

DRAFT - FDA Questions for Circulatory System Devices Panel
July 21st, 2011
H100004 - Berlin Heart EXCOR® Pediatric Ventricular Assist Device (VAD)

1. Primary Effectiveness Endpoint Results

An HDE application must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. The Sponsor's pre-specified hypothesis test for the primary effectiveness endpoint was to compare the hazard rates of the EXCOR treatment group to the ECMO control group.

The Sponsor seems to have met the pre-specified primary effectiveness endpoint. The hazard ratio for the Cohort 1 comparison (unadjusted for matching) was 0.043 (p -value=0.004); and the hazard ratio for the Cohort 2 comparison (also unadjusted for matching) was 0.02 (p -value=0.004). However, these results may not have sufficiently adjusted for differences between the EXCOR and the ECMO patients.

The following table summarizes the success rates of Cohorts 1 and 2 as well as those for the ECMO control group.

Group	Total	No. Survived
Cohort 1 - ITT	24	21 (87.5%)
ECMO - Control Group	48	36 (75.0%)
Cohort 2 - ITT	24	22 (91.7%)
ECMO - Control Group	48	32 (66.7%)

The prespecified secondary endpoints included:

1. Days of transplant-eligible support; and
2. Ability to de-intensify concomitant hemodynamic support by analyzing the subject's 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.

Q1a. Please comment on the difference in success rates (survival to transplant or successful wean) between patients treated with the EXCOR and ECMO.

Q1b. Please comment on your interpretation of the secondary endpoint results.

2. Primary Safety Endpoint Results

The overall serious adverse event (SAE) rates and the upper bounds of the confidence interval for Cohort 1 and 2 study patients were below the pre-specified success criterion of 0.25 SAEs per patient day of support (shown in the table below). However, 33% of patients in both Cohorts 1 and 2 had neurologic complications, which occurred at a higher rate compared to other types of adverse events. This rate was also higher in Cohorts 1 CAP, 3A and 3B.

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 2	24	107	1376	0.078	0.094

Q2a. Please comment on the clinical significance of the stroke rate and neurologic outcomes that were observed in patients treated with the EXCOR.

Although pