FDA Executive Summary

Prepared for the
September 20, 2013 meeting of the
FDA's Pediatric Advisory Committee

H100004

Berlin Heart Inc. EXCOR Pediatric Ventricular Assist Device

INTRODUCTION AND BACKGROUND

In accordance with the Pediatric Medical Device Safety and Improvement Act, this review provides a safety update based on the post-marketing experience with the use of the Berlin Heart Inc. EXCOR Pediatric Ventricular Assist Device (PVAD) in pediatric patients since approval. The EXCOR PVAD is a pulsatile ventricular assist device intended as a bridge-to-cardiac transplant (BTT) in the pediatric population. It was approved in December 2011 by the Center for Devices and Radiological Health under Humanitarian Device Exemption (HDE) application H100004.

The purpose of this review is to provide the Pediatric Advisory Committee with post- marketing safety data so the committee can advise the Food and Drug Administration (FDA) on potential new safety concerns associated with the use of this device in children. This memorandum will include summaries of the pre-market clinical study, post-market medical device reporting (MDR) for adverse events, post-approval studies, and the peer-reviewed literature associated with the device. At the panel meeting, the Agency will ask for your input on whether the probable benefit/risk profile of the device for the pediatric population continues to support the HDE for which the exemption was granted.

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.

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.

Device Description

The EXCOR® consists of one or two extracorporeal pneumatically driven blood pumps (depending on univentricular or biventricular support), cannulae to connect the blood pumps to the atrium or ventricle and to the great arteries, respectively, and the IKUS driving unit. The complete system demonstrating biventricular (biVAD) support, in addition to the single pump, are depicted in Figure 1

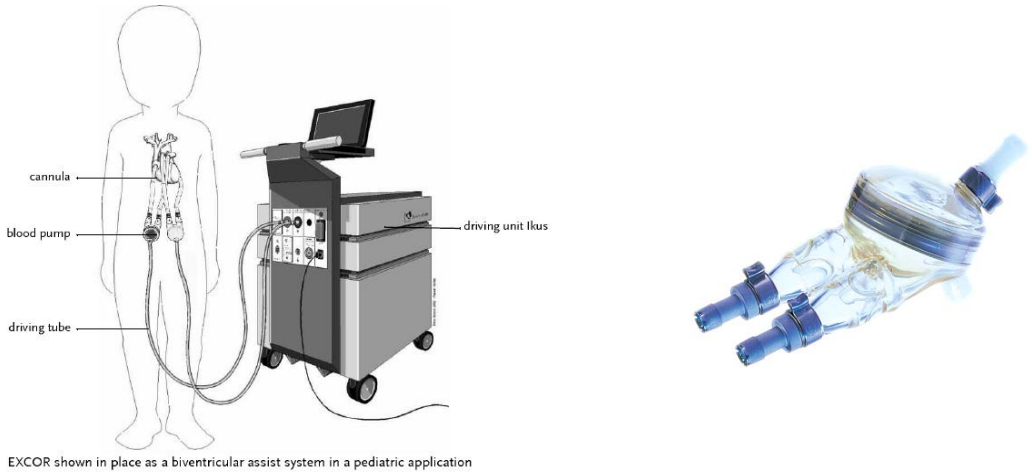

Figure 1: EXCOR Pediatric VAD System and single pump

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. Figure 2 shows recommended pump sizes to be used for specified weight ranges are as follows:

Range	**Size**
0-8 kg	10 ml
8-25 kg	25 ml
15-30 kg	30 ml
30-55 kg	50 ml
35-60 kg	60 ml

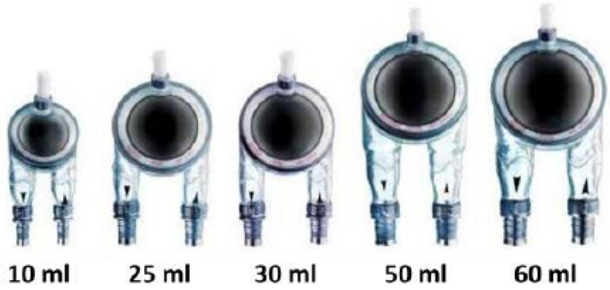

Figure 2: Various pump sizes

For biVAD implants, the combinations of 60/50, 30/25 or 10/10 ml blood pumps are recommended, with the larger pump size or rate placed on the left side to prevent pulmonary congestion.

Regulatory History

The EXCOR PVAD was granted Humanitarian Use Device designation on January 3, 2001 by FDA's Office of Orphan Products Development. Berlin Heart, Inc. conducted a clinical study of the EXCOR PVAD in support of their HDE application, and submitted results to FDA in June 2010. The July 2011, FDA Circulatory System Devices Advisory Panel voted 16-0 that the device provided a reasonable assurance of safety and that the probable benefit of the device outweighed the known risks. The EXCOR PVAD was approved on December 16, 2011. As a condition of approval, the sponsor was requested to conduct a post-approval study (PAS) to evaluate whether safety and outcomes of the device use in the commercial setting are comparable to the safety and outcomes of the device use in the IDE study.

PREMARKET DATA: THE IDE CLINICAL TRIAL

Design Objective & Background

The sponsor conducted a clinical investigation in support of the development of the EXCOR Pediatric VAD. The design of the trial considered the currently available modalities to support children at imminent risk of death from heart failure despite medical management. However, these choices were limited and associated with a complex support method and high complication rates. Extracorporeal membrane oxygenation (ECMO) has been the standard of care in the US for children requiring mechanical circulatory support as a bridge-to-cardiac transplantation and therefore was chosen as a historical control. The historical control data was obtained using the Extracorporeal Life Support Organization (ELSO) registry which houses the most extensive registry of subjects treated with ECMO in North America. However, when the clinical study was designed, it was known that the control would be a weak comparator for the safety evaluation as the control data was housed in an unmonitored registry that did not contain adverse event definitions and did not require mandatory reporting of adverse events. Therefore, the registry was used for comparison for the probable benefit evaluation. In collaboration with the FDA, the INTERMACS adverse event definitions were incorporated and the safety endpoint was chosen based solely on the level of safety for EXCOR Pediatric control group compiled from the ELSO registry. Additionally, several safety measures were incorporated into the study design including neurological testing, laboratory assessments, and clinical exams such as CT Scans.
The primary population for the EXCOR Pediatric was chosen to capture children at imminent risk of death from heart failure and listed for cardiac transplantation. The age and size range of patients eligible for the device is wide-ranging. This prompted the division of the study subjects into the two primary cohorts based upon body surface area (BSA). Additionally, due to the growing use of the device under the emergency use guidelines, it was expected that continuous compassionate use requests would arise from institutions. This prompted the addition of the third compassionate use cohort.

Furthermore, a substudy of implants prior to the IDE approval was incorporated so that as much data as possible from past emergency use patients could be collected and provided to support approval of the device.

This study was a prospective, multi-center, single arm study including three cohorts and a retrospective sub-study (data for implants prior to IDE approval on May 9, 2007). The primary study population of 48 subjects aged 0-16 years consists of the following cohorts:

- Cohort 1: 24 subjects with a body surface area (BSA) < 0.7 m^2; and
- Cohort 2: 24 subjects with a body surface area (BSA) ≥ 0.7 m^2 to < 1.5 m^2.

Key Inclusion 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- 2A (i.e. critical cardiogenic shock to progressive decline in non-cardiac end organ function or ambulatory ability)
    b) Support with extra-corporeal membrane oxygenation (ECMO) or other mechanical circulatory support device
    OR
    c) Unable to separate from cardiopulmonary bypass (must be listed for heart transplantation at time of transfer to the operating room)
2. United Network for Organ Sharing status 1A or equivalent) for cardiac transplantation
3. Two-ventricle circulation, including cardiomyopathy, repaired structural heart disease
4. Age 0 to 16 years; corrected gestational (CGA) at least 37 weeks
5. Weight $\geq$ 3 kg and $\leq$ 60 kg

Key Exclusion Criteria

1. Support on ECMO for ≥10 days
2. Cardiopulmonary resuscitation duration ≥30 min within 48° prior to device implantation
3. Body weight < 3.0 kg or BSA > 1.5 m2
4. Presence of mechanical aortic valve, significant AI or PI
5. Evidence of irreversible non-cardiac end-organ dysfunction
6. Bleeding diatheses
7. Complex cardiac lesions or single ventricle physiology

A third cohort of subjects was enrolled under compassionate use regulations and is classified in the study as Cohort 3. These subjects followed the study protocol unless otherwise noted within the approval documentation for the subject. All CU patients were required to be eligible and listed for heart transplant according to the United Network for Organ Sharing (UNOS) Status 1A definition, but faled to meet one or more entrance criteria of the Study Cohorts (Cohorts 1 and 2). This cohort is further divided into groups based on the subject's BSA (as done with Cohorts 1 and 2). These cohorts are defined as the following:

- Cohort 3A: the subject's BSA is < 0.7 m^2; and
- Cohort 3B: if the BSA is ≥ 0.7 m^2 and <1.5 m^2.

Control Group

The historical ECMO control group was compiled from the ELSO registry. The database was filtered to best match the EXCOR Pediatric IDE study population. Subjects for comparison included subjects from both genders, age 0-16 years, weight greater than 3 kg, cardiac only indication for ECMO support, with support initiation from year 2000 onward, who met critical eligibility criteria. The dataset for the ELSO registry included baseline and outcomes data comparable to the EXCOR Pediatric dataset. The ECMO controls were matched to the EXCOR

Pediatric subjects for comparison of the efficacy objective. The adverse events collected in the ELSO registry were not comparable to those collected within this protocol. FDA requested the INTERMACS definitions be used in the IDE study and noted that the ELSO adverse events would neither be comparable, nor used for evaluation of the safety. However, FDA requested the ELSO events to be included for review.

Study Endpoints

The Primary Safety Endpoint

The safety of EXCOR Pediatric was evaluated by presenting the serious adverse event (SAE) rate where the rate is calculated as the number of events per days on EXCOR. No greater than 0.25 events per day were expected during the time period from implant to transplant or recovery. Study success in terms of safety was demonstrated if the upper bound of a two-sided 95% Poisson exact confidence interval is less than 0.25.

The Primary Effectiveness Endpoint

The primary objective of the study was to demonstrate that the survival rate in subjects treated with the EXCOR Pediatric is different from the survival rate in the historical control subjects treated with ECMO as a bridge to cardiac transplant. Time to survival was defined as the time from initiation of mechanical support to the transplant or recovery. This was analyzed by creation of survival curves for the primary cohort and the matched ECMO control group using the Kaplan-Meier method. A propensity score analysis was performed by an independent statistician blinded to the outcomes in order to statistically select the matched ECMO control group from the ELSO registry database.

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.

Additional Supportive Analyses

In addition to the pre-specified primary and secondary endpoints, the Sponsor also conducted four analyses to support the primary safety and probable benefit analyses.

1. Neurological Status - assessed using the Pediatric Stroke Outcomes Measure (PSOM).
    Note: PSOM is an evaluation using a grading system of severity. Each of 5 spheres (right sensorimotor, left sensorimotor, language production, language comprehension, and cognitive performance) are scored 0 (normal) to 2 (severe deficit). The composite score can range from 0 to 10.

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 - sites were trained to record system parameters including rate, systolic & 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.

IDE Clinical Study Results

A total of 204 patients were implanted with the EXCOR between June 21, 2007 and December 20, 2010 (the date of the data-lock for Panel). Table 1 shows a summary of subject enrollment.

Table 1: Summary of Total Implants

	IDE site Implants	Non-IDE Site Implants	Total
BSA < 0.7m^2			
Cohort 1 – primary study population	24	n/a	**24**
Cohort 1 CAP	20	n/a	**20**
Cohort 3A (CU/EU)	35	72	**107**
Subtotal	*79*	*72*	***151***
BSA ≥ 0.7m^2 < 1.5m^2			
Cohort 2 – primary study population	24	n/a	**24**
Cohort 3B (CU/EU)	6	23	**29**
Subtotal	*30*	*23*	***53***
TOTAL	**109**	**95**	**204**

Effectiveness

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. Table 2 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.

Table 2: Primary Effectiveness Study and Control Groups (Updated Control Group Data)

Group	Total	Max	#	#	Survival Time

		Time on Device (days)	Successes	Failures	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

Cohort 1 Results - Effectiveness

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 and a maximum of 30 days compared to the primary cohort subjects who were supported a median of 27.5 and maximum of 174 days. Half of Cohort 1 subjects were supported longer than the entire ECMO control group. Cohort 1 ITT group demonstrated improved survival compared to the control (log-rank p-value=0.0002). Figure 3 shows the KM curves for Cohort 1 ITT and the ECMO control group.

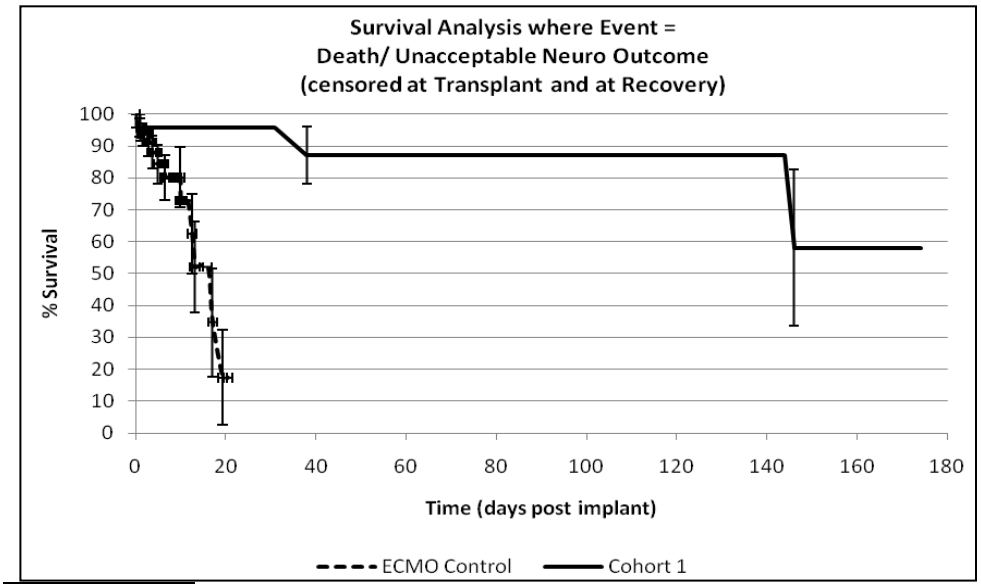

Figure 3: Cohort 1 – Kaplan-Meier survival curves comparing treatment and control patients

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 4

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%.

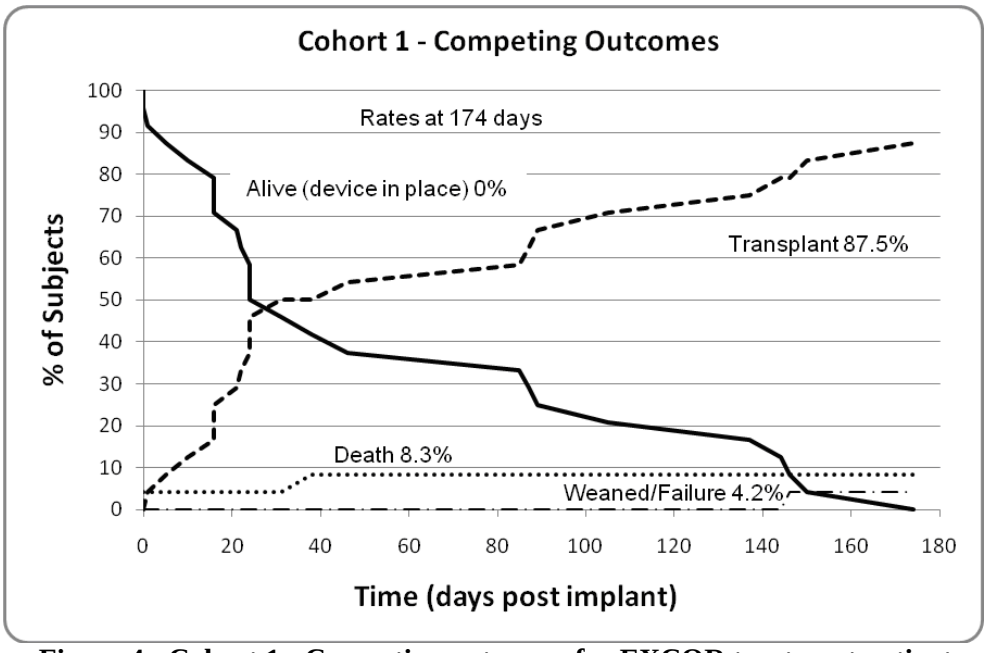

Figure 4: Cohort 1 - Competing outcomes for EXCOR treatment patients

Figure 5 shows the "Competing Outcomes" for the Cohort 1 control group. The longest support time was 20.5 days at which time 75% were weaned from ECMO for recovery or transplant.

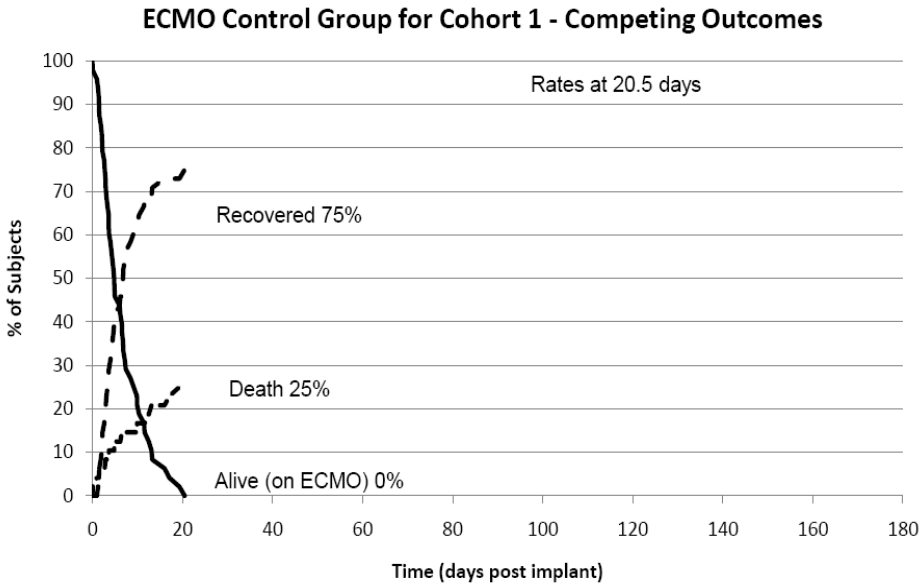

Figure 5: Cohort 1 - Competing outcomes for ECMO control patients

A total of 87.5% (21/24) of the subjects in Cohort 1 were transplanted or successfully weaned from EXCOR. This compares to a total of 75% (36/48) of the control group who were

successfully weaned (p=.0002 Cohort 1 compared to control). Based upon this data, the pre-specified primary effectiveness endpoint was met for Cohort 1.

