (93.1%)
	Possible BTT-Likely to be eligible	6 (3.2%)	13 (4.1%)
	Possible BTT-Mod Likelihood	3 (1.6%)	3 (0.9%)
	Possible BTT-Unlikely to be eligible	0 (0.0%)	1 (0.3%)
	Bridge to Recovery	1 (0.5%)	3 (0.9%)
	Other	1 (0.5%)	2 (0.6%)
Patient Profile/ Status	1 Critical Cardiogenic Shock	81 (43.3%)	154 (48.1%)
	2 Progressive decline	100(53.5%)	152 (47.5%)
	3 Stable but Inotrope dependent	5 (2.7%)	11 (3.4%)
	4 Recurrent advanced heart failure	0 (0.0%)	1 (0.3%)
	7 Advanced NYHA Class 3	1 (0.5%)	1 (0.3%)
	Not reported	0 (0.0%)	1 (0.3%)
Pre-implant support: ECMO		66 (35.3%)	123 (38.4%)
Pre-implant support: Ventilator		134 (71.7%)	237 (74.1%)
Pre-implant support: Inotropes		169 (90.4%)	288 (90.0%)
Pre-implant support: VAD		7 (3.7%)	11 (3.4%)
History of transfusions		147 (78.6%)	256 (80.0%)
Heart Failure Classification Pre-implant	NYHA I	1 (0.5%)	1 (0.3%)
	NYHA II	1 (0.5%)	5 (1.6%)
	NYHA III	2 (1.1%)	3 (0.9%)
	NYHA IV	42 (22.5%)	70 (21.9%)
	Ross Class II	3 (1.6%)	5 (1.6%)

Variable	Category	Study Group (IDE + PAS)	Database Group (IDE + Comp Use + PAS)
		n=187	**n=320**
	Ross Class III	5 (2.7%)	9 (2.8%)
	Ross Class IV	122 (65.2%)	210 (65.6%)
	Not reported	11 (5.9%)	17 (5.3%)

Table 18. Primary and Secondary Diagnoses for Study and Database Groups

Variable	Category	Study Group (IDE + PAS) **n=187**	Database Group (IDE + Comp Use + PAS) **n=320**
Primary Cardiac Diagnosis	CHD	49 (25.2%)	91 (28.4%)
	Dilated cardiomyopathy (DCMP)	99 (52.9%)	169 (52.8%)
	Myocarditis	23 (12.3%)	39 (12.2%)
	RCMP/Hypertrophic Cardiomyopathy (HCMP)	9 (4.8%)	13 (4.1%)
	Other	7 (3.7%)	8 (2.5%)
Secondary	None	115 (61.5%)	197 (61.6%)
Cardiac Diagnosis	DCMP	30 (16.0%)	56 (17.5%)
	Congenital Heart Disease	15 (8.0%)	21 (6.6%)
	Coronary Artery Disease	4 (2.1%)	4 (1.3%)
	RCMP	3 (1.6%)	5 (1.6%)
	Heart Disease	3 (1.6%)	10 (3.1%)
	Myocarditis	3 (1.6%)	3 (0.9%)
	CHD/Heart disease	3 (1.6%)	4 (1.3%)
	CHD/DCMP	1 (0.5%)	1 (0.3%)
	CHD/CAD	1 (0.5%)	1 (0.3%)
	DCMP/Heart disease	0 (0.0%)	2 (0.6%)
	RCMP/Heart disease	0 (0.0%)	1 (0.3%)
	Other	5 (2.7%)	6 (1.9%)
	Unknown	4 (2.1%)	9 (2.8%)

Effectiveness Evaluation

Effectiveness was assessed by measuring survival (defined by the interval of time from initiation of mechanical support as a bridge to transplant or recovery to explant). Subjects were censored at time of explant. Subjects who were explanted due to recovery of their ventricular function but died within 30 days were counted as a failure with time to failure being the explant date. Subjects who were explanted due to escalation to ECMO or alternative device of support were counted as a failure with time to failure being the explant date. Figure 12 details the Kaplan-Meier survival curve for the endpoint of death for the all implant group.

