FDA Executive Summary

Prepared for the **September 23, 2014** meeting of the FDA's Pediatric Advisory Committee

H100004

Berlin Heart Inc. EXCOR Pediatric Ventricular Assist Device

Introduction

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.

Post-Market Data --- Medical Device Report (MDR)

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/ environment, including:
    - rare, serious, or unexpected adverse events;
    - adverse events that occur during long-term device use;
    - adverse events associated with vulnerable populations;
    - off-label use; and
    - 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. Other limitations of MDRs and MAUDE include:

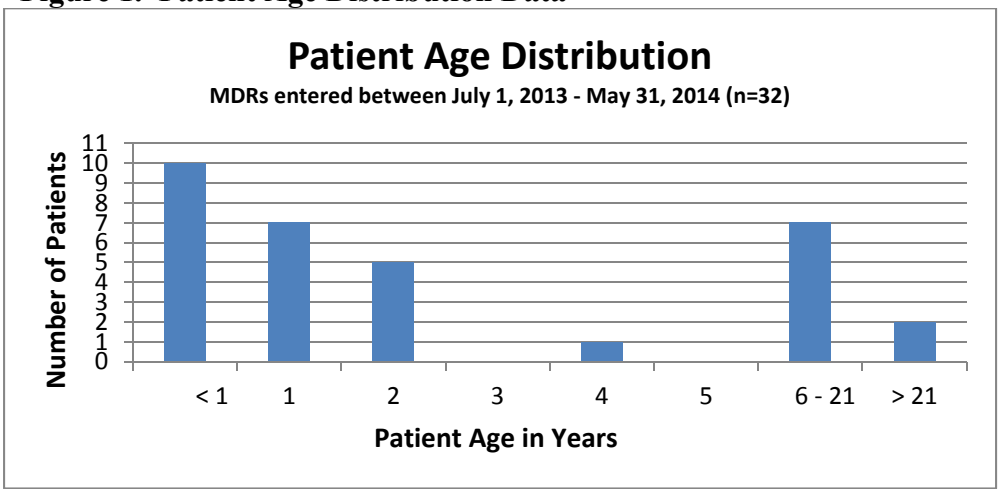
- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with 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.

Pediatric Advisory Panel MDR Analysis: Berlin Heart EXCOR Pediatric Ventricular Assist Device

The Agency conducted queries in the MAUDE (Manufacturer and User Facility Device Experience) database on June 2, 2014 for all Medical Device Reports (MDRs) associated with Berlin Heart EXCOR Pediatric Ventricular Assist Device (VAD). The date range included reports entered from July 1, 2013 through May 31, 2014, as the previous year's review ended on June 30, 2013. The query resulted in 33 MDRs which were individually reviewed for factors such as reported device and patient problems, event type, report source, patient age, patient sex, reporting country and the time to event occurrence (TTEO). The TTEO is based on the implant duration specified in the event text of the MDR or calculated as the time period between the date of implant and date of event. These factors are characterized in this analysis summary.

The queries resulted in the identification of 33 unique MDR reports with 31 MDRs reported by the manufacturer and 2 MDRs reported from user facilities (UF). Patient age data was provided in 32 of the 33 MDRs. There were 30 pediatric patients ranging from 3 months to 13 years of age with an average age of 3 years. There were 2 adult patients ages 62 and 64 years old. Patient gender information was provided in 32 of the 33 reports of which 15 were female and 17 were male patients (including the 2 adults). See Figure 1 for age distribution data for reports entered into MAUDE between July 1, 2013 and May 31, 2014.

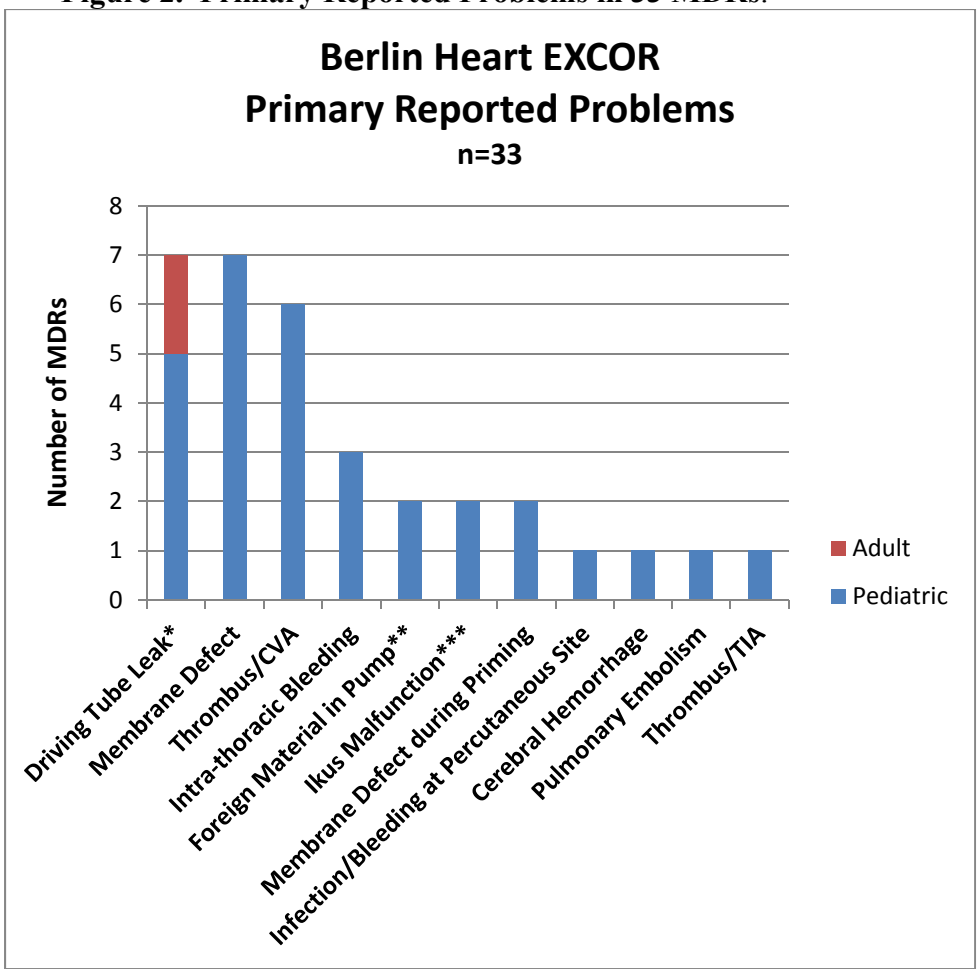
Figure 1. Patient Age Distribution Data



Reporting Country was available in 32 of the 33 MDRs and included the United States for 21 MDRs and 11 MDRs reported from Out-of-US (OUS). Countries included the United Kingdom (2), Germany (2), Argentina (1), Canada (1), Italy (1), Japan (1), Poland (1), Spain (1) and Sweden (1).

Reported Problems
The 33 MDRs were individually reviewed and analyzed for the primary reported problem. Figure 2 depicts the number of MDRs categorized by primary reported problem.

Figure 2. Primary Reported Problems in 33 MDRs.



*There are two (2) adult patients who experienced a Driving Tube Leak

** There are two MDRs related to Foreign Material in the Pump. These MDRs are related to one event with a pediatric patient involving his RVAD and LVAD.