Cohort 2 Results - Effectiveness

Two of the Cohort 2 subjects (8.3%) failed 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. The 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. Cohort 2 ITT group demonstrated improved survival compared to the control group survival rates (log-rank p value=0.0001). Figure 6 shows the KM curves for the endpoint of death for Cohort 2 treatment and control groups.

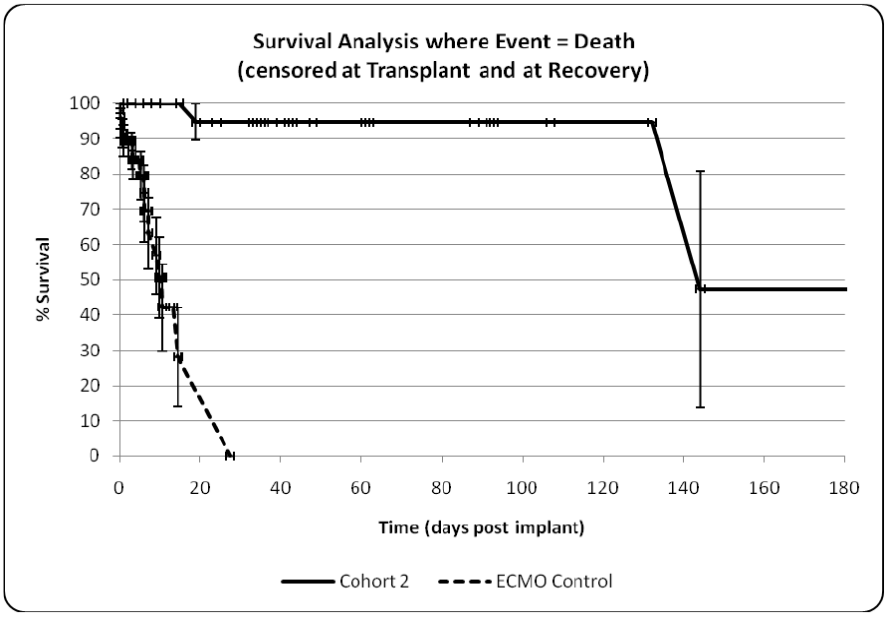

Figure 6: Cohort 2 – Kaplan-Meier survival curves comparing treatment and control patients

Competing outcomes plots for Cohort 2 treatment and control patients are presented below.

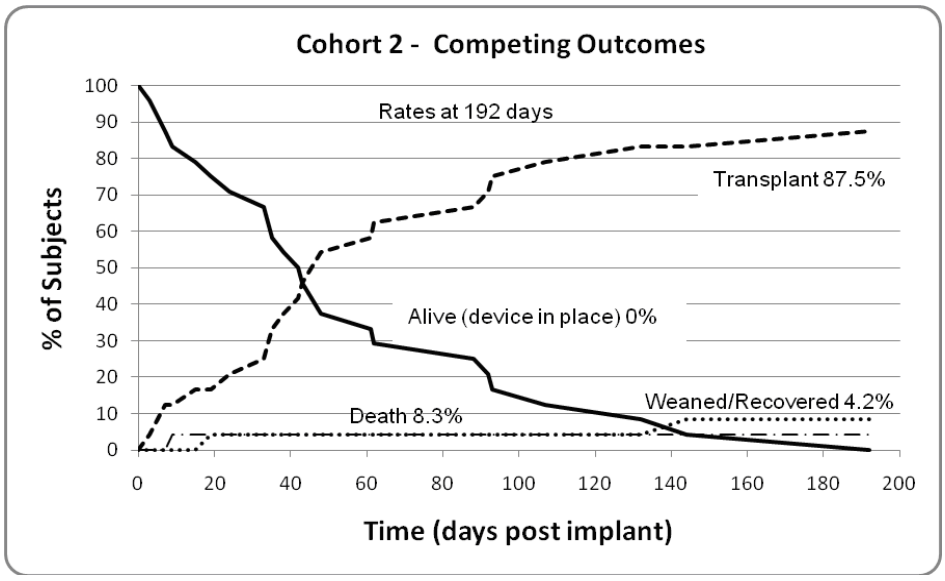

Figure 7: Cohort 2 – Competing outcomes for EXCOR treatment patients

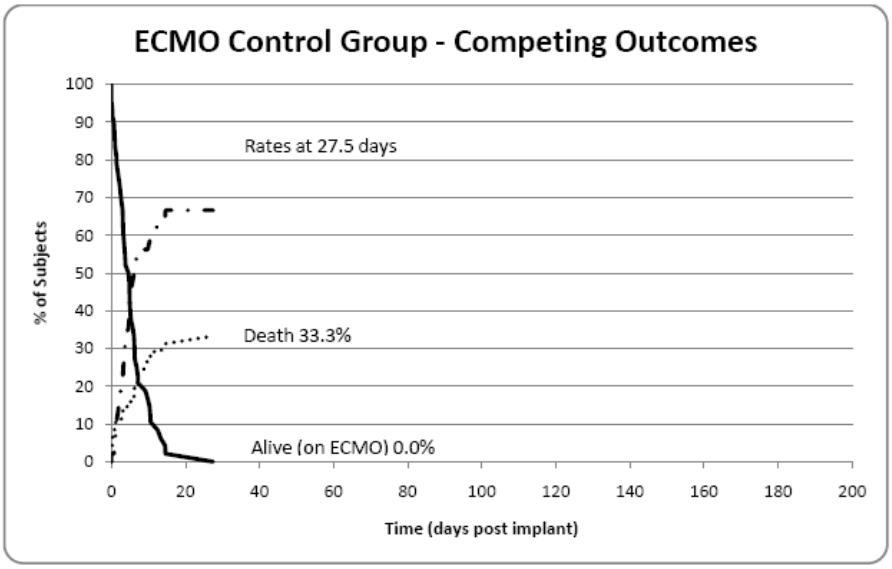

Figure 8: Cohort 2 – Competing outcomes for ECMO control patients

A total of 91.7% (22/24) of the subjects in Cohort 2 were transplanted or successfully weaned from EXCOR. This compares to a total of 66.7% (32/48) of the ECMO control group who were successfully weaned (p=.0001 Cohort 2 compared to the control). Based upon this data, the pre-specified primary effectiveness endpoint was met for Cohort 2.

Additional Observations

The rate of mortality increased when patients with single ventricle circulation and the use of ECMO pre-implant were enrolled. Overall mortality for CU/EU subgroups (Cohort 3) was higher than mortality rates observed for the primary study Cohorts 1 and 2. Competing Outcomes curve for all 136 CU/EU (Cohort 3) patients are shown in Figure 9.

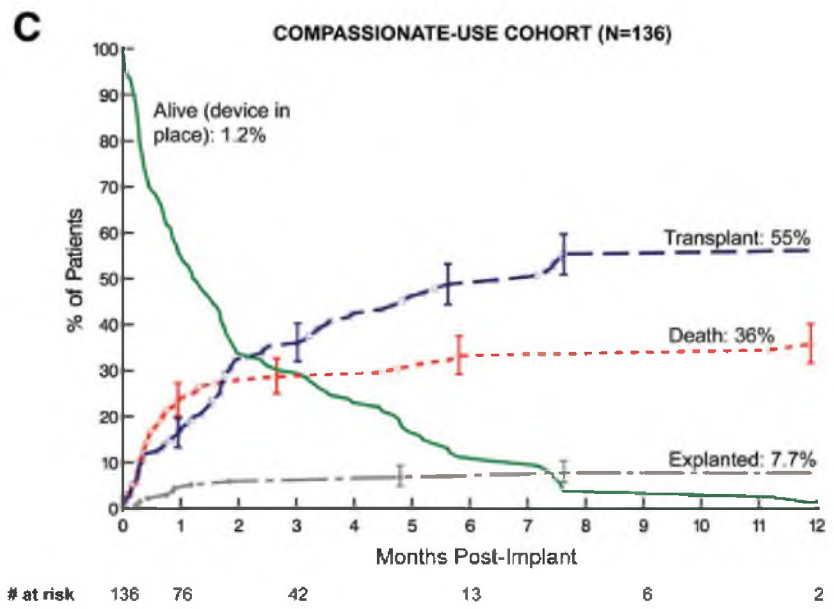

Figure 9: Competing Outcomes for CU/EU (All Cohort 3) EXCOR treated patients

Safety Endpoint Results

The primary safety endpoint for the study was to summarize the SAE rate calculated as less than 0.25 SAEs per patient-day of support on EXCOR. These data are summarized in Table 3.