Figure 12. Kaplan-Meier Freedom from Death for All Implant Group (n=565)

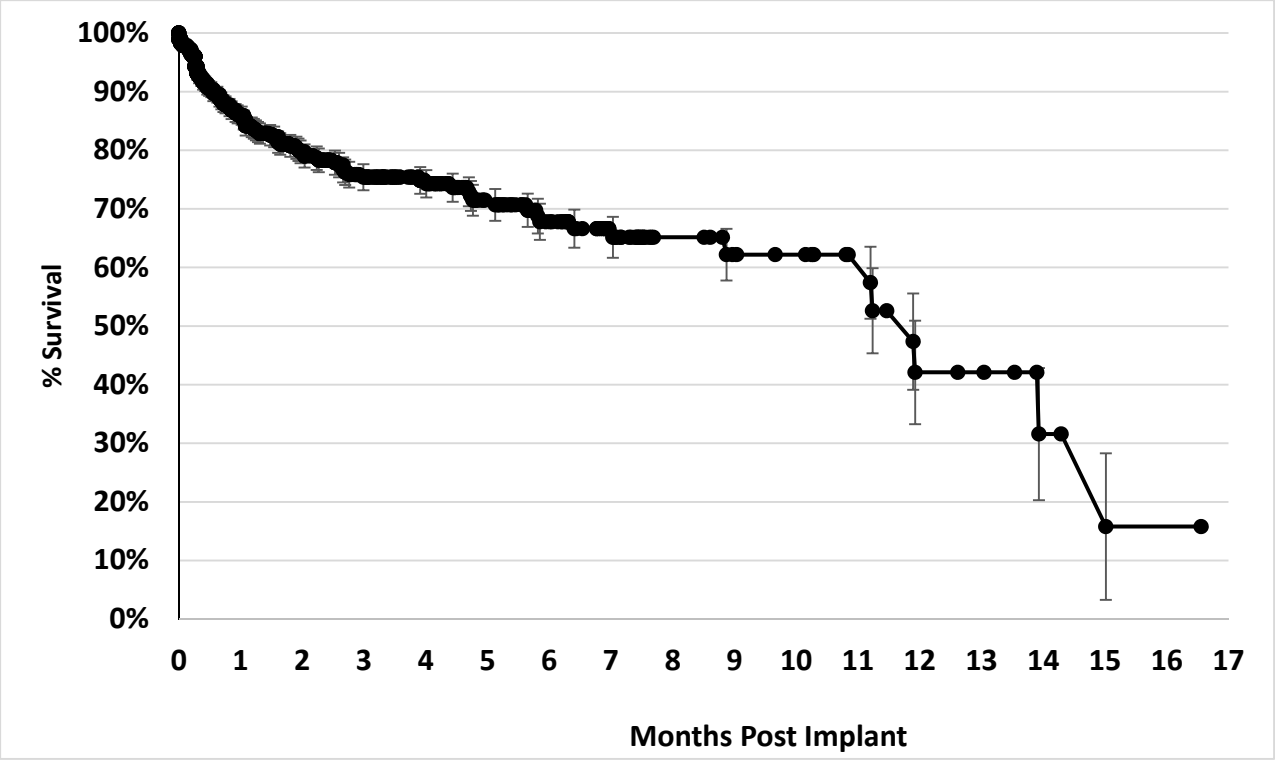


Table 19. Kaplan – Meier Freedom from Death for All Implant Group (n=565)

	Interval Beginning (Months Post Implant)																
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
# At Risk	565	356	227	175	130	90	68	45	25	20	18	13	8	7	3	2	1
Total # Died	0	70	93	104	105	110	114	115	116	117	117	117	121	121	122	122	123
Survival %	100	86.1	79.7	75.4	74.9	71.4	67.7	66.6	65.1	62.2	62.2	62.2	42.1	42.1	31.6	31.6	15.8
Std Error %	0	1.6	1.9	2.2	2.3	2.6	3.1	3.2	3.5	4.4	4.4	4.4	8.8	8.8	11.3	11.3	12.5

A total of 73.3% (414 of 565) were successfully transplanted (n=394) or weaned due to recovery of their ventricular function (n=20). Twenty-eight (28) patients required

escalation of support to ECMO or another supportive device or were weaned due to poor prognosis and died within 30 days of being weaned. A total of 123 patients (21.8%) died as a result of withdrawal of support.

Subjects participating in a study (Study Group) were successfully weaned or transplanted in 78% of the cases. The Study Group subjects were supported on the device for a median time of 42 days and the median time of support was 47 days for the All Implant Group. Table 20 details the outcomes and support time for each group.

Table 20. Outcomes and Support Time

Outcome	**Study Group** (IDE + Comp Use[1] + PAS) **n=187**	**Database Group** (IDE + Comp Use[2] + PAS) **n=320**	**All Implant Group** **n=565**
Transplant	139 (74.3%)	215 (67.2%)	394 (69.7%)
Weaned	6 (3.2%)	13 (4.1%)	20 (3.5%)
Wean-Failure*	9 (4.8%)	12 (3.8%)	28 (5.0%)
Death	33 (17.7%)	80 (25.0%)	123 (21.8%)
Success**	145 (77.5%)	228 (71.3%)	414 (73.3%)
Support Time, Median [Range]	42.0 [0 – 457]	40.5 [0 – 457]	47.0 [0 – 504]

*Failure if escalated to other support or weaned from support and died within 30 days
**Successful transplant or wean of those who met an endpoint
[1] Compassionate use cases occurring at study sites
[2] Compassionate use cases occurring at both the study and non-study sites

The available clinical data suggested that patients who were on ECMO prior to implant and those with congenital heart disease (CHD) were less successful than subjects that did not receive pre-implant ECMO and who did not have a CHD diagnosis. Outcomes for these sub-groups are presented in Table 21 for the Database Group (N=320).