***Ikus refers to the Stationary Driving Unit

Among the 33 MDRs, the most commonly reported problems were "Membrane Defect" in 7 MDRs (21%) and "Drive Line Leak" in 7 MDRs (21%) consistent with the previous year's analysis. The next most commonly reported problem was "Thrombus/CVA", 6 (18%) and "Intra-thoracic Bleeding" 3 (9%). CVA, thrombus and bleeding were not reported for MDRs entered in MAUDE through the June 30, 2013 for last year's analysis. However, these events were reported in the Post Approval Study (PAS) for that time period. It is worth noting that there has been a shift in MDR reporting practices since the previous analysis as MDR reportability requirements were discussed with the firm in 2013 and Berlin Heart has made

changes to address the feedback received from FDA. The firm performed a retrospective analysis of events and consequently reported MDRs according to regulatory requirements.

Type of Event

The type of events reported in the 33 MDRs includes zero (0) death reports, 13 injury reports, 18 malfunctions and two (2) "other" reports, which upon individual review, were determined to be malfunctions for a total of 20 malfunctions events. Table 1 lists the total MDR count for each primary reported problem along with the type of event and TTEO. Following the table, the primary reported problems are further detailed to include specific event, patient information, TTEO and required intervention.

Table 1. Reported Problems, Type of Event and TTEO of the 33 MDRs

	MDR Count	Death	Injury[1]	Malfunction[2]	TTEO (months)
Pre-Procedural	**2**	**0**	**0**	**2**	
Membrane Defect during Priming	2	0	0	2	0
Post-Procedural	**31**	**0**	**13**	**18**	
Thrombus/CVA	6	0	6	0	0.43 - 3.5
Thrombus/TIA	1	0	1	0	1.5
Pulmonary Embolism	1	0	1	0	UNK
Cerebral Hemorrhage	1	0	1	0	3.5
Intra-thoracic Bleeding	3	0	3	0	0.16 - 1
Infection/Bleeding at Percutaneous Site	1	0	1	0	7
Membrane Defect	7	0	0	7	1 - 11
Driving Tube Leak	7	0	0	7	UNK
Foreign Material in Pump	2	0	0	2	0.27 - 1
Ikus Malfunction	2	0	0	2	NA
Total	**33**	**0**	**13**	**20**	

[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 priming of the pump.

- **Membrane Defect during Priming (n=2)**
  During priming in both events, the blood side membrane was not completely smooth in the diastolic position. There were wrinkles in the membrane that would not flatten. New pumps were primed and there was no harm to the patients. These events differ from the membrane defects which occur during use on the patients and are described later in this analysis. However, it is unknown if the underlying cause of the membrane defect during priming is related to the reported post-procedural membrane defects.

Post-Procedural Events (n=31)

There were 31 MDRs related to post-procedural events. There were no death reports, 13 injuries and 18 malfunctions. Further information on the reported problem and event details are described below:

Injury Events

- **Thrombus/CVA (n = 6)**
  There were six (6) events where a thrombus was reported or suspected and patient outcome resulted in a CVA (cerebrovascular accident). The six (6) events occurred in the US.
  - A 14 month old female underwent pump exchange due to thrombus/fibrin clot two weeks after implant. The pump was clamped for 120 seconds during the pump exchange and the patient likely experienced hypo-perfusion state during the procedure. Afterwards, the patient was less responsive and developed rhythmic jerking of the left leg as well as the right arm and forced rightward gaze. Computed Tomography (CT) findings are consistent with a severe ischemic injury with large hypodense areas including most of right cerebral hemisphere, left frontal aspect and left occipital lobe with extensive basal ganglia involvement. Approximately 7 weeks later, due to poor prognosis and transplant ineligibility, the patient was discharged to home with the family.
  - Five days after implant, an 11 year old female developed a thrombus in the pump. Berlin Heart clinical support was contacted by the UF and recommended a pump exchange. The treating clinician elected not to exchange the pump remarking that the clot was not large enough. Two weeks later patient was intubated and air was introduced into the gut and gastric pnematosis developed. The patient was not responding to normal stimuli and a CT scan indicated non-hemorrhagic infarction in the right thalamus and right internal capsule. One week later, the patient's family requested discharge due to poor prognosis and ineligibility for transplant.
  - Almost two months after implant, a four (4) month old female demonstrated signs of neurologic dysfunction. CT results indicated an acute infarct within the left occipital lobe. The site had been monitoring the blood pump for white punctual

deposits per instructions in the IFU. The patient was transplanted after 204 days of support.

- Nine days after implant, a six (6) month old male had a suspected thrombus in the pump. Berlin Heart clinical support recommended pump exchange but the recommendation was rejected by surgeon. Thrombus disappeared and five days later, the surgeon recommended pump exchange. Two days after pump exchange, the patient experienced seizure activity and loss of right-sided movement. CT revealed a several day old bilateral cerebral infarct.
- A four (4) month old female experienced seizures 17 days post implant. Medications were therapeutic and no deposits were noted in the pump. Head CT showed several acute infarcts and a small bleed. Pump was exchanged the following day for suspected thrombus.
- Thirteen days post implant, a 10 month old female was noted to have a deposit on the outflow valve of the pump with some areas of darkness. During pump exchange the same day, the tubing connected to the de-airing needle inadvertently became dislodged when clinicians were restarting the pump resulting in blood loss and need to stop pump because of concern for possible air entry. To insure adequate de-airing prior to restarting pump, the outflow cannula was clamped for 4 – 5 minutes and Cardiopulmonary Resuscitation (CPR) was administered during this time. Given the amount of time of poor perfusion, the site elected to keep her more deeply sedated, paralyzed, and temperature controlled. Head CT showed three areas of ischemic infarction in the right frontal, parietal, and caudate nucleus. These likely represented air emboli given the difficulties with pump exchange. The patient was sedated and paralyzed to provide for the maximum neuro-protection strategy after her pump change. Two days later patient converted to a cerebral bleed. It was determined UF did not follow proper pump change procedures when the event occurred and the site has been re-educated. The patient was removed from all medication and was moving all extremities. Follow-up CT indicated cerebral bleed is stable. Patient opened eyes but couldn't be totally assessed due to age. Overall condition was improving.

- **Thrombus/TIA (n = 1)**
  Approximately 1.5 months post implant, an 11 month old male experienced a large clot in the pump overnight. The following morning, prior to scheduled pump exchange, the clot disappeared. The patient then experienced seizures and complete right-sided paralysis. Head CT showed a non-occlusive thrombus in a branch of the middle cerebral artery (MCA). Symptoms completely resolved over the next hour. No further symptoms were observed following this event.

- **Intra-thoracic Bleeding (n = 3)**
  - There were three (3) injury events of intra-thoracic bleeding. Five days after implant, a six (6) year old female had a chest tube output of 200-300cc of fluid. The event was reported to be due to management of anticoagulation therapy. The patient received two units of packed red blood cells (PRBCs), and anticoagulation therapy was adjusted. The issue resolved without permanent injury.

- One month after implant, an 11 month old male with an aspirin sensitivity experienced a chest bleed after aspirin therapy was restarted. The patient underwent a surgical chest exploration and wash-out and received four units of PRBCs. The event resolved after surgical intervention and anticoagulation adjustment.
- A six (6) year old female experienced an aortic dissection one month post implant. The patient was playing and became short of breath with severe back and chest pain. The patient required CPR and intubation. The chest x-ray indicated a widening mediastinum. Fluid and blood resuscitation was started due to poor filling and emptying of blood pumps. Surgical exploration identified an aortic dissection with profound bleeding. The dissection was surgically repaired and the patient was returned to ICU in stable condition, later extubated and returned to stable condition.