Table 3: Summary of adverse events by patient day of support for primary study subjects

Group	N	Events	Total Time on Support (Days)	Rates Success Criterion <0.25	
				Events per Patient-Day	Upper bound of CI
Cohort 1	24	96	1411	0.068	0.083
Cohort 1 CAP	20	74	1330	0.056	0.070
Cohort 3A	35	135	1993	0.068	0.080
Cohort 2	24	107	1376	0.078	0.094
Cohort 3B	6	40	240	0.167	0.227

Cohort 1 Results – SAE Summary

The total time on support of the Cohort 1 subjects was 1411 days. There were 96 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]. A summary of SAEs for Cohort 1 study patients is presented in Table 4.

Table 4: Summary of Serious Adverse Events for Cohort 1 Patients

Event		Total Events	Number of subjects with event	% of 24
Major Bleeding		15	10	41.7%
Cardiac Arrhythmia		1	1	4.2%
Sustained Ventricular	1			
Pericardial Fluid Collection		3	3	12.5%
With Tamponade	1			
Without Tamponade	2			
Hemolysis		1	1	4.2%
Late	1			
Hepatic Dysfunction		1	1	4.2%
Hypertension		12	12	50.0%
Major Infection		35	15	62.5%
Localized Non-Device	25			
Percutaneous Site or Pocket	4			
Sepsis	6			
Neurological Dysfunction		8	7	29.2%
Ischemic CVA	8			
Renal Dysfunction		3	2	8.3%
Acute	3			
Respiratory Failure		3	3	12.5%
Right Heart Failure		2	2	8.3%
Arterial Non-CNS Thromboembolism		1	1	4.2%
Venous Thromboembolism Event		1	1	4.2%
Other		10	6	25.0%
ANY EVENT (subject has at least one SAE)			22	91.7%

Other Events:
(1) Acute respiratory distress syndrome
(1) Aortic root reconstruction
(1) Cardiac arrest following clamping of outflow
(1) Elevated hepatic enzymes
(1) Global hypoxic ischemic brain injury following clamping of outflow
(1) Pancreatitis
(1) Pleural effusion
(1) Seizure
(2) Subdural hematoma

Cohort 2 Results – SAE Summary

The total time on support of the Cohort 2 subjects was 1376 days. There were 107 SAEs for this cohort yielding a rate of 0.078 events per patient-day. The 95% Poisson confidence interval was calculated as: [0.064, 0.094]. A summary of SAEs for Cohort 2 study patients is presented in Table 5

Table 5: Summary of Serious Adverse Events for Cohort 2 Study Patients

Event		Total Events	Number of patients with event	% of 24
Major Bleeding		22	12	50.0%
Cardiac Arrhythmia		6	4	16.7%
Sustained Ventricular	2			
Sustained Supraventricular	4			
Pericardial Fluid Collection		4	3	12.5%
With Tamponade	2			
Without Tamponade	2			
Hemolysis		1	1	4.2%
Late	1			
Hepatic Dysfunction		1	1	4.2%
Hypertension		8	8	33.3%
Major Infection		24	12	50.0%
Localized Non-Device	18			
Sepsis	6			
Neurological Dysfunction		9	7	29.2%
Ischemic CVA	7			
Hemorrhagic CVA	2			
Psychiatric Episode		1	1	4.2%
Renal Dysfunction		4	3	12.5%
Acute	2			
Chronic	2			
Respiratory Failure		9	6	25.0%
Right Heart Failure		3	3	12.5%
Other		15	6	25.0%
ANY EVENT (subject has at least one SAE)			19	79.2%

Other Events:
(1) Aortic cannula dislodgement
(1) Aortic reconstruction
(1) Arterial CNS and non-CNS Thromboembolism
(1) Ascending aortic narrowing
(1) Hemothorax
(1) Hyperfibrinogemia requiring plasmapharesis
(1) Hypotension
(1) IV/SVS stenosis
(2) Pleural effusion
(4) Pneumothorax
(1) Subdural hematoma

Although the overall SAE rate for both Cohorts was below the success criterion, certain AEs appear to occur at a higher rate than others – specifically that for neurological events. FDA also noted that the overall SAEs and mortality rates were adversely affected by the use of pre-implant ECMO for both of the primary study cohorts.

Pump Replacement

Pump replacement, though not considered an SAE, was relatively common, performed primarily for visible thrombus within the blood circuit. Clot was especially likely to form at the inflow and outflow valves of the pumping chamber, and was primarily detected by mandated visual inspection every 4 hours. Once detected, the pump was changed out rapidly via a non-invasive procedure due to the extracorporeal nature of the pumping chamber.

Table 6: Pump Replacement

Cohort	n	# Subjects with at least 1 replacement	Total number of replacements	Replacements per Subject	Total Days on Support	Replacements per Days on Support	Time to first replacement (days)
1	24	11	20	0.8 ± 1.1 0 - 3	1411	0.01 ± 0.03 0.00 - 0.13	29.9 ± 27.3 4 - 105
1 CAP	37	22	61	1.7 ± 2.0 0 - 8	2688	0.03 ± 0.04 0.00 - 0.18	23.6 ± 43.7 2 - 209
3A	47	21	43	0.9 ± 1.4 0 - 5	2844	0.02 ± 0.03 0.00 - 0.11	25.6 ± 36.0 3 - 168
2	24	13	23	1.0 ± 1.2 0 - 4	1376	0.02 ± 0.03 0.00 - 0.11	19.2 ± 8.4 10 - 39
2 CAP	9	3	4	0.4 ± 0.7 0 - 2	351	0.01 ± 0.01 0.00 - 0.03	21.3 ± 11.6 8 - 28
3B	7	5	11	1.6 ± 1.7 0 - 5	251	0.05 ± 0.06 0.00 - 0.18	11.0 ± 5.3 5 - 17
TOTAL	**148**	**75**	**162**	**1.1 ± 1.5 0 - 8**	**8921**	**0.02 ± 0.03 0.00-0.18**	**23.4 ± 32.1 2 - 209**

FDA noted the following factors regarding the need for pump exchange due to visible thrombus:

1. Pump exchange due to thrombus occurred in a controlled manner.
2. Most thrombi were observed at the inflow or outflow valves of the pumping chamber
3. The pump design is transparent and allows for visualization of the blood flow and surfaces. Clinicians are extremely cautious and aggressive towards changing the pump when there is any concern for suspected thrombus.
4. There does not appear to be a correlation with the initiation or weaning phases and pump changes or the size of device implanted
5. Anticoagulation regimen adherence (or lack thereof) did not seem to correlate with the occurrence of pump thrombosis.
6. Pump replacement due to thrombus was not substantially different in IDE vs. non-IDE sites.

The Sponsor has provided tabulation of SAE incidence by the absence of or need for pump change in all 109 IDE site patients summarized in Table 7. Notably, death was lower and rate of transplantation was higher in patients requiring pump change due to thrombus. However, the incidence of thromboembolic sequelae including neurologic dysfunction (TIA, ischemic CVA, hemorrhagic CVA) and arterial non-CNS and venous thrombosis were all substantially higher in patients requiring pump change due to thrombus.

Table 7: Tabulation of SAE incidence by pump change status in all 109 IDE site patients

Endpoint/SAE or SAE category	No Pump Change N (% of 52)	Pump Change N (% of 57)
Death	10 (19.2%)	6 (10.5%)
Transplant (*excludes those still on device*)	37/50 (74.0%)	45/54 (83.3%)
Primary DX: Congenital Heart Disease	17 (32.7%)	12 (21.1%)
Pre-implant ECMO	21 (40.4%)	19 (33.3%)
Any SAE	44 (84.6%)	53 (93.0%)
Major Bleeding	25 (48.1%)	24 (42.1%)
Cardiac Arrhythmia-Sustained VT	2 (3.8%)	4 (7.0%)
Cardiac Arrhythmia-Sustained SVT	2 (3.8%)	4 (7.0%)
Pericardial Fluid Collection-With Tamponade	4 (7.7%)	4 (7.0%)
Pericardial Fluid Collection-Without Tamponade	5 (9.6%)	4 (7.0%)
Hemolysis-Early	0 (0.0%)	1 (1.8%)
Hemolysis-Late	1 (1.9%)	3 (5.3%)
Hepatic Dysfunction	4 (7.7%)	5 (8.8%)
Hypertension	20 (38.5%)	22 (38.6%)
Major Infection-Localized Non-Device	15 (28.8%)	28 (49.1%)
Major Infection-Percutaneous Site or Pocket	0 (0.0%)	5 (8.8%)
Major Infection-Internal Pump Component or	1 (1.9%)	0 (0.0%)

Endpoint/SAE or SAE category	No Pump Change N (% of 52)	Pump Change N (% of 57)
Inflow/Outflow		
Major Infection-Sepsis	11 (21.2%)	12 (21.1%)
Psychiatric Episode	1 (1.9%)	0 (0.0%)
Neurological Dysfunction-TIA	0 (0.0%)	2 (3.5%)
Neurological Dysfunction-Ischemic CVA	7 (13.5%)	18 (31.6%)
Neurological Dysfunction-Hemorrhagic CVA	1 (1.9%)	3 (5.3%)
Neurological Dysfunction-New abnormality of head US	0 (0.0%)	1 (1.8%)
Renal Dysfunction-Acute	6 (11.5%)	6 (10.5%)
Renal Dysfunction-Chronic	1 (1.9%)	1 (1.8%)
Respiratory Failure	11 (21.2%)	16 (28.1%)
Right Heart Failure	7 (13.5%)	10 (17.5%)
Arterial Non-CNS Thromboembolism	1 (1.9%)	4 (7.0%)
Venous Thromboembolism Event	0 (0.0%)	2 (3.5%)
Wound Dehiscence	0 (0.0%)	1 (1.8%)
Other	14 (26.9%)	18 (31.6%)
Other Ischemic w/o symptoms	0 (0.0%)	1 (1.8%)
Other Covert Stroke	0 (0.0%)	1 (1.8%)

Neurological Events in Patients Requiring Pump Change Due to Thrombus

FDA requested further data regarding long term sequelae of clinically important strokes in patients requiring pump change due to thrombus versus those who did not. The results are shown in Table 8, using the patients last recorded PSOM score as the comparator. These last PSOM scores reflect the total outcome (in addition to events occurring during device support, results could also be attributed to the bypass run for transplant, the transplanted organ, the immunosuppressive therapy, etc.) and were used because pre-transplant PSOM scores were not collected routinely, especially at the end of the support interval just prior to transplant. Overall survival 1 year post explant of the PP patient group is 39 of 44 subjects (88.6%).