Of the 320 subjects in the Database group, 123 were on ECMO prior to the EXCOR Pediatric implant. Only 61% of the subjects who were on ECMO prior to implant were successfully transplanted/weaned compared to 78% of the subjects not on ECMO prior to EXCOR Pediatric. Of the 320 subjects in the Database Group, 91 were diagnosed with CHD. Only 52% of the subjects with CHD were successfully transplanted/weaned compared to 79% of the subjects which did not have a CHD diagnosis.

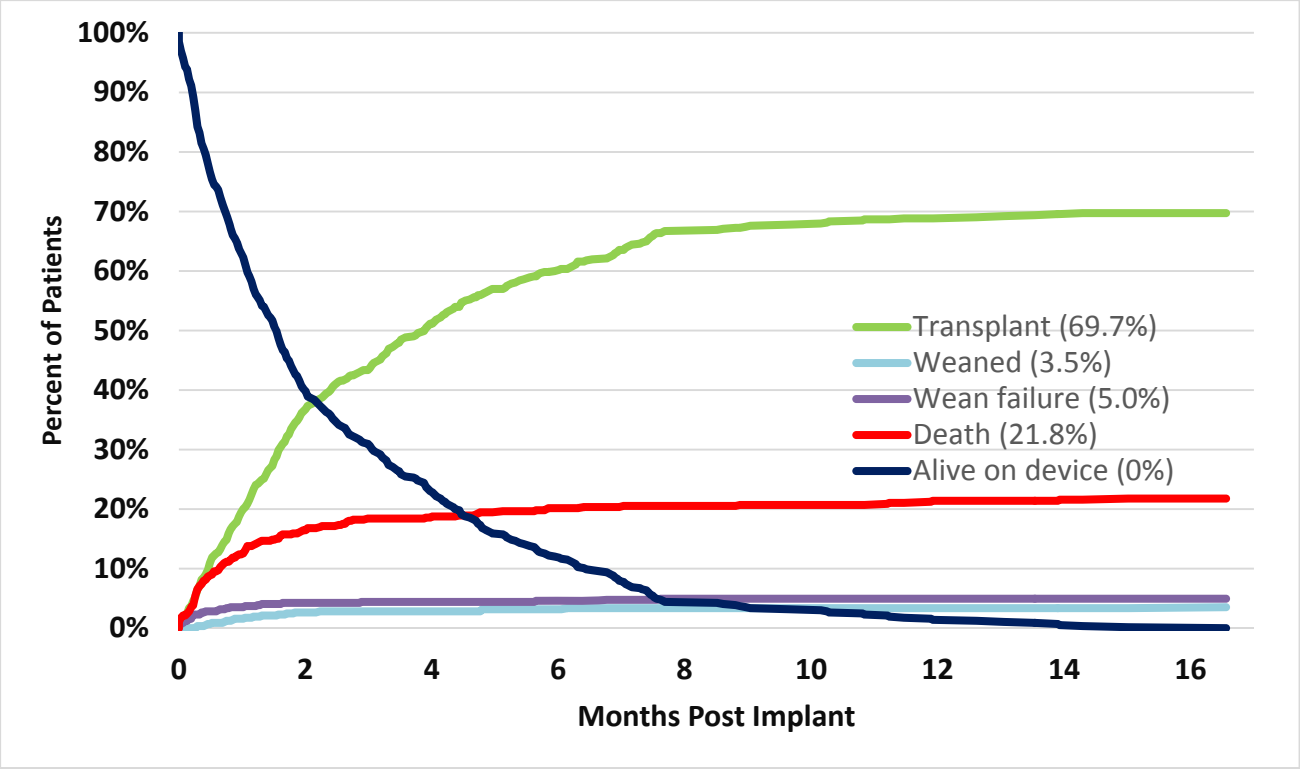
Table 21. Outcomes and Support Time by Pre-implant ECMO and CHD Diagnosis, Database Group