- **Pulmonary Embolism (n = 1)**
  A one (1) year old male started having respiratory issues. Several pulmonary emboli were noted on ultrasound. A small punctual deposit was noted on RVAD (right ventricular assist device) for approximately one month. The pump was exchanged and TPA (tissue plasminogen activator) was initiated. Repeat testing two days later indicated the absence of previous emboli. The patient was transplanted 11 days later. The TTEO from the date of implant was not reported.

- **Cerebral Hemorrhage (n = 1)**
  A 13 month old male presented with right arm weakness and a focal seizure 3.5 months post implant. A head CT showed a hemorrhagic stroke in right parietal area. The hospital reported no clear evidence of infarct on CT scan, all anticoagulation levels were therapeutic, and there were no clots in the pump for weeks prior to the event. Clinicians stopped all anticoagulation. Two follow-up CT scans showed no progression of hemorrhagic area. Residual right arm weakness continued after the event.

- **Infection/Bleeding at Percutaneous Site (n = 1)**
  An infection and bleeding at the percutaneous site occurred in a nine (9) month old patient seven (7) months after implant. The patient underwent a percutaneous site exploration which identified a small arterial bleed as the cause which was then repaired. The issue resolved and the patient was transplanted one week later.

Malfunction Events

- **Membrane Defect (n = 7)**
  There were seven (7) malfunction reports related to membrane defects to either the blood or air membrane of the pump. These events were reported previously (the 2013 analysis summery) as “membrane rupture” events. Through further investigation by Berlin Heart, the MDRs submitted during this timeframe are described as a “membrane defect” with issues such as the pump failing to fill or eject properly, pillowing of the membrane, blood is seen in front of or in the area around the stabilization ring in the blood side layer or air side layer of the triple layer membrane. In all reports, the pump was exchanged and there was no hemodynamic compromise to the patients. Patient age was available in all MDRs

for a range of 8 months to 8 years. One (1) of the events occurred in the US and six (6) were OUS events. The TTEO ranges calculated for these events were 1 – 11 months with an average 4.5 months.

According to the manufacturer analysis identified in these MDRs, "The blood pump is designed with a triple layer membrane separating the air chamber from blood chamber for safety reasons. The entire membrane consists of an air-side layer, a middle layer and a blood-side 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 pump cycles, and to change the pump if a problem is detected. The firm updated the labeling in December 2013 to include instructions for identifying and troubleshooting problems with the membrane of the pump.

- **Driving Tube Leaks (n = 7)**
  There were seven (7) malfunction events involving air leaks or a crack in the driving tube/drive line of the device. 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 blood pump. In all cases, the required intervention was a driving tube exchange without harm to the patient. The firm identifies in their analysis of these events, a fatigue or stress problem likely due to external forces and during the time of usage in very active patients. The events involved patients ranging in age from 1-2 years, 12 - 13 years and the adult patients at 62 and 64 years of age. The implant date or event date were not reported in these MDRs; therefore, TTEO was not calculated.

- **Foreign Material in the Pump (n = 2)**
  There were two (2) malfunction reports related to foreign material in the pump. The two MDRs were related to the same patient on the same day with both the right and left pumps. The foreign material was identified as a 15mm by 3mm pool of liquid (condensation) between the blood layer and middle layer of the triple layer membrane but the amount of fluid was insufficient to identify the type of fluid. No leakage or damage to any of the membrane layers was detected. The two year old patient had been outside in the 90 degree heat during the day. Both pumps were exchanged and there was no consequence to the patient. One pump had been in place for 8 days and the other for 29 days. This issue is addressed in the IFU with required action if such an event occurs.

- **Ikus Stationary Driving Unit Malfunction (n = 2)**
  There were two (2) UF MDRs related to the Ikus. The implant date was not reported in these MDRs; therefore, TTEO was not calculated.
  - There was a pressure fault alarm in one system and the device was exchanged. There was no harm to the one year old patient. The firm determined that there was no device failure and the driving tube was likely disconnected or not connected properly to the unit when the error occurred. The reported alarms are not reproducible when the driving tube is connected as intended.

- A three (3) month old patient experienced a "powering down" sound of the driver with a "left driver failure" alarm and driver failure. The Ikus switched into backup mode and the pump was filling and ejecting less effectively at first, but quickly became adequate after a few pumps. The patient had been bradycardic and was retching at the time prior to the event with the Ikus. There were no reported changes in the patient's hemodynamic status. The Ikus was then exchanged for another. No manufacturer analysis was available as this event was reported by the UF.

Conclusions

- The firm updated the labeling in December 2013 to address post market experience based on recommendations made by the FDA and Pediatric Advisory Committee. The labeling enhancements include updates to the contraindications for device implant, potential patient adverse events such as death, air embolism, infection, and neurological events, and expected/potential device problems as noted in the MDRs to include type of problem and troubleshooting recommendations.

- The reported device issues identified in the MDRs over the past 11 months are similar to reported events from the previous year.

- The reported patient problems such as CVA, TIA, bleeding, cerebral hemorrhage and infection were not previously submitted to FDA as MDRs prior to the 2013 Pediatric Advisory Committee (PAC) meeting, but were reported in the PAS and characterized by FDA to the PAC in that regard. These reportable events have since been submitted to FDA as MDRs.

- The risks/complications reported in the MDRs have been reported in the Investigational Device Exemption (IDE) study, have been identified in the IFU and reflect known complications of 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 2 outlines the assessment plan over the course of the study.

Table 2. 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
Initiation of subject enrollment (actual): January 2013
Completion date for enrollment (actual): March 2014
Expected date for subject device follow-up completion: October 2014
Expected date for final report for study endpoints: December 2014

Expected date to complete follow-up of all study participants: October 2016
Expected date to submit final report: November 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 Body Surface Area (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
The database closing date for this report is July 11, 2014.

Table 3: Number of IRB Approvals, Sites, and Patients

Study Element	Current no.	%
Number of IRB Approvals	26	52
Number of study sites enrolled	26	52
Number of subjects enrolled	39	100
Follow-up rate	39	100

- The age ranged from 1 day to 16.3 years (median 22.8 months or 1.9 years).
- The weight ranged from 3.4 to 70.0 kg (median 10.6 kg).
- The Race distribution is 71.8% Caucasian 5.1% African American, 2.6% Asian 20.5% Other/not disclosed.
- The body surface area (BSA) ranged from 0.23 to 1.76 m^2 (median 0.49 m^2)
- Females constitute 51.3% (20) of the population

Summary of Interim Results
Primary Safety Findings
The mean number of days of support was 94.8. There were 0.025 events per patient days (92 events in total). The top 3 SAEs were major bleeding, major infection and neurological dysfunction. Sixteen of 39 PAS patients (41.0%) experienced major bleeding, 14 experienced major infection (35.9%) and 13 experienced CVA (33.3%). Ten patients died after device implant, of which 5 patients died from CVA, 1 died from pulmonary respiratory failure, 1 died

from CNS encephalopathy, 1 died from gastrointestinal bleeding, 1 died from multisystem organ failure who also had a CVA event, and 1 died 3 days after being transitioned from EXCOR to ECMO (Table 3). Four of the 10 subjects who died were on ECMO prior to the EXCOR® Pediatric implant. There are no reports of device malfunctions (pump and non-pump failures). Adverse events occurred in 32 out of 39 patients (Table 5).