Table 8: Final Neurological outcome by PSOM Score based on need fr Pump Change for Thrombus

Cohort	Number of surviving patients	Total last PSOM score: Sum for all patients	Average last PSOM score per patient	Number of subjects with last PSOM $\geq$ 1.0 (Average score – Patients with PSOM $\geq$ 1)
Without pump change for thrombus				
1	11*	8	0.72	3 (2.0)
2	10**	6	0.60	3 (1.3)
With pump change for thrombus				
1	11	23.5	2.15	6 (3.5)
2	11*	29	2.64	7 (4.1)

The overall incidence of pump change due to visible thrombus and the higher incidence of ischemic neurologic events seen in these patients is cautionary. There do not appear to be any specific events, anticoagulation deficiencies, or co-morbidities that have been identified as contributing to the incidence of pump thrombus. The pump and its design could be suspected as the primary contributors to the high incidence thrombus formation in these patients. The need for pump change due to thrombus may play a role in the high incidence of neurologic complications seen in the study populations and CU/EU cohorts. Despite the frequency and severity of outcomes related to the need for pump change due to thrombus and ischemic neurologic events, the majority of patients were able to complete therapy (successful transplant or wean) 77.2% of the time with either no neurologic events or good neurologic outcome.

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 (PSOM scores $\geq$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) and 2 had severe deficits (PSOM score of 3 at 34 days post and score 4 at 54 days post).

In Cohort 2, 7 of the 24 subjects experienced a neurological event (29.2%). Two 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) and 2 had severe deficits (PSOM scores of 10 at 29 and 38 days post). Table 9 summarizes this information.

Table 9: 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 ≥ 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%)

Of the study cohort, 70.8% of Cohort 1 (17/24) and 75% of Cohort 2 (18/24) patients survived to transplant or were successfully weaned with either no neurologic events or a good neurologic outcome (no or mild deficit by PSOM <1). Neurological dysfunction in compassionate use patients (3A and 3B) was also high for patients treated at both IDE (9/41, 30.0%) and non-IDE sites (32/95, 33.7%). In addition 4 of 6 weaned patients in the IDE cohorts had "unacceptable" neurologic function and died prior to 30 days.

Despite the high incidence of severe neurological events overall (and specifically in patients requiring pump change due to thrombus), the nature and rate of these events did not preclude transplant eligibility or successful transplant in the majority of effected patients. However, long term neurologic outcome and HRQOL in these patients remains unknown.

PREMARKET DECISION

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 device was accompanied by significant risks including neurological events and the need for pump changes due to thrombus. In light of the other clinically-available alternatives, FDA concluded that the device provides probable benefit to this very limited patient population and that the probable benefits of the device outweigh its known risks. This conclusion was supported unanimously by the July 2011 Circulatory System Devices Panel and FDA approved the HDE on December 16, 2011. As long-term outcomes as a result of neurologic events and strokes remained unknown, the sponsor was ordered to conduct a post-approval study to further assess the issue as well as help evaluate whether there is a learning curve associated with the device, and help further understand thrombus formation by examination of explanted pumps.

COMPARABLE DEVICES

The EXCOR device is specifically indicated for mechanical circulatory support as a bridge to cardiac transplant for pediatric patients with severe left ventricular or biventricular dysfunction. Treatment options for this disorder are limited for this population. Although extracorporeal membrane oxygenation (ECMO) devices are commercially available and may be used for this purpose, they are not FDA-approved or cleared for this indication.

ANNUAL DISTRIBUTION NUMBER

The Pediatric Medical Device Safety and Improvement Act of 2007 amended section 520(m) of the Food and Drug Administration Amendments Act and allowed HDEs indicated for pediatric use and approved on or after September 27, 2007, to be sold for profit as long as the number of devices distributed in any calendar year does not exceed the annual distribution number (ADN). The ADN for the EXCOR PVAD is 16,988 and takes into account the fact that each patient may need 1 pump for implant, 1 pump for reserve, and 1.1 pump changes per patient per pump if used as an LVAD and twice that number if used as a BVAD.

DEVICE DISTRIBUTION IN THE UNITED STATES

From December 16, 2011 to December 16, 2012, there were a total of 310 EXCOR PVADs sold in the U.S. Of these, 99 devices have been implanted in 78 patients in the United States.

POSTMARKET DATA: MEDICAL DEVICE REPORTS (MDRs)

Overview of Manufacturer and User Facility Device Experience (MAUDE) Database

Each year, the FDA receives several hundred thousand medical device reports (MDRs) of suspected device-associated deaths, serious injuries and malfunctions. The MAUDE database houses MDRs submitted to the FDA by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters such as health care professionals, patients and consumers. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDR reports can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems used in a "real world" setting, including
    - rare, serious, or unexpected adverse events
    - adverse events that occur during long-term device use
    - adverse events associated with vulnerable populations
    - use error

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. In addition, the incidence or prevalence of an event cannot be determined from this

reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. Because of this, MDRs comprise only one of the FDA's several important postmarket surveillance data sources.

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
- Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.
- MAUDE data is subjected to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.
- MAUDE data does not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions.

MDRs Associated with the Berlin Heart EXCOR Pediatric Ventricular Assist Device

The Agency conducted queries of the MAUDE database on July 19, 2013 for all Medical Device Reports (MDRs) associated with Berlin Heart EXCOR Pediatric Ventricular Assist Device from HDE approval (December 16, 2011) through June 30, 2013. The queries resulted in the identification of 21 unique MDR reports (18 by the manufacturer; 3 from user facilities). Patient gender information was provided in 15 of the 21 reports of which nine (9) were female and six (6) were male patients. Patient age data was provided in 11 of the 21 MDRs and included 10 pediatric patients ranging from 14 months to 14 years of age. The average age of the known pediatric patients was 3 years.

Reporting country was available in 20 of the 21 MDRs and includes United States for 6 MDRs and 14 for Out-of-US (OUS), including Germany (5), Italy (3), Argentina (1), Canada (1), Finland (1), France (1), Hungary (1) and Sweden (1).

Table 10 lists the total MDR count for each primary reported problem along with the type of event, intervention and TTTEO (time to the event occurred) when available. Following the table, the primary reported problems are further detailed to include specific event, patient information and required intervention.

Table 10. MDR Summary

	MDR Count	Death	Injury[1]	Malfunction[2]	Intervention	TTTEO (months)

Pre-Procedural	**2**	**0**	**0**	**2**		
Membrane Puncture	1	0	0	1	None required	
Particulate in Chamber	1	0	0	1	None required	
Post-Procedural	**19**	**1**	**2**	**16**		
Driving Tube Leak	8	0	0	8	Tube replaced	UNK
Membrane Rupture	7	1	0	6	Pump replaced	2 – 8
Pump Issue	1	0	0	1	Pump replaced	2
Pneumatic System Valve Malfunction	1	0	0	1	Switched to back up unit	UNK
Decreased Flow/Fibrin Formation	1	0	1	0	RVAD and LVAD Pumps exchanged	*$RVAD_1$ explant at 4 mo; $RVAD_2$/LVAD explant at 5 mo
Cannula Rupture/Air Embolism	1	0	1	0	Pump exchanged, hyperbaric chamber and hypothermia	4
Total	**21**	**1**	**2**	**18**		

*First Right Ventricular Assist Device (RVAD) was explanted at 4 months for decreased flow. Fibrin formation occurred 1 month later and RVAD and Left Ventricular Assist Device (LVAD) explanted.

[1] Serious Injury per regulatory definition (CFR803.3) includes an event that is life-threatening or results in permanent impairment of a body function or permanent damage to a body structure or necessitates medical or surgical intervention(s) to preclude permanent impairment of a body function or permanent damage to a body structure.

[2] A malfunction means the failure of a device to meet its performance specifications or otherwise perform as intended; it is reportable when it is likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Pre-Procedural events (n = 2)

There were two pre-procedural malfunction events which occurred during set-up of the device.

- **Particle in the Blood Chamber (n=1)**
  One event was related to a particle in the blood chamber of the pump identified as a polyvinyl chloride particle. The IFU requires the user to check every blood pump before use and during priming. There was no patient contact with the device in this event.

- **Membrane Puncture (n = 1)**
  One event of a needle puncture during setup caused a leak in all 3 layers of membrane, another pump was used and there was no patient involvement.

Post-Procedural Events (n=19)

There were 19 events which occurred post-procedure.

- **Ruptured Membrane (n = 7)**
  Seven MDRs were related to membrane rupture: 1 death report and 6 malfunction reports. Three events occurred in the US and four were OUS events.

  The death event involved a 14 month old male where the aorta was over sewn during the bi-VAD implant and was used for total support. The IFU indicates use for ventricular assist and not total support. At 86 days, the pump was exchanged due to decreased pump function. Visual inspection showed the stabilization ring rotated approximately 180° and

pressure testing revealed a microleak in the drive membrane. The cause of death was pulmonary edema. As previously stated, confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report.

There were six reported malfunctions of membrane rupture to the blood or air membrane of the pump. In all reports, the pump was exchanged and there was no hemodynamic compromise. Patient age was available in four of the six events for a range of 18 months to 14 years. The TTTEO ranges from 2 – 8 months with the average at 4 months.

According to manufacturer analysis "The blood pump is designed with a triple layer membrane for safety reasons. There is an air layer, middle layer and blood layer. In case of disruption in one of the triple layers, there are two more layers that will maintain the integrity of the air and blood chambers." The IFU warns the user to visually check pump function, including filling and ejecting over several cycles and to change the pump if a problem is detected.

- **Driving Tube Leaks (n = 8)**
  There were 8 malfunction events involving leaks in the driving tube/drive line. The leaks were identified as being at the point of connection to the blood pump or at the passage from the thinner to thicker diameter tube close to the pump. All cases required a driving tube exchange. The firm identifies "it is very likely that the leakage was caused by external forces during the time of usage" as the patients were described as being very active. There was no change in patient hemodynamics or pump function reported. One MDR indicates the driving tube was clamped, thus resulting in damage to the tube. Patient age was available in four of the MDRs and identified as 20 months, 3 years, 4 years and an adult of 30 years. One event occurred in the US and seven were OUS.

- **Cannula Rupture/Air Embolism (n = 1)**
  There was one reported injury of an air embolism of a 20 month old female occurring 4 months post implant. After patient arrest and resuscitation, blood was detected near the inflow connector. Inside the pump, bubbles and foam were visible and CT scan identified an air embolism. The affected portion of cannula was trimmed and the pump was exchanged. It was reported that the patient is doing well at this time.

- **Decreased Flow/Fibrin Formation (n = 1)**
  For a patient supported with a bi-VAD system, an injury report was related to an alarm indicating problems with filling and emptying of the RVAD at 4 months necessitating RVAD exchange. A second issue occurred > 1 month later described as a "membrane-like fibrin tissue" in the RVAD and LVAD inflow cannula. Both pumps were exchanged and the patient was described as stable. No patient demographic information was available. For the purposes of this review, these events have been combined and are considered to be one case.
- **Pneumatic System Control Valve Malfunction - (n = 1)**
  During start up procedure, it was determined the blood pump was not filling and inspection confirmed right pneumatic output on IKUS was not working. Investigation revealed a stuck or defective valve resulting in pressure being pumped into the throttle instead of to the pump. The patient was switched to the backup driver and pump was

filling properly. No changes in patient's hemodynamic status were reported. No patient demographic or TTTEO information was included in the report.

- **Pump Issue (n = 1)**
  There was a malfunction report of a 2 year old female with poor ejection at 2 months after implant, driver replaced and device hand-pumped with no effect. The pump was exchanged. There were no changes in the patient's hemodynamic status.

A total of 21 MDRs have been received since from HDE approval in 2011. MDRs related to tubing leaks and membrane rupture accounted for over ¾ of the 19 events reported once the device was implanted. In the majority of these cases the issue was addressed by change of the affected component (pump or drive tubing) without any significant compromise or sequelae to the patient. One MDR noted a patient death, although the degree of association with the membrane rupture is not known. Some of the mechanical problems reported in the MDRs are not specifically addressed in the IFU including membrane rupture, driving tube leaks, cannula rupture/air embolism and pneumatic system malfunction although these issues would not be totally unexpected in similar mechanical assist devices.

POSTMARKET DATA: POST-APPROVAL STUDIES (PAS)

Overview

As a condition of approval, the sponsor is required to conduct one post-approval study (PAS) to assess the safety and demonstrate that the serious adverse event (SAE) rate in subjects implanted with the EXCOR is not greater than the rate in the IDE study. The study is an "all-comers" prospective registry (maintained by the sponsor) of patients implanted with the EXCOR VAD. The SAE rate (per patient-days) in the PAS is hypothesized to be less than the upper bound of the rate seen in the IDE of 0.07 (0.03 margin). The primary safety hypothesis can be stated as:

H_0: $SAE_{PAS} \geq 0.10$

H_1: $SAE_{PAS} < 0.10$

Study Population and Sample Size

The patient population will consist of transplant eligible children in need of mechanical circulatory support who consent to be enrolled into the registry. Only consented pediatric patients implanted following FDA approval on December 16, 2011 will be included.

A total sample size of 49 patients was calculated – 39 patients to meet the primary goal and 10 patients to account for attrition. Assuming that the true rate is 0.07, a sample of 39 subjects followed for an average of 58 days each provides 80% power to reject the null hypothesis with a one-sided alpha=0.05 test and so demonstrate non-inferiority. Up to 50 sites are expected.

Primary Endpoints

For safety, the serious adverse event definitions are as defined in the IDE study (and as collected in the INTERMACS registry). The events include:

- Major Bleeding (Clinical Events Committee [CEC] adjudicated)
- Cardiac Arrhythmias

- Pericardial Fluid Collection (with and without Tamponade)
- Hemolysis
- Hepatic Dysfunction
- Hypertension
- Major infection (CEC adjudicated)
- Myocardial Infarction
- Neurological Dysfunction (CEC adjudicated)
- Psychiatric Episode
- Renal Dysfunction
- Respiratory Failure
- Right Heart Failure
- Arterial Non-CNS Thromboembolism
- Venous Thromboembolism
- Wound Dehiscence
- Other (event that causes clinical relevant changes in the subject's health)

The endpoint is defined as transplant, recovery of left ventricular function or death (CEC adjudicated).

Secondary Endpoints
The following secondary endpoints will be summarized:

- Device Malfunctions (CEC adjudicated)
    - Number of failures (pump and non-pump failures)
- Site evaluation of explanted pumps for suspected thrombus
    - Data and diagram of location, size and type
- Assessment of the learning curve
    - Low (5 or less implants performed since 2000) and high volume sites
    - IDE and non-IDE sites
    - Early (first 2 implants) and late procedures at a site during the registry

Enrollment Plan and Follow-up (length and frequency)
The study will enroll at least 49 subjects implanted with the device per device labeling and who consent to be enrolled into the post approval study after the study commencement at any implanting site with IRB approval for participation. Study enrollment is expected to take 10-12 months and subjects will be followed until they reach an outcome. A subject will be considered lost to follow-up if in the post-explant portion of follow-up the site makes two documented unsuccessful attempts to contact the patient for data collection and neurological assessment. Table 11 outlines the assessment plan over the course of the study.

Table 11. Assessment schedule

STUDY ITEM	Pre-Implant	POST IMPLANT FOLLOW-UP						POST EXPLANT	
		Implant	3 Weeks	6 Weeks	3 Months	6 Months	Long-term*	Hospital Discharge	12 and 24 Months
Inclusion/Exclusion Verified, Informed Consent Obtained, Medical History Documented	√								
Laboratory (e.g. Medication, Anticoagulation) Parameters Documented	√	√	√	√	√	√	√		
Adverse Events	√	√	√	√	√	√	√		
Device Performance Parameters		√	√	√	√	√	√		
PEDI	√		√	√	√	√	√	√	√
PSOM (at time of SAE and 30 and 60 days post neurological event)								If neuro SAE	If neuro SAE
PedNIHSS (and at time of SAE)	√		√	√	√	√	√		
Functional Status II® Measure	√		√	√	√	√	√	√	√
PedsQL	√		√	√	√	√	√	√	√

*Every 3 months while on device

Data to be collected at the appropriate assessment periods are detailed within the protocol.

Study Timeline

Expected date of initiation of subject enrollment	January 2013
Expected number of subjects enrolled per month	5
Expected date for subject enrollment completion	November 2013
Expected date for subject device follow-up completion	March 2014
Expected date for final report for study endpoints	May 2014
Expected date to complete follow-up of all study participants	March 2016
Expected date to submit final report	April 2016

Statistical Plan

The primary safety endpoint will be calculated as the total number of SAEs divided by the sum of days all subjects are supported on the device. The null hypothesis is that the registry SAE rate will be ≥ 0.10 (alpha error of <0.05).

The primary effectiveness endpoint of time on device will be calculated and summarized using means, standard deviations, medians and ranges. The primary effectiveness endpoint will be calculated as the time to outcome where outcome is defined as transplant, recovery or death.

As a secondary analysis, the primary endpoints will be also be summarized by stratifying the subjects into two groups based on body surface area (BSA) and again by age. The cutoffs will be chosen as the BSA used in the pre-market study (0.7 m^2) and the age of 4 years per a supplementary analysis requested by FDA during the IDE.

Long term post explant follow-up data will be summarized following the completion of the follow-up period for all enrolled subjects. All reported adverse events will be classified based on relatedness to the device, procedure, concomitant medication or patient management.

Status of Post-Approval Study and Results

Subject accountability

At the time of the July 13, 2013 report, data entry is ongoing and the CEC has not adjudicated any events - all events are reported as entered into the database.

Number of IRB Approvals, Sites, and Patients

Study Element	Current no.	%
Number of IRB Approvals	21	42
Number of study sites enrolled	10	20
Number of subjects enrolled	15	31
Follow-up rate	15	100

- The age ranged from 4 months to 16 years (mean 132.4 months or 11 years).
- The weight ranged from 6.5 to 59.0 kg (mean 21.7 kg).
- Race, body surface area (BSA) and gender were not reported.

Summary of Interim Results

Primary Safety Findings

The mean number of days of support was 40.2. There were 0.055 events per patient days (33/[603]). The following adverse events occurred in ten out of fifteen patients (Table 12):

Table 12. Summary and adverse events within patients

AE	# Events	#Patients	Events per patient
Seizure	2	1	2
Infection – Sepsis	4	4	1
Venous Thromboembolism	1	1	1
Respiratory Failure	5	3	1.7
Major Bleeding	8	4	2
Ischemic CVA	5	4	1.3
Hemorrhagic CVA	1	1	1
Renal Failure	1	1	1
Right Heart Failure	1	1	1
Hypertension	2	2	1
Other	3	2	1.5
TOTAL	**33**	**10**	**3.3**

Appendix A provides additional information regarding the adverse events. Most adverse events were resolved with medications and were deemed by the investigator to be patient-related. Of the two events that were deemed to be device-related, one was an ischemic CVA (58 days) and the other was hematoma (15 days). There is no data regarding device malfunctions and thrombosis.

Neurological Events

Four of 15 subjects (26.7%) experienced an ischemic cerebrovascular attack (CVA). A summary of the investigator assigned outcome regarding the six CVA events (in four patients) is shown in Table 13. There is no information regarding the severity of the stroke (i.e. disabling and non-disabling). Two out of the three deaths in the study were preceded by CVA (no SAE's preceded

the third death). Anticoagulant treatment was stopped for all CVA and all events were reported by the investigator as patient-related.

- In patient 014-203, the device was implanted in a patient with an infection. Sepsis occurred at day 5 followed by ischemic CVA at day 14.
- In patient 028-201, the ischemic CVA event (day 28) was also deemed to be device related. There was no pump exchange or subsequent SAEs associated with this patient.
- In patient 022-201, the resolved ischemic CVA at day 13 was followed by a pump exchange and an additional ischemic CVA at day 16.
- In patient, 016-201, an ischemic CVA event occurred at day 24 followed by renal insufficiency and a hemorrhagic CVA at day 28. There are no reports of thrombosis following this pump exchange.

Table 13. Investigator Assigned Outcomes by Type of CVA

Event	Investigator assigned Outcome	Total
Hemorrhagic CVA	Death	1
Ischemic CVA	Death	1
	Ongoing	3
	Resolved	1

Primary Effectiveness Findings

There have been 3 deaths, 5 transplants, 6 patients still on device, and 1 explant (Table 14). For patients < 1 year of age, there were 1 explant, 4 on system, 1 death, and 0 transplants. For patients aged > 1 year, there were 0 explants, 2 on system, 2 deaths, and 4 transplants.

Table 14. EXCOR Pediatric PAS Study Subjects (Outcomes by Age)

Age	Outcome	Weight (kg)	EXCOR® Pediatric Pump(s)	Days Of Support*
4 months	Explant	6.5	10 ml	40
6 months	On system	7.2	10 ml	21
6 years	Death	15.6	25/25 ml	0
7 months	On system	6.9	10 ml	19
8 months	On system	7.8	10 ml	17
8 months	On system	8.5	25 ml	88
<1 year summary	*1 explant, 4 on system, 1 death, 0 transplants*			
15 months	On system	12.2	25/25 ml	54
15 months	Transplant	9.1	10 ml	39
2 years	Transplant	10.7	25/25 ml	159
11 year	Transplant	30.3	60/50 ml	15
11 years	Death	23	30/30 ml	14
11 years	Death	50	60 ml	28
12 years	On system	42	30 ml	14
12 years	Transplant	59	60/60 ml	48
16 years	Transplant	36.9	50/50 ml	47
≥1 year summary	*0 explants, 2 on system, 2 deaths, 4 transplants*			

**as of 07/19/13 for subjects still on support*

Secondary findings

- Device Malfunctions (CEC adjudicated)
  - Number of failures - none/not reported
  - Pump and non-pump failures – none/not reported
- Site evaluation of explanted pumps for suspected thrombus – not reported

- Assessment of the learning curve – not reported

Non-PAS Implanted Patients

To date, 110 subjects have been implanted with the device following HDE approval (12/16/11); the first 46 patients were implanted before approval of the PAS protocol (July 27, 2012). Limited data regarding implant date, age, weight, device ml, and outcome (transplant, death, explant, or on-pump) has been reported for these patients. The weight ranged from 2.9-112.0 kg and ages from 8 days to 18 years of age. All patients were from US sites.

The outcomes for these patients are summarized below:

Outcome	n/N	(%)
Transplant	76/110	(69.1%)
Weaned successfully	1/110	(0.9%)
Death	16/110	(14.5%)
Converted therapy to other support	4/110	(3.6%)
Currently on support	13/110	(11.8%)

PAS Assessment

Based on the physician indicated outcomes, the primary safety endpoint is below the pre-specified performance goal of 0.10 SAEs per patient days. It must be noted that these outcomes have not yet been adjudicated by the CEC, so these rates may change upon adjudication. The most commonly reported SAE is CVA. Four of 15 PAS patients experienced a CVA (26.7%), of which two of these patients died. The rates seen within the small PAS sample are in line with the premarket studies where 29.2% of Cohort 1 patients (body surface area [BSA] < 0.7 m2) and 35% of Cohort 2 patients (BSA > 0.7 m2 to < 1.5 m2) experienced a neurological event. There was only one case in which CVA followed a device exchange; therefore it is premature to conclude an association.

The effectiveness of this device in the PAS cannot be determined at this time due to the limited data presented by the sponsor.

POST MARKET DATA: LITERATURE REVIEW

A search of the PubMed database for articles published December 2011 – June, 2013 was conducted using prespecified criteria and the following search terms: "berlin heart" or "Berlin EXCOR" or "heart EXCOR" or Excor yielded 204 articles. The following limits were placed yielding 35 articles: publication date “12/1/2011” and English. Upon several passes of the titles,

abstracts and texts, 26 articles were excluded as follows: n <10 (n=4), case report (n=11), non-human (n=2), treatment not specific to device (n=1), and other (n=1). The remaining eight articles are the subject of this review.

There were four (4) prospective and four (4) retrospective cohort studies. [1-9] Four studies were conducted in the U.S. and four in Europe. The sample sizes ranged from 14 to 204 patients. The ages ranged from 0-21 years. In one study of both adult and pediatric patients, the ages ranged from 1.5-63 years. [6] The mean time on support ranged from 28-68 days with the highest time on support reported as 363 days in the bridge to transplant (BTT) population.[9] Seven studies examined BTT only and one study examined both BTT and destination therapy. All studies examined the device in the left ventricular (LVAD) and biventricular (BVAD) positions.

Pediatric-Only Studies (n=8)

Survival

While on support, two studies reported a 0% recovery rate for cardiomyopathy (CMP) patients.[4,9] One study reported that 21% of 14 patients died while on support.[9] Fraser et al. (2012) showed survival on the device was superior to ECMO, with VAD patients median survival as 144-174 days compared to ECMO patients survival 10-13 days. Success, as defined by the ability to achieve the prolonged support time needed for successful bridge to transplantation, was 67-75% in ECMO patients (none were alive on ECMO) and 88-92% in VAD patients.

One year survival was estimated to be between 79-92%.[1,5] In a review of 181 children who underwent heart transplantation between May 1986 and December 2011, Hertzer et al. (2013) reported long term survival rates in BTT pediatric patients of 78, 63 and 48% at 5, 10 and both at 15 and 20 years post-transplantation, respectively. Transplant rates ranged from 13.8% to 92% with lower transplant rates reported in patients being treated for CHD and higher rates for cardiomyopathy (CMP) patients. Patients with BSA<0.7m^2 had respectively the same 30- day survival as patients with BSA 0.7-1.5m^2 (96%), but lower rates of success at the end of circulatory support (survival and no neurological events) than patients with BSA 0.7-1.5m^2 (88% at vs. 92%) [4]. Lower weight was also identified as a risk factor for late mortality (>2 months).[1]

Safety

The most commonly reported complications were infection and neurological events. Infection rates ranged from 7% (1/14) to 63% (30/48). There were three studies in which neurological events occurred in 29% of patients.[1,4,9] In a study of 25 pediatric patients implanted with the device between, January 2002 and January 2012, 9 patients had evidence of acute brain injury (BI) including intracranial hemorrhage (n = 5) and cerebral ischemia (n = 4).[8] Freedom from BI at 30, 60, and 90 days from VAD implantation was 80.7, 69.9, and 43.3%, respectively. Neurological events (thromboembolic, ischemic, and hemorrhagic stroke) were the main cause of death in three studies: 20% (N=48), 29% (N=204), and 11% (N=27).[1,3,4] In a study of patients with and without brain injury (BI), body weight greater than 10 kg was associated with increased risk of stroke 88% in BI patients vs. 43.7% no BI (p=0.04).[8] Notably, a retrospective study of pediatric heart transplant patients before (1998-2005) and after (2005-2012) the routine use of the Berlin Heart EXCOR device showed that the use of mechanical circulatory support increased post-transplant mortality at 30 days compared to non-use (7 vs 1%, $P < 0.05$), the proportion of neurological complications (23 vs 8%, $P < 0.01$), and major respiratory sequelae (20 vs 4%, $P < 0.001$).[2]

Study Enrolling Adults and Pediatrics (n=1)

Survival

One study examined use of the device in the left and/or right ventricle during end-stage heart failure in a primarily adult population, which also included several pediatric patients.[6] Ozbaran et al. (2013) reported on 45 adults and 9 pediatric patents, but did not present all results by age group. The mean time on support was 256+-200 days for adults and 384+-207 days in pediatric patients. Twenty percent (20%) of patients died during support, 59% of patients were transplanted, 1.9% recovered, 19% were alive on the device. The overall survival rate until transplantation or after weaning was 80%.

Safety

Four patients experienced thromboembolic cerebral complications, including transient ischemic events and prolonged reversible ischemic neurological deficits; one of whom experienced a severe stroke. Of the patients who died on circulatory support, two died from hemorrhagic neurological complications. There were 19 required pump-head exchanges in 17 patients due to visible thrombus or fibrin deposit in the pump head or due to membrane rupture. The number and proportion of patients with membrane rupture was not stated.

Literature Conclusions:

Although the use of the Berlin Heart Excor Pediatric VAD prolongs survival to transplantation, it is associated with risks such as infection and neurological events. The rates of these events reported in the literature are similar to that seen in the premarket study in which infection was the most common clinical event (50-62%) and to precede thrombus (29-49%) and neurologic dysfunction occurred in 29-35% of premarket patients. It is noted that the literature review includes the results from the premarket study.[4] Lower weight is associated with an increase in late mortality and risk of stroke; however, this may be related to the frailty of the patient. Based on the literature review, the results regarding membrane rupture are inconclusive as the study did not report the number of ruptures and the ages/BSA of the patients in which these events occurred.

SUMMARY

Since HDE approval, FDA has received 21 MDRs describing a select set of mechanical malfunctions. In general, these types of events are consistent with those seen in the premarket EXCOR study or known to occur with mechanical assist devices. The mandated PAS is early on, and actively recruiting and enrolling subjects. Preliminary results (not yet adjudicated) are showing safety events (types, rates) consistent with what was seen in the premarket IDE study. However, longer term data, in particular as relates to stroke outcomes is still pending. An assessment of the peer-reviewed literature likewise has not identified any new significant safety signals when compared to the premarket or preliminary PAS data.

REFERENCES

1. Almond CS, Morales DL, Blackstone EH, et al. Berlin Heart EXCOR pediatric ventricular assist device for bridge to heart transplantation in US children. *Circulation.* Apr 23 2013;127(16):1702-1711.

2. Botha P, Solana R, Cassidy J, et al. The impact of mechanical circulatory support on outcomes in paediatric heart transplantation. *Eur J Cardiothorac Surg.* May 13 2013.

3. Brancaccio G, Filippelli S, Michielon G, et al. Ventricular assist devices as a bridge to heart transplantation or as destination therapy in pediatric patients. *Transplant Proc.* Sep 2012;44(7):2007-2012.

4. Fraser CD, Jr., Jaquiss RD, Rosenthal DN, et al. Prospective trial of a pediatric ventricular assist device. *N Engl J Med.* Aug 9 2012;367(6):532-541.

5. Hetzer R, Weng Y, Delmo Walter EM. State of the art in paediatric heart transplantation: the Berlin experience. *Eur J Cardiothorac Surg.* Feb 2013;43(2):258-267.

6. Ozbaran M, Yagdi T, Engin C, et al. Long-term paracorporeal ventricular support systems: a single-center experience. *Transplant Proc.* Apr 2013;45(3):1013-1016.

7. Ozturk C, Ayik F, Oguz E, et al. Evaluation of changes in quality of life among Turkish patients undergoing ventricular assist device implantation. *Transplant Proc.* Jul-Aug 2012;44(6):1735-1737.

8. Polito A, Netto R, Soldati M, et al. Neurological Complications During Pulsatile Ventricular Assistance With the Berlin Heart EXCOR in Children: Incidence and Risk Factors. *Artif Organs.* Apr 5 2013.

9. Sharma MS, Forbess JM, Guleserian KJ. Ventricular assist device support in children and adolescents with heart failure: the Children's Medical Center of Dallas experience. *Artif Organs.* Jul 2012;36(7):635-639.

Appendix A: Details of Adverse Events in PAS Subjects

ID, Implant Date Outcome, Outcome Date (days of support)	Event	Days to Event	Treatment	Investigator assigned Outcome	Investigator assigned Relatedness
035-201 implant 01/03/13 Transplant 06/11/13 (159 days)	Seizure	2	Medication Rx (Ativan)	Resolved	Patient
	Seizure	11	Medication Rx (fosphenytoin)	Ongoing	Patient
	Major infection-Sepsis	13	Medication Rx (antibiotics)	Resolved	Patient
	Other: Mediastinal exploration and evacuation of a large hematoma, drainage of right pleural effusion	15	Surgical (Mediastinal exploration)	Resolved	Device
	Venous Thromboembolism	61	Medication Rx (restarted heparin drip)	Ongoing	Patient
014-201 implant 03/12/13 Transplant 04/27/13 (47 days)	Respiratory Failure	2	Intubation; Surgical (bronchoscopy)	Resolved	Patient
	Respiratory Failure	12	Intubation	Resolved	Patient
	Major Bleeding	12	Blood transfusion; Surgical (chest tube; bronchoscopy)	Resolved	Concomitant medications
	Major Bleeding	28	Blood transfusion; Medication Rx (stopped bivalirubin for 12 hours)	Resolved	Concomitant medications
	Major infection-Sepsis	29	Medication Rx (started antibiotics)	Ongoing (patient positive for MRSA)	Patient
	Respiratory Failure	29	Intubation	Resolved	Patient
022-201 implant 03/21/13 Explant 04/30/13 (40 days)	Ischemic CVA	13	Intubation; Medication Rx (ativan)	Ongoing	Procedure (pump replacement)
	Ischemic CVA	16	Medication Rx (Phenobarbitol and PRN ativan)	Ongoing	Patient
014-203 implant 04/12/13 Death 04/26/13 (14 days)	Major infection-Sepsis	5	Medication Rx (antibiotics, anti- fungal)	Ongoing (infection prior to VAD placement)	Patient
	Ischemic CVA	14	Medication Rx (stopped heparin)	Death	Patient and Concomitant-medications
028-201 implant 04/22/13 On support (88 days)	Major Bleeding	1	Blood transfusion; Surgical (Mediastinal exploration, evacuation of hematoma, broviac removal)	Resolved	Procedure
	Ischemic CVA	58	Medication Rx	Resolved	Device, Patient

016-201 implant 05/23/13 Death 06/20/13 (28 days)	Ischemic CVA	24	Other (EEG monitoring)	Ongoing	Patient
	Other: Renal insufficiency	25	Dialysis	Ongoing	Patient
	Hemorrhagic CVA	28	Medication Rx (stopped all anticoagulation)	Death	Patient
010-201 implant 05/26/13 On support (54 days)	Major infection – Sepsis	-5	Medication Rx (Vanco, cefepime, micafungin)	Resolved	Patient
	Right Heart Failure	1	Surgical	Resolved	Patient
022-202 implant 05/28/13 Transplant 07/06/13 (39 days)	Hypertension	4	Medication Rx (Nipride)	Resolved	Patient
	Other, Ventricular ectopy	5	Medication Rx (Esmolol)	Resolved	Concomitant medications
	Respiratory Failure	8	Intubation	Resolved	Concomitant medications
	Pericardial Effusion without tamponade	9	Surgical Rx (Drainage through sub- xiphoid approach)	Resolved	Procedure
006-201 implant 06/05/13 Transplant 06/20/13 (15 days)	Hypertension	1	Medication Rx (Nipride cont. infusion)	Ongoing	Patient
	Major Bleeding	5	Blood transfusion; Surgical (mediastinal exploration, pericardial effusion removed) Medical Rx (Persantin put on hold, Heparin drip stopped)	Resolved	Procedure, Concomitant medication
	Respiratory Failure	6	None	Ongoing (remains intubated)	Patient
037-201 implant 06/28/13 On support (21 days)	Major Bleeding	3	Blood transfusion	Resolved	Concomitant medication
	Major Bleeding	6	Blood transfusion	Resolved	Patient

KEY: CVA – cerebrovascular accident, EEG – electrocardiogram, Rx – therapy/treament