Outcome	ECMO prior to Implant		Primary Diagnosis Group	
	Not on ECMO n=197	On ECMO n=123	Non-CHD n=229	CHD n=91
Transplant	147 (74.6%)	68 (55.3%)	169 (73.8%)	46 (50.6%)
Weaned	6 (3.1%)	7 (5.7%)	12 (5.2%)	1 (1.1%)
Wean-Failure*	5 (2.5%)	7 (5.7%)	7 (3.1%)	5 (5.4%)
Death	39 (19.8%)	41 (33.3%)	41 (17.9%)	39 (42.9%)
Success**	153 (77.7%)	75 (61.0%)	181 (79.0%)	47 (51.7%)
Support Time, Median [Range]	45.0 [0 – 457]	35.0 [0 – 424]	42.0 [0 – 457]	39.0 [0 – 435]

*Failure if escalated to other support or weaned from support and died within 30 days
**Successful transplant or wean of those who met an endpoint

Figures 13-17 show the "Competing Outcomes" for the All Implant Group (Figure 13) and important clinically defined subgroups from the Database Group (Figures 14-17). The lines shown on each graph represent the incidence of each of the defined outcomes at all points of time. At any time point the sum of the proportions of all listed outcomes equals 100%.

Figure 13. Competing Outcome Plot for All Implant Group (N=565)



Figures 14 and 15 show the "Competing Outcomes" by pre-implant use or non-use of ECMO for patients in the Database Group.

Figure 14. Competing Outcome Plot for Database Group: No ECMO prior to implant (n=197)

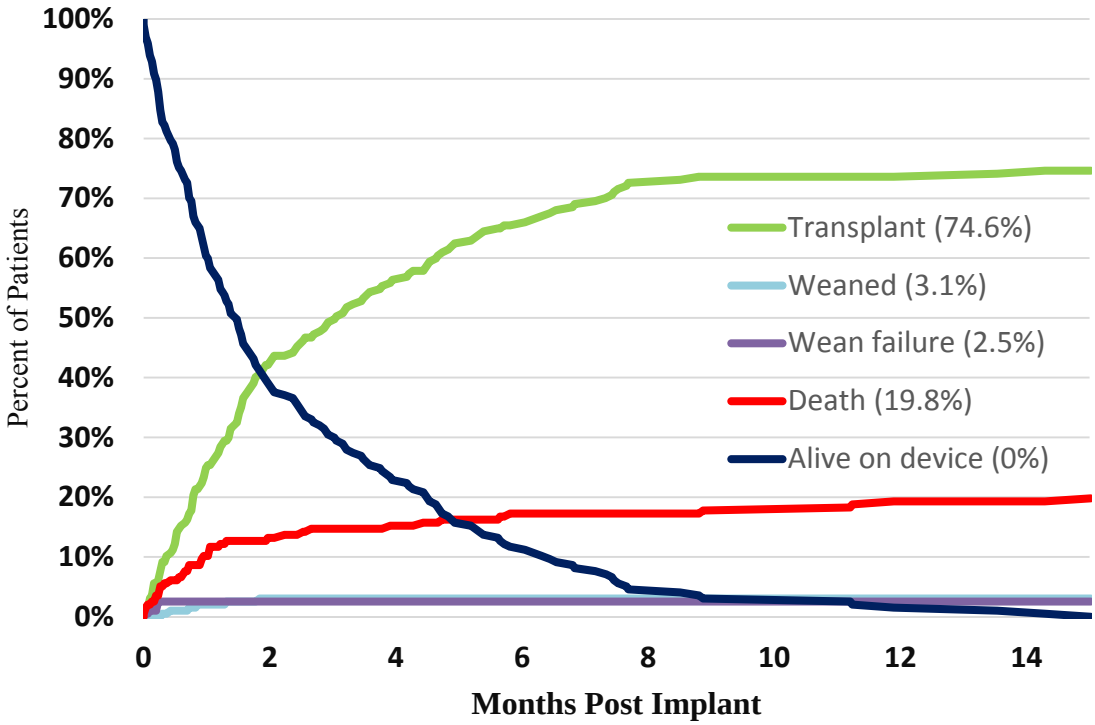
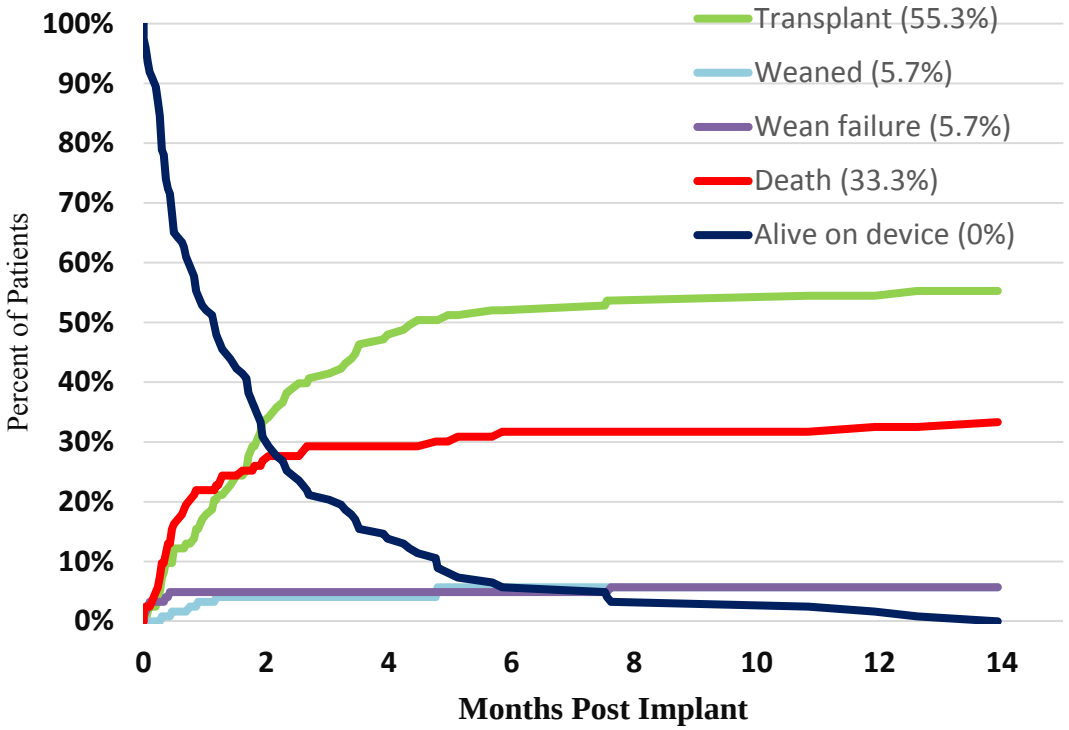