Table 4: EXCOR® Pediatric PAS Study Subjects who have died

ID	Implant Date	Days Of Support	Primary cause of death [Secondary cause of death]
014-203	04/12/13	14	CNS: Intracranial hemorrhage
016-201	05/23/13	28	CNS Intracranial hemorrhage
028-202	07/01/13	0	Pulmonary Respiratory Failure [Cardiovascular Failure; Hemorrhage Pulmonary; CHD]
004-201	07/31/13	7	Not adjudicated as patient was transitioned from EXCOR to ECMO on 08/07/13 and died on 08/10/13
071-201	08/21/13	55	CNS Multiple strokes [Multisystem organ failure]
042-202	09/04/13	77	CNS Multiple infarcts [CHD, Infection]
004-202	09/16/13	79	CNS Encephalopathy [DCM, Infection]
001-201	09/19/13	6	Ischemic stroke
008-202	12/06/13	1	Hemorrhage: GI [Other: Perforation of esophagus]
014-206	01/19/14	119	Multisystem organ failure

Note:
1. Four of the 10 subjects who died were on ECMO prior to the EXCOR® Pediatric implant.
2. Subject 028-202 was adjudicated by the CEC as a failed implant as the subject was unable to be separated from bypass and adequate oxygen saturation was unable to be maintained. The patient died after being removed from ECMO support.

Table 5. Summary and adverse events within patients

Event Category	# events	# subjects with event (n=39)	Events/ Subject (n=39)
Adjudicated SAEs			
Major Bleeding	19	16 (41.0%)	0.49
Major Infection:	18	14 (35.9%)	0.46
Localized non-device	4	4 (10.3%)	0.10
Percutaneous Site and/or Pocket Infection	7	5 (12.8%)	0.18
Internal Pump Component, Inflow or Outflow Tract Infection	2	2 (5.1%)	0.05
Sepsis	5	5 (12.8%)	0.13
Neurological dysfunction:	17	13 (33.3%)	0.44
TIA	0	0 (0.0%)	0.00
Ischemic CVA	8	6 (15.4%)	0.21
Hemorrhagic CVA	5	5 (12.8%)	0.13
Ischemic/Hemorrhagic CVA	4	3 (7.7%)	0.10
New abnormality of head ultrasound	0	0 (0.0%)	0.00
EEG positive for seizure activity with or without clinical seizure	0	0 (0.0%)	0.00
Other, Covert stroke	3	3 (7.7%)	0.08
Other, Seizure	2	2 (5.1%)	0.05
Other, Encephalopathy	1	1 (2.6%)	0.03
Other SAEs			
Pericardial effusion with tamponade	1	1 (2.6%)	0.03
Pericardial effusion without tamponade	3	3 (7.7%)	0.08
Hepatic Dysfunction	2	2 (5.1%)	0.05
Hypertension	4	4 (10.3%)	0.10
Respiratory failure	8	6 (15.4%)	0.21
Right heart failure	3	3 (7.7%)	0.08
Venous Thromboembolism	3	2 (5.1%)	0.08
Psychiatric episode	1	1 (2.6%)	0.03
Other	7	6 (15.4%)	0.18
TOTAL	**92**	**32 (82.1%)**	**2.36**

SAEs were also summarized separately in categories according to the subjects' BSA and age

(Table 5). The data divides out such that the same subjects who have a BSA < 0.7 m^2 are also less than 4 years old and the same subjects who have a BSA >= 0.7 m^2 are ≥ 4 years old. One 4.9 year old subject who is underweight (weight 14.9 kg, BSA 0.62 m^2) is the exception and falls into the <0.7 m^2 category for the larger BSA group. The order of the top 3 SAEs is the same in the two BSA groups; however, patients with BSA >= 0.7 m^2 had higher SAE rates than patients with <0.7 m^2.

Table 6: Summary SAEs by Body Surface Area Grouping

	BSA < 0.7 m^2 n=23		**BSA ≥ 0.7 m^2 n=16**	
Event Category	**# events**	**# subjects with event**	**# events**	**# subjects with event**
Adjudicated SAEs				
Major Bleeding	9	8 (34.8%)	10	8 (50.0%)
Major Infection:	11	7 (30.4%)	7	7 (43.8%)
Localized non-device	3	3 (13.0%)	1	1 (6.3%)
Percutaneous Site and/or Pocket Infection	5	3 (13.0%)	2	2 (12.5%)
Internal Pump Component, Inflow or Outflow Tract Infection	2	2 (8.7%)	0	0 (0.0%)
Sepsis	1	1 (4.3%)	4	4 (25.0%)
Neurological dysfunction:	10	7 (30.4%)	7	6 (37.5%)
TIA	0	0 (0.0%)	0	0 (0.0%)
Ischemic CVA	6	4 (17.4%)	2	2 (12.5%)
Hemorrhagic CVA	3	3 (13.0%)	2	2 (12.5%)
Ischemic/Hemorrhagic CVA	1	1 (4.3%)	3	2 (12.5%)
New abnormality of head ultrasound	0	0 (0.0%)	0	0 (0.0%)
EEG positive for seizure activity with or without clinical seizure	0	0 (0.0%)	0	0 (0.0%)
Other, Covert stroke	2	2 (8.7%)	1	1 (6.3%)
Other, Seizure	2	2 (8.7%)	0	0 (0.0%)
Other, Encephalopathy	1	1 (4.3%)	0	0 (0.0%)
Other SAEs				
Pericardial effusion with tamponade	0	0 (0.0%)	1	1 (6.3%)
Pericardial effusion w/out tamponade	2	2 (8.7%)	1	1 (6.3%)

Hepatic Dysfunction	1	1 (4.3%)	1	1 (6.3%)
Hypertension	2	2 (8.7%)	2	2 (12.5%)
Respiratory failure	3	3 (13.0%)	5	3 (18.8%)
Right heart failure	3	3 (13.0%)	0	0 (0.0%)
Venous Thromboembolism	1	1 (4.3%)	2	1 (6.3%)
Psychiatric Episode	0	0 (0.0%)	1	1 (6.3%)
Other	6	5 (21.7%)	1	1 (6.3%)
TOTAL	**53**	**17 (73.4%)**	**39**	**15 (93.8%)**

Appendix A provides additional information regarding the adverse events. Most adverse events were adjudicated by the clinical events committee (CEC), and were resolved with medications or patient management. Thirty-six (36) serious adverse events were related to the device and 23 to the procedure. There is no data presented regarding device malfunctions.

Neurological Events

Thirteen of 39 subjects (33.3%) experienced a cerebrovascular attack (CVA). A summary of the CEC adjudicated SAEs regarding the 17 CVA events (in 13 patients) is shown in Table 6. All cerebrovascular attack (CVA) events (17) were deemed related to device (93.8%) and/or other factor such as procedure (33.3%) or patient management (37.5%), except for one case which was pending to be determined There is no information regarding the severity of the stroke (i.e. disabling and non-disabling).

Table 7. CEC Adjudicated CVA Events.