Figure 15. Competing Outcome Plot for Database Group: ECMO prior to implant (n=123)



Figures 16 and 17 show the plots stratified by primary diagnosis of CHD or non-CHD for Database Group patients.

Figure 16. Competing Outcome Plot for Database Group: Non-CHD (n=229)

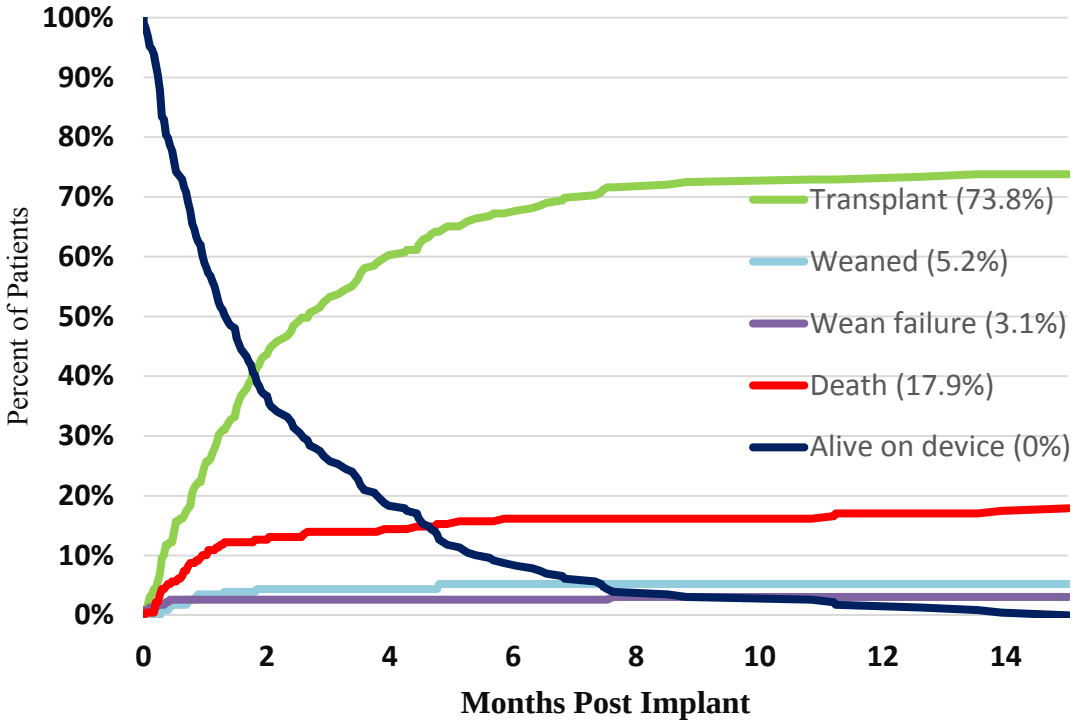
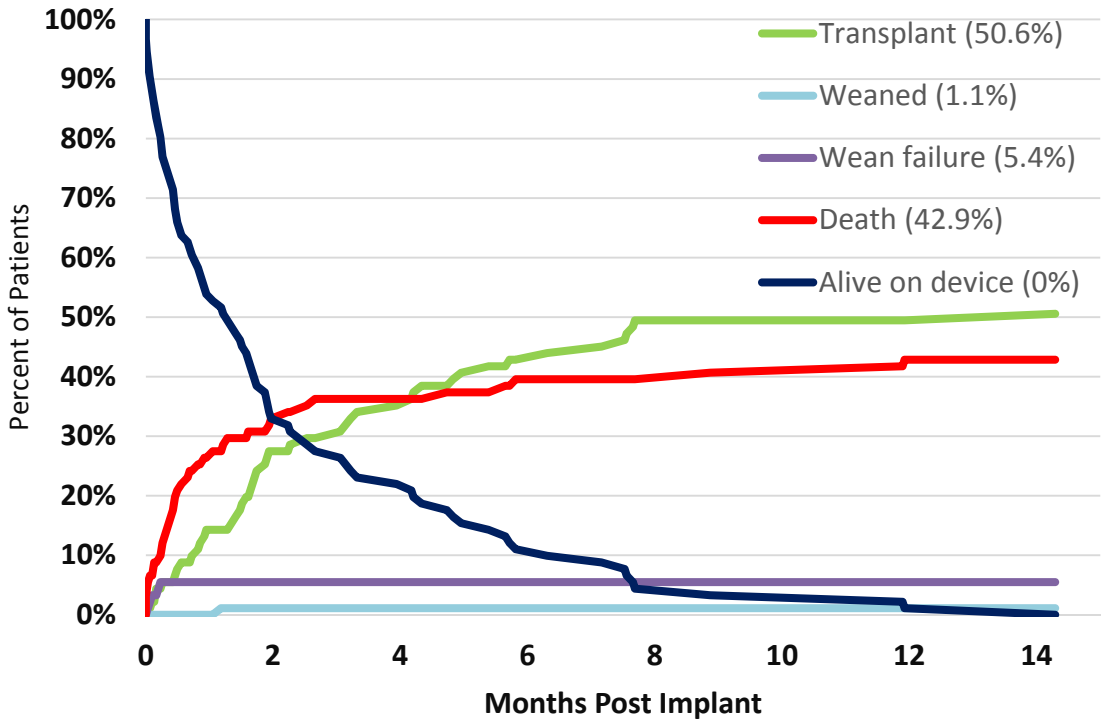


Figure 17. Competing Outcome Plot for Database Group: CHD (n=91)



Safety Evaluation

Serious Adverse Events (SAEs) were collected on study subjects per the study protocol. The IDE data submitted to FDA in the February 2011 HDE application along with the Compassionate use data at the IDE sites (109 subjects total) were centrally adjudicated by a clinical events committee (CEC). A subset of the events (major bleeding, major infection, neurological dysfunction) was adjudicated per protocol in the post approval study (39 subjects). SAEs for the non-study data were gathered through Berlin Heart's complaint system per MDR guidelines. Table 22 summarizes the SAEs and rates per patient-day. No unanticipated adverse events have been reported to date.

Table 22. Serious Adverse Event Summary

Serious Adverse Event	**Study Group** (IDE + Comp Use[1] + PAS) **n=187**		**Database Group** (IDE + Comp Use[2] + PAS) **n=320**		**All Implant Group** **n=565**	
Total Days of support:	**13137 days**		**22,742 days**		**43551 days**	
	# events	**Event Per Patient Day**	**# events**	**Event Per Patient Day**	**# events**	**Event Per Patient Day**
Major Bleeding	120	0.0091	231	0.0102	247	0.0057
Major Infection	181	0.0138	280	0.0123	294	0.0068
Neurological Dysfunction	57	0.0043	101	0.0044	134	0.0031
Cardiac Arrhythmia	19	0.0014	32	0.0014	32	0.0007
Hemolysis	7	0.0005	11	0.0005	11	0.0003
Hepatic Dysfunction	17	0.0013	35	0.0015	35	0.0008
Hypertension	59	0.0045	81	0.0036	81	0.0019
Myocardial Infarction	1	0.0001	1	0.0000	1	0.0000
Pericardial Fluid Collection	22	0.0017	37	0.0016	37	0.0008
Pericardial Effusion	4	0.0003	4	0.0002	4	0.0001
Psychiatric Episode	3	0.0002	5	0.0002	5	0.0001
Renal Dysfunction	19	0.0014	34	0.0015	34	0.0008
Respiratory Failure	55	0.0042	114	0.0050	114	0.0026
Right Heart Failure	25	0.0019	39	0.0017	39	0.0009
Thromboembolism-Arterial Non CNS	4	0.0003	7	0.0003	8	0.0002
Thromboembolism-Venous	5	0.0004	8	0.0004	8	0.0002
Wound Dehiscence	1	0.0001	2	0.0001	2	0.0000
Other: Seizure	5	0.0004	15	0.0007	17	0.0004
Other: Silent Stroke	5	0.0004	5	0.0002	5	0.0001
Other	66	0.0050	94	0.0041	101	0.0023