ID, Implant Date	SAE	SAE Onset Date	Days to event	Treatment	Current Status, Date, (days of support)	Relatedness
035-201 01/03/13	Neuro-Hemorrhagic CVA	01/04/13	1	Medication Rx (Ativan)	Transplant 06/12/13 (160 days)	Device, Procedure, Patient management, Concom meds
022-201 03/21/13	Neuro-Ischemic CVA	04/04/13	14	Intubation/Medication Rx (Ativan)	Explant 04/30/13 (40 days)	Device, Procedure
	Neuro-Ischemic CVA	04/07/13	17	Medication Rx (Phenobarbitol and PRN Ativan)		Device, Procedure
014-203 04/12/13	Neuro-Hemorrhagic CVA	04/26/13	14	Medication Rx (Heparin stopped)	CVA Death 04/26/13 (14 days)	Device
028-201 04/22/13	Neuro-Ischemic CVA (Left occipital)	06/20/13	59	Medication Rx (ASA, Enoxaprin, Dipyridimole)	Transplant 11/16/13 (208 days)	Device
	Neuro-Ischemic CVA (Right occipital (chronic))	06/20/13	59	Medication Rx (ASA, Enoxaprin, Dipyridimole)		Device
016-201 05/23/13	Neuro-Ischemic/ Hemorrhagic	06/14/13	22	Other (EEG Monitoring)	CVA Death 06/20/13 (28 days)	Device
071-201 08/21/13	Neuro-Ischemic/ Hemorrhagic	08/26/13	5	Medication/Other (TAT EEG and Neuro consult. Maintain Higher BP and lower Anti XA. 3% NaCl for goal Na 140-150 and pCO2	CVA Death 10/15/13 (55 days)	Device, Procedure, Concom meds

				goal 35-40)		
042-202 09/04/13	Neuro-Ischemic/ Hemorrhagic	09/18/13	14	Other (Physical, Occupational and Speech Therapy)	CVA Death 11/20/13 (77 days)	Device, Concom meds
	Neuro-Ischemic/ Hemorrhagic	10/14/13	40	None		Device, Concom meds
001-201 09/19/13	Neuro-Ischemic CVA	09/22/13	3	None	CVA Death 09/25/13 (6 days)	Device, Procedure, Patient management
033-201 11/20/13	Neuro-Ischemic CVA	03/20/14	120	Surgical Rx (Clot in right middle cerebral artery removed but clot in right internal carotid artery not able to be removed, pt developed subarachnoid hemorrhage and hydrocephalous requiring externalized ventriculostomy)	On device (233 days)	Device, Patient management
007-202 12/19/13	Neuro-Ischemic CVA	01/03/14	15	Blood tx/Medication Rx/Other (Cooled, paralyzed, sedated (Neuro protective therapy)	Transplant 03/07/14 (78 days)	Device, Patient management

	Neuro-Hemorrhagic CVA	01/06/14	18	Medication Rx/Other (Anticoagulation medications held; sedated, cooled paralyzed per neuro protection protocol, neurology consult)		Device, Patient management
014-206 01/09/14	Neuro-Hemorrhagic CVA	03/08/14	58	Blood tx/ Intubation/ Medication/ Surgical Rx (craniotomy, anticoagulation reversed and on hold)	Non-CVA Death 05/08/14 (119 days)	Device, Patient management, Concom meds
028-204 02/24/14	Neuro-Hemorrhagic CVA	03/18/14	22	Other (Withheld all anti-coagulation at this time.)	Transplant 06/24/14 (120 days)	TBD
004-201 07/31/13	Neuro-Ischemic CVA	07/31/13	0	Medication Rx (clonzazepam, ativan, and clonidine; IV benzos and narcotics for comfort)	Escalated to ECMO Death (not adjudicated) <= 30 08/07/13 (7 days)	Device, Procedure, Pt Mgmt

Primary Effectiveness Findings

There have been 10 deaths, 22 transplants, 5 patients still on device, 2 explant (2 died within 30 days), and 1 patient weaned successfully (Table 7). For patients < 1 year of age, there were 1 explant, 2 on system, 1 death, 7 transplants. For patients aged > 1 year, there have been 2 explant (1 transitioned from EXCOR to ECMO and died 3 days later), 3 patients still on system, 9 deaths, 15 transplants, and 1 patient weaned successfully.

Table 8. EXCOR Pediatric PAS Study Subjects (Outcomes by Age)

**as of 07/11/14 for subjects still on support*

Age (yrs)	**Gender**	**Race**	**Weight (kg)**	**BSA (m2)**	**EXCOR® Pediatric Pump(s)**	**Outcome**	**Days Of Support***
0.0	Male	Caucasian	4.1	0.24	10 ml	Death	1
0.2	Female	Caucasian	4.3	0.27	10 ml	Transplant	63
0.2	Male	Caucasian	3.4	0.23	10/10 ml	On device	184
0.3	Female	Other	6.5	0.33	10 ml	Explant	40
0.4	Female	Caucasian	5.7	0.32	10 ml	Transplant	20
0.4	Female	Caucasian/ African Am.	5.7	0.31	10 ml	Transplant	54
0.5	Female	Caucasian	7.4	0.37	10 ml	Transplant	77
0.6	Male	Caucasian	7.2	0.37	10 ml	Transplant	100
0.6	Female	Caucasian	6.9	0.36	10 ml	Transplant	42
0.7	Female	Caucasian	7.8	0.39	10 ml	On device	374
0.9	Female	Caucasian	8.6	0.41	25 ml	Transplant	78
<1 year summary	**1 explant, 2 on system, 1 death, 7 transplants**						
1.1	Female	Caucasian	8.1	0.40	10 ml	Weaned-Success	13
1.2	Female	African American	8.6	0.41	25/25 ml	Death	55
1.3	Male	Other	10.6	0.46	25/25 ml	Transplant	105
1.3	Male	Caucasian	9.0	0.43	10 ml	Transplant	39
1.5	Male	Unknown/ Undisclosed	8.8	0.43	10 ml	On device	218
1.6	Female	Caucasian	8.5	0.41	25 ml	Transplant	208
1.6	Female	Caucasian	10.6	0.49	25 ml	Transplant	29
1.7	Male	Unknown/ Undisclosed	11.4	0.52	25 ml	Transplant	229
1.9	Male	Caucasian	10.2	0.49	25 ml	Explant (Death)	7

2.0	Female	Caucasian	10.7	0.50	25/25 ml	Transplant	160
2.8	Female	Caucasian	9.5	0.48	25 ml	Death	79
4.9	Male	Caucasian	14.9	0.62	25 ml	Transplant	120
5.4	Male	Other	20.8	0.83	30/25 ml	Transplant	164
6.5	Female	Asian	21.5	0.80	25/25 ml	Death	0
6.7	Female	Caucasian	22.1	0.84	30/25 ml	Transplant	138
8.0	Female	Caucasian	27.0	0.99	30/30 ml	Death	119
10.1	Male	Caucasian	26.5	0.97	30 ml	On device	233
11.4	Male	Caucasian	23.0	0.91	30/30 ml	Death	14
11.5	Female	Other	50.0	1.47	60 ml	Death	28
11.5	Male	Caucasian	30.3	1.01	60/50 ml	Transplant	15
11.9	Female	Caucasian	32.5	1.15	50 ml	On device	238
12.0	Male	Unknown/ Undisclosed	43.0	1.35	50 ml	Death	6
12.2	Female	Caucasian	53.0	1.51	30 ml	Transplant	259
13.0	Male	Caucasian	59.4	1.63	60/60 ml	Transplant	48
13.4	Male	Caucasian	40.4	1.28	50 ml	Death	77
15.2	Male	Caucasian	70.0	1.76	60/50 ml	Transplant	8
15.7	Male	African American	40.8	1.39	60/50 ml	Transplant	9
16.3	Male	Caucasian	36.9	1.26	50/50 ml	Transplant	45
≥1 year summary	**2 explants, 3 on system, 9 deaths, 15 transplants, 1 patient weaned successfully**						

**as of 07/11/14*

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, 163 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 32 years of age.

The outcomes for these patients are summarized below:

Outcome	n/N	(%)

Transplant	114/163	(69.9%)
Weaned successfully	5/163	(3.1%)
Death	23/163	(14.1%)
Converted therapy to other support	8/163	(4.9%)
Currently on support	13/163	(8.0%)

PAS Assessment

Based on the CEC adjudicated outcomes, the primary safety endpoint is below the pre-specified performance goal of 0.10 SAEs per patient days. For example, the top 3 SAEs are major bleeding (0.0052 AEs per patient day), major infection (0.0049 AEs per patient day), and neurological dysfunction (0.0046 AEs per patient day). All are well below the performance goal. Patients with BSA $\geq 0.7m^2$ had overall higher incidence of SAEs (93.8%) than patients with BSA$\leq 0.7m^2$ (73.4%), which may indicate that large pump size is associated with higher incidence of SAEs. The top 3 SAEs in 23 patients with BSA $\leq 0.7m^2$ are major bleeding (8 patients, 34.8%), major infection (7 patients, 30.4%), and CVA (7 patients, 30.4%). The top 3 SAEs in 16 patients with BSA $\geq 0.7m^2$ are major bleeding (8 patients, 50.0%), major infection (7 patients, 43.8%), and CVA (6 patients, 37.5%). The SAE rates seen within the PAS sample are lower than or in line with the premarket studies where the top 3 SAEs in Cohort 1 patients (BSA$< 0.7\ m^2$) are major infection (62.5%), major bleeding (41.7%), and CVA (29.2%); and in Cohort 2 patients (BSA $\geq 0.7m^2$) are major infection (50.0%), major bleeding (50%), and CVA (35%). The average on support time in the PAS study (94.8 days) is much longer than that in the IDE study (55.6-58.8 days). CVA was also the leading cause of death in the PAS patient and in the IDE study. Five of 10 deaths in the PAS were due to CVA, less than that in the IDE study where CVA events were the primary cause of 3 of 4 deaths.

The primary effectiveness endpoint assesses transplant, recovery or death. The 39 subjects have been supported by the device from 0 to 374 days with an average time of 94.8 days (standard deviation=90.6) and median of 63 days (IQR=20, 160). The primary effectiveness endpoint will be summarized after all enrolled subjects have met an endpoint.

POSTMARKET DATA: LITERATURE REVIEW

Literature Review Presented at the 2013 PAC

In preparation for the 2013 PAC meeting, a search of the literature was conducted searching for articles published December 2011- June 2013. The results of that search are detailed below. The search 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 were summarized in the literature 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.[1,2] One study reported that 21% of 14 patients died while on support.[2] 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%.[3,4] 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%) [1]. Lower weight was also identified as a risk factor for late mortality (>2 months).[3]

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.[1-3] 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).[5] 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).[1,3,6] 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).[5] 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%, $P < 0.001$).[7]

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.[8] 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.[1] 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.

Updated Literature Review for the 2014 PAC
In June 2014, a search of the PubMed database for articles published since last literature update (June 2013) was conducted using prespecified criteria detailed above. This yielded 241 articles. The following limits were placed yielding 42 articles: publication date "from 06/01/2013 to 05/31/2014" and English. Upon several passes of the titles, abstracts and texts, 37 articles were excluded as follows: review or commentary (n=10), case report (n=15), non-human (n=1), treatment not specific to device (n=6), other (n=5). The remaining 5 articles are the subject of this review.

There was 1 prospective and 4 retrospective cohort studies. [9-13] Two studies were conducted in the United States, and the other three studies were conducted in Europe. The sample sizes ranged from 25 to 281 patients. The ages ranged from 0-17 years. The time on support ranged from 1-842 days. The age range and on-support time are similar to previous literature review. All five studies examined BTT only and evaluated the device in the left ventricular (LVAD) and biventricular (BVAD) positions.

Pediatrics (n=5)

Survival
While on VAD support, four studies reported recovery rate ranging from 0% for patients with

single ventricular anatomy to 19% for overall patients.[9-12] After receiving VAD implant, 42.4% to 87.2% of patients were reportedly survived to transplant, which was affected by the availability of donor organ, pre-existing condition, and physician experience. [9-12] The on-support mortality rates ranged from 7.7% to 32%. Cassidy et al. analyzed 102 children who received Berlin Heart support, 84% survived to transplant or successfully weaned from the device, and 81% of the patients survived to discharge.[11] The authors found neither age nor duration of support influenced outcome. Risk factors of on-support mortality include stroke, ongoing requirement for ventilation, and diagnosis other than dilated cardiomyopathy. Although the number of children treated with a BH increased over time (p-value=0.01), pediatric transplants per year have not increased significantly (p-value=0.07). These findings are consistent with those found in the previous literature review.

Safety

The most commonly reported complications were neurological events, thrombosis formation, infection, bleeding and renal failure, similar to previous reported adverse events. Depending on patient follow-up time, the rates of neurological events ranged from 25.4% to 80.7%.[9-12] 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).[12] Freedom from BI at 30, 60, and 90 days from VAD implantation was 80.7, 69.9, and 43.3%, respectively. Miera et al. found large pump size was associated with increased risk of thromboembolism.[11] Institution experience was inversely associated with the occurrence of cerebrovascular events.[11] The risk of cerebrovascular events is highest in the immediate postoperative period before therapeutic anticoagulation is achieved.[9]

The most common causes of death were reported as multiorgan failure, catastrophic strokes, respiratory failure, cardiac failure, and overwhelming sepsis. Multiorgan failure was reported as primary cause of death in two studies, representing 33.3% and 43.8% of all causes. Catastrophic strokes accounted for 20% and 37.5% of all causes of deaths.[10,13]

SUMMARY

Although the use of the Berlin Heart Excor Pediatric VAD prolongs survival to transplantation, it is associated with risks such as major bleeding, major infection, and neurological dysfunction. 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%) to precede thrombus (29-49%) and neurologic dysfunction occurred in 29-35% of premarket patients. The top 3 severe adverse events in the PAS are major bleeding (41.0%), major infection (35.9%), and neurological dysfunction (33.3%). The rates observed in literature and seen within the PAS sample are lower than or similar to the premarket studies. Consistent with finding from the premarket study and the literature, patients with BSA $\geq 0.7m^2$ had overall higher SAE rates than patients with $\leq 0.7m^2$, which may indicate that large pump size is associated with higher SAE rate. CVA is the leading cause of death in patient implanted with the device, accounting for 50% of 10 patient deaths in the PAS sample, which is lower than the premarket data (3 out of 4 deaths, 75%).

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Appendix A:
EXCOR® Pediatric PAS Serious Adverse Event Listing

ID, Implant Date	Event Adjudicated (Yes/No)	SAE	SAE Onset Date	Days to event	Treatment	Outcome, Date, (days of support)	Relatedness
035-201 01/03/13	Yes	Neuro-Hemorrhagic CVA	1/4/2013	1	Medication Rx (Ativan)	Transplant 06/12/13 (160 days)	Device, Procedure, Patient management, Concom meds
	Yes	Other: Seizure	1/4/2013	1	Medication Rx (Fosphenytoin)		Device, Procedure, Patient management, Concom meds
	Yes	Major Infection-Localized non-device	1/15/2013	12	Medication Rx (on antibiotics)		Patient management, Concom meds
	No	Other: Mediastinal exploration	1/18/2013	15	Surgical Rx (Mediastinal exploration)		Device
	No	Thromboembolism-Venous	3/4/2013	60	Medication Rx (Restarted heparin drip)		Patient management

014-201 03/13/13	No	Respiratory Failure	3/15/2013	2	Intubation/Other (Bronchoscopy)	Transplant 04/27/13 (45 days)	Patient management
	Yes	Major Bleeding	3/25/2013	12	Blood tx/Surgical Rx (Chest tube placed, bronchoscopy performed, bivalirubin concentration reduced)		Procedure, Concom meds
	No	Respiratory Failure	3/25/2013	12	Intubation		Patient management
	Yes	Major Bleeding	4/11/2013	29	Blood tx/Medication Rx (bivalirubin stopped for 12 hours, stopped aspirin)		Patient management, Concom meds
	Yes	Major Infection-Sepsis	4/12/2013	30	Medication Rx (Started on antibiotics)		Patient management
	No	Respiratory Failure	4/12/2013	30	Intubation		Patient management
022-201 03/21/13	Yes	Neuro-Ischemic CVA	4/4/2013	14	Intubation/Medication Rx (Ativan)	Explant 04/30/13 (40 days)3	Device, Procedure
	Yes	Neuro-Ischemic CVA	4/7/2013	17	Medication Rx (Phenobarbitol and PRN Ativan)		Device, Procedure
014-203 04/12/13	Yes	Major Infection-Sepsis	4/17/2013	5	Medication Rx (On antibiotics and anti-fungal)	Death 04/26/13 (14 days)	Procedure, Patient management
	Yes	Neuro-Hemorrhagic CVA	4/26/2013	14	Medication Rx (Heparin stopped)		Device

028-201 04/22/13	Yes	Major Bleeding	4/23/2013	1	Blood tx/Surgical Rx (Mediastinal exploration, evacuation of hematoma, broviac removal)	Transplant 11/16/13 (208 days)4	Procedure
	Yes	Neuro-Ischemic CVA (Right occipital (chronic))	6/20/2013	59	Medication Rx (ASA, Enoxaprin, Dipyridimole)		Device
	Yes	Neuro-Ischemic CVA (Left occipital)	6/20/2013	59	Medication Rx (ASA, Enoxaprin, Dipyridimole)		Device
016-201 05/23/13	Yes	Neuro-Ischemic/ Hemorrhagic	6/14/2013	22	Other (EEG Monitoring)	Death 06/20/13 (28 days)5	Device
	No	Other: Renal Insufficiency	6/15/2013	23	Dialysis		Patient management
010-201 05/26/13	Yes	Major Infection-Sepsis	5/21/2013	-5	Medication Rx (Vanco, cefepime, micafungin)	Transplant 09/08/13 (105 days)	Procedure, Patient management
	No	Right Heart Failure	5/27/2013	1	Surgical Rx/Other (RVAD)		Patient management

	Yes	Major Infection-Percutaneous site and/or pocket	7/1/2013	36	Medication Rx (Vancomycin, Cefepime)		Device, Patient management
	Yes	Major Infection-Percutaneous site and/or pocket	8/26/2013	92	Other (antibiotics, debridement, cleaning & packing of inflow cannula)		Device, Patient management
022-202 05/28/13	No	Hypertension	6/1/2013	4	Medication Rx (Nipride)	Transplant 07/06/13 (39 days)	Patient management
	No	Other: Ventricular Ectopy	6/2/2013	5	Medication Rx (Esmolol)		Device
	No	Respiratory Failure	6/5/2013	8	Intubation		Concom meds
	No	Pericardial effusion without tamponade	6/6/2013	9	Surgical Rx (Pericardial effusion drainage via sub-xiphoid approach)		Procedure
006-201 06/05/13	No	Hypertension	6/6/2013	1	Medication Rx (Nipride cont. infusion started 6/7/13)	Transplant 06/20/13 (15 days)	Patient management
	Yes	Major Bleeding	6/10/2013	5	Blood tx/Medication Rx/Surgical Rx (Persantin put on hold, Heparin drip stopped x2hrs; mediastinal exploration, large amt hematoma and pericardial effusion removed.)		Procedure, Patient management, Concom meds

	No	Respiratory Failure	6/11/2013	6	None		Patient management
037-201 06/28/13	Yes	Major Bleeding	7/1/2013	3	Blood tx/Surgical Rx (chest tube placement, exploration chest, transfusion)	Transplant 10/06/13 (100 days)	Procedure, Patient management, Concom meds
	No	Other: Atrial fibrillation	7/10/2013	12	Cardioversion or Defibrillation		Patient management
042-201 07/02/13	Yes	Major Infection-Percutaneous site and/or pocket	11/2/2013	123	Medication Rx (Vancomycin)	On device (374 days)	Device, Patient management
	Yes	Other: Covert stroke	12/4/2013	155	None		Device, Patient management
005-201 07/05/13	No	Pericardial effusion with tamponade	7/14/2013	9	Blood tx/Medication Rx/ Surgical Rx/ Other (Pericentesis)	Transplant 03/21/14 (259 days)	Patient management, Concom meds
	No	Psychiatric Episode	12/2/2013	150	Other (Psychotherapy sessions.)		Device, Concom meds
071-201 08/21/13	Yes	Neuro-Ischemic/ Hemorrhagic	8/26/2013	5	Medication/Other (TAT EEG and Neuro consult. Maintain Higher BP and lower Anti XA. 3% NaCl for goal Na 140-150 and pCO2 goal 35-40)	Death 10/15/13 (55 days)	Device, Procedure, Concom meds
	No	Right Heart Failure	9/3/2013	13	Surgical Rx (placement of RVAD to treat right sided heart failure)		Patient management
	No	Hepatic Dysfunction	9/9/2013	19	Not reported		Patient management

	Yes	Other: Covert stroke	9/24/2013	34	Not reported		Device, Patient management
	Yes	Major Bleeding	9/27/2013	37	Not reported		Patient management
	Yes	Major Bleeding	9/30/2013	40	Not reported		Patient management
023-201 08/30/13	Yes	Other: Seizure	8/30/2013	0	Intubation/Medication Rx (Ativan and fosphenotoin)	Transplant 04/16/14 (229 days)	Device
	No	Respiratory Failure	9/8/2013	9	Intubation		Patient management
	No	Right Heart Failure	9/13/2013	14	Cardiac cath/Surgical Rx (ECMO and PD cath placed)		Patient management
	Yes	Major Infection-Internal pump component, Inflow or Outflow tract	4/14/2014	227	Medication Rx (Amikacin, Vancomycin, Meropenem)		Device, Patient management
042-202 09/04/13	Yes	Neuro-Ischemic/ Hemorrhagic	9/18/2013	14	Other (Physical, Occupational and Speech Therapy)	Death 11/20/13 (77 days)	Device, Concom meds
	Yes	Major Infection-Sepsis	9/26/2013	22	Medication Rx (Cultures taken. Broad spectrum antibiotic coverage, fungal coverage, chest exploration and		Device, Procedure, Patient management

					washout/ debridement)		
	Yes	Major Bleeding	10/1/2013	27	Blood Tx		Procedure, Patient management, Concom meds
	Yes	Neuro-Ischemic/ Hemorrhagic	10/14/2013	40	None		Device, Concom meds
	No	Thromboembolism-Venous	10/19/2013	45	Medication Rx (Added plavix, but discontinued it because of no platelet effect)		Patient management
	No	Thromboembolism-Venous	10/20/2013	46	Medication Rx (added Clopidogrel/plavix, but stopped as it never showed any platelet inhibition.)		Patient management
004-202 09/16/13	Yes	Major Bleeding	9/19/2013	3	Blood tx/Other (Platelets transfused, steroids stopped, heparin initially reduced from 34 to 25 units, subsequently stopped, dipyridamole held, protonix continuous infusion started.)	Death 12/04/13 (79 days)	Procedure, Patient management, Concom meds
	No	Respiratory Failure	9/24/2013	8	Intubation		TBD
	Yes	Major Infection-Localized non-device	10/11/2013	25	Medication Rx		Patient management

	Yes	Other: Encephelopathy	11/21/2013	66	Medication Rx		Device, Patient management
	Yes	Major Infection- Percutaneous site and/or pocket	11/25/2013	70	Not reported		Device, Procedure, Patient management
001-201 09/19/13	Yes	Neuro-Ischemic CVA	9/22/2013	3	None	Death 09/25/13 (6 days)	Device, Procedure, Patient management
041-201 10/14/13	Yes	Major Bleeding	10/14/2013	0	Blood Tx	Transplant 11/03/13 (20 days)	Procedure, Patient management
042-203 11/14/13	Yes	Major Infection- Internal pump component, Inflow or Outflow tract	12/11/2013	27	Medication Rx (Vanco and zosyn started 12/11/13, rivampin added on 12/16/13)	Transplant 01/16/14 (63 days)	TBD
046-201 11/15/13	Yes	Major Bleeding	12/3/2013	18	Blood tx/Surgical Rx (cauterized areas of bleeding endoscopically in OR)	On device (238 days)	Patient management, Concom meds

	Yes	Major Bleeding	4/15/2014	151	Blood tx/Medication/Surgical Rx (APC (argon plasma coagulation) of oozing areas in pylorus via endoscopy, octreotide and protonix infusions)		Patient management, Concom meds
033-201 11/20/13	Yes	Major Bleeding	11/25/2013	5	Blood tx/Medication Rx (Heparin Stopped)	On device (233 days)	Patient management
	Yes	Major Infection-Percutaneous site and/or pocket	12/18/2013	28	Medication Rx (IV antibiotics)		Device, Procedure, Patient management
	Yes	Neuro-Ischemic CVA	3/20/2014	120	Surgical Rx (Clot in right middle cerebral artery removed but clot in right internal carotid artery not able to be removed, pt developed subarachnoid hemorrhage and hydrocephalous requiring externalized ventriculostomy)		Device, Patient management
008-202 12/06/13	Yes	Major Bleeding	12/6/2013	0	None	Death 12/07/13 (1 days)	Procedure, Patient management
007-202 12/19/13	Yes	Neuro-Ischemic CVA	1/3/2014	15	Blood tx/Medication Rx/Other (Cooled, paralyzed, sedated (Neuro protective therapy)	Transplant 03/07/14 (78 days)6	Device, Patient management
	No	Hypertension	1/4/2014	16	Medication Rx (Nipride and Sildenafil)		Device, Patient management

	Yes	Neuro-Hemorrhagic CVA	1/6/2014	18	Medication Rx/Other (Anticoagulation medications held; sedated, cooled paralyzed per neuro protection protocol, neurology consult)		Device, Patient management
006-202 12/23/13	Yes	Major Infection-Localized non-device	12/26/2013	3	Blood tx/Medication Rx/Other (Clindamycin was reinstituted, (pt previously treated for pos BAL before implant), and the PICC was Dc'd)	Transplant 12/31/13 (8 days)	Patient management
014-204 12/30/13	Yes	Major Bleeding	2/7/2014	39	Blood tx/Surgical Rx (Patient taken emergently to OR, placed on CBP and 5 min of circulatory arrest to identify and repair aortic leak)	Transplant 05/17/14 (138 days)7	Device
	Yes	Major Infection-Percutaneous site and/or pocket	4/21/2014	112	Blood tx/Medication Rx/Other (Dressing change, IV vancomycin and cefepime for 10 days)		Device, Patient management
014-205 01/08/14	No	Pericardial effusion without tamponade	1/22/2014	14	Other (Chest tube placed)	On device (184 days)	Device, Patient management
014-206 01/09/14	No	Pericardial effusion without tamponade	1/13/2014	4	Surgical Rx (1/30 pt returned to OR	Death 05/08/14	Concom meds

					for washout and clot removal. Chest tubes placed)	(119 days)	
	Yes	Neuro-Hemorrhagic CVA	3/8/2014	58	Blood tx/ Intubation/ Medication/ Surgical Rx (craniotomy, anticoagulation reversed and on hold)		Device, Patient management, Concom meds
	No	Hepatic Dysfunction	3/19/2014	69	Medication Rx (Stopped all medication that could have adverse effects. Feeding changed to low protein)		TBD
	No	Respiratory Failure	5/7/2014	118	Intubation/Medication Rx (increased lasix to control and reduce pulmonary edema)		Patient management
014-207 01/23/14	Yes	Major Bleeding	2/1/2014	9	Blood tx/Other (Chest tubes)	Transplant 07/06/14 (164 days)	Procedure, Patient management, Concom meds
	Yes	Major Infection-Sepsis	4/5/2014	72	Medication Rx (Antibiotics started)		Device
004-204 02/13/14	Yes	Major Infection-Localized non-device	2/18/2014	5	Medication Rx (Patient received 2 days of vancomycin and cefotaxime while cultures were pending. Then switched to piperacillin/tazobactam and gentamicin and completed 5 day course.)	Transplant 03/14/14 (29 days)	Unrelated

	Yes	Major Bleeding	2/20/2014	7	Blood Tx (Heparin was held. pRBCs transfused.)		Procedure, Patient management, Concom meds
028-204 **02/24/14**	Yes	Major Bleeding	2/24/2014	0	Blood tx/Surgical Rx (Mediastinal exploration (later in the day on 2/24/2014))	Transplant 06/24/14 (120 days)	Device, Procedure, Patient management
	Yes	Neuro-Hemorrhagic CVA	3/18/2014	22	Other (Withheld all anti-coagulation at this time.)		TBD
	No	Other: Left pneumothorax	3/23/2014	27	Surgical Rx (Chest Tube placement for left pneumothorax.)		Patient management
	No	Other: Acute Abdominal Pain	5/1/2014	66	Intubation/Medication/Surgical Rx (Diagnostic laparoscopy)		Patient management
004-201 **07/31/13**	Yes	Neuro-Ischemic CVA	7/31/2013	0	Medication Rx (clonzazepam, ativan, and clonidine; IV benzos and narcotics for comfort)	Escalated to ECMO Death (not adjudicated) <= 30 08/07/13 (7 days)	Device, Procedure, Pt Mgmt
	No	Other: septal hematoma	8/6/2013	6	Surgical Rx (Patient was converted to ECMO, chest irrigated with antibiotic irrigation (no obvious source of bleeding).)		Procedure, Pt Mgm
006-203	No	Hypertension	3/10/2014	0	Medication Rx (Nipride started @	Transplant 03/19/14	Pt Mgmt

03/10/14					1mcg/kg/min to be titrated to maintain MAP 75-95. Morphine continuous infusion increased.)	(9 days)	
	Yes	Other: Covert stroke	3/10/2014	0	None		Procedure, Pt Mgmt
	Yes	Major Bleeding	3/14/2014	4	Blood tx/Medication/Surgical Rx (Haparin was stopped/dc'd. Urology took to OR for cystoscopyw/ suprapubic tube placement into bladder. Volume boluses)		Pt Mgmt, Concom meds

Note:
3 MDR reported for this patient's ischemic event
4 MDR reported for this patient's ischemic event
5 MDR reported for this patient's ischemic event
6 MDR reported for this patient's ischemic event
7 MDR reported for this patient's major bleeding event