[1] Compassionate use cases occurring at study sites
[2] Compassionate use cases occurring at both the study and non-study sites

Summary of Neurological Dysfunction Events and Outcomes

The results of the Berlin Heart EXCOR Pediatric studies demonstrate that 73.3% of patients survived to successful weaning or cardiac transplantation. The majority of patients (64%) survived to successful weaning or cardiac transplantation with no neurologic adverse events. Study results demonstrated that patients on the device who did not meet the strict entrance criteria of the IDE study and those who were not implanted at experienced centers experienced a higher rate of mortality.

Table 23. Outcomes and Neurological Events

Outcome	**Study Group** (IDE + Comp Use[2] + PAS) **n=187**	**Database Group** (IDE + Comp Use[3] + PAS) **n=320**	**All Implant Group** **n=565**
Successful transplant or wean[1]	145 (77.5%)	228 (71.3%)	414 (73.3%)
No Ischemic/hemorrhagic Neurological events	143 (76.5%)	257 (80.3%)	477 (84.4%)
Successful transplant or wean with no neurological events	116 (62.0%)	189 (59.1%)	359 (63.5%)

[1]Successful transplant or wean of those who met an endpoint
[2] Compassionate use cases occurring at study sites
[3] Compassionate use cases occurring at both the study and non-study sites

Table 24. Incidence of each category of Stroke for each Group

Stroke Category	**Study Group (IDE + Comp Use[1] + PAS) N=187**		**Database Group (IDE+ Comp Use[2] + PAS) N=320**		**All Implant Group N=565**	
	Total Events	**# (%) with Event**	**Total Events**	**# (%) with Event**	**Total Events**	**# (%) with Event**
Ischemic	42	37 (19.8%)	63	55 (17.2%)	85	76 (13.5%)
Hemorrhagic	14	13 (7.0%)	16	15 (4.7%)	26	23 (4.1%)
Ischemic or Hemorrhagic	56	44 (23.5%)	79	63 (19.7%)	111	88 (15.6%)

[1] Compassionate use cases occurring at study sites
[2] Compassionate use cases occurring at both the study and non-study sites

Table 25. Incidence of Treatment Failure/Success for Each Category of Stroke

Stroke Category		**N**	**Treatment Failure n=151**	**Treatment Success n=414**
Ischemic	No events	489	121 (24.7%)	368 (75.3%)
	At least one event	76	30 (39.5%)	46 (60.5%)
Hemorrhagic	No events	542	144 (26.6%)	398 (73.4%)
	At least one event	23	7 (30.4%)	16 (69.6%)
Ischemic or Hemorrhagic	No events	477	118 (24.7%)	359 (75.3%)
	At least one event	88	33 (37.5%)	55 (62.5%)

Summary of Death/Withdrawal of Support

A total of 123 of 565 subjects (21.8%) died as a result of withdrawal of support. The 123 subjects were supported a median time of 22 days ranging from 0 to 457 days.

Of the 320 subjects in the database group, 80 subjects died (25%). Of the 80 subjects who died, 41 (51%) were on ECMO prior to the EXCOR Pediatric implant. The use of ECMO prior to EXCOR Pediatric implant is identified with increased mortality and increased occurrence of adverse events.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The totality of data from the IDE Cohorts, PAS Study and all Non Study patients shows the device is effective for its intended use – *to provide mechanical circulatory support as a bridge to cardiac transplantation for pediatric patients with severe isolated left ventricular or biventricular dysfunction who are candidates for cardiac transplant*. Patients treated with this device are at imminent risk of death at the time of implantation and for patients less than $1.2m^2$ BSA, no other approved devices or modalities of effective mechanical support are available. Use of ECMO, the previous standard of care, has been used off-label in these patients, but is associated with a higher incidence of

severe complications and provides less effective support with regards to reaching a successful outcome (transplant or successful wean). Patients treated with ECMO prior to transitioning to EXCOR Pediatric implant support, in addition to those with a CHD diagnosis, have a substantially higher risk of death in comparison to patients treated with EXCOR Pediatric as a first mechanical circulatory support therapy and those without a CHD diagnosis.

In a review of the totality of all US implants, the observed effectiveness outcomes remained durable over time. The initial studies leading to HDE Approval have been confirmed over several years of use in various settings and patient sub-groups and remain consistent and predictable. Clinically meaningful benefit has been consistently demonstrated in the outcomes to date, justifying a determination of effectiveness for these patients.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in a clinical studies conducted to support PMA approval as described above. Some events such as bleeding an infection can be resolved quickly with medical intervention. Other events such as neurological dysfunction may resolve over longer periods of time, with some children returning to normal function while others have some residual effects (e.g. weakness, paralysis) or delay in function while yet others may be removed from the transplant list and disqualified from receiving a heart transplant. Safety of the device was substantiated as required for the HDE Approval, and the totality of the data continues to show that with real world use, overall safety outcomes have remained the same or improved with experience.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical studies conducted to support PMA approval as described above. Support on the EXCOR Pediatric provides significant durations of mechanical support needed for organ procurement for transplant or recovery of native heart function (successful weaning) in pediatric patients who are at extreme risk of imminent death with no other treatment options. Prior support with ECMO (prior to EXCOR Pediatric implant), and patients with heart failure due to CHD had lower chances of successful outcome, but nevertheless benefitted from EXCOR Therapy.

Additional factors to be considered in determining probable risks and benefits for the EXCOR Pediatric included: EXCOR allows significantly longer duration of support, a critical factor for pediatric heart organ procurement for transplantation. The smaller pediatric patients (BSA < $1.2m^2$) rely on Berlin Heart EXCOR since there is not a suitable FDA approved alternative (i.e. there is an unmet need in vulnerable population).

Stroke rates observed from the totality of available data, including the HDE post-approval data and real-world post-approval usage, have remained relatively constant with respect to data review under the HDE. The use of novel anticoagulation regimens will be

evaluated in the sponsor's post-approval study. However, the stroke rate of approximately 30% is tolerated within this patient population given the lack of an alternative treatment option.

1. Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support that for pediatric candidates with severe isolated left ventricular or biventricular dysfunction who are candidates for cardiac transplant and require circulatory support, the benefits of using EXCOR Pediatric outweigh the risks.

D. Overall Conclusions

The totality of the clinical data submitted in the PMA application provides reasonable assurance that the EXCOR Pediatric is safe and effective in providing mechanical circulatory support as a bridge to cardiac transplantation for pediatric patients.

XIV. CDRH DECISION

CDRH issued an approval order on June 6, 2017. The final conditions of approval cited in the approval order are described below.

OSB Lead PMA Post-Approval Surveillance – Berlin Heart Novel Surveillance: The applicant is required to provide data to FDA from a registry which captures all-comers (pediatric age range only, <22 years of age) utilizing the Berlin Heart EXCOR (BHE) device as a bridge to cardiac transplant and ensure that surveillance occurs for the BHE over the next five (5) years.

Surveillance through this registry will monitor the following: procedural safety and implant success, adverse events while on BHE device, anticoagulation therapy used while on BHE device, duration of device use, device malfunction or failure, and patient outcomes (survival to transplant, survival to cardiac recovery, death, or patient transfer to different device). Adverse events monitored include but are not limited to: stroke (hemorrhagic or ischemic), transient ischemic attacks, infection, thromboembolism, pump thrombosis requiring pump exchange, major bleeding, new or worsening right heart failure, hepatic dysfunction, new or worsening kidney failure, new or worsening arrhythmias. Device safety issues or malfunctions should also be monitored and reported.

As part of this surveillance, the applicant will perform an analysis of a primary endpoint. The primary endpoint is the occurrence of stroke (including ischemic or hemorrhagic) while on BHE support. A minimum of 62 individual enrollees into the registry will allow comparison to a pre-specified performance goal for stroke while on device of 30%. The upper bound of the 95% confidence interval for the registry observed stroke rate will be compared to this pre-specified performance goal. Furthermore, the applicant will work

with the registry to also collect data regarding anticoagulation protocol to determine if differences exist in the safety and effectiveness of this device for populations on newer anticoagulation regimens.

Secondary endpoints include the rate per patient-month of thrombotic events including but not limited to transient ischemic attack, and pump thrombosis requiring pump exchange. Additional secondary endpoints include the rate of above-mentioned surveillance-captured adverse events per patient-month, and a summary of device effectiveness by proportion of subjects experiencing a successful outcome (defined as survival to recovery/successful weaning, survival to transplant, or survival on-BHE device and transplant eligible at 180 days)). Surveillance reports should be provided on a semi-annual basis for the first two years after PMA approval, and then annually thereafter.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

FDA Summary of Safety and Probably Benefit – H100004; EXCOR Labeling
Submitted Manuscript July 2016: Berlin Heart EXCOR use in Patients with Congenital Heart Disease; Morales, Zafar, Almond et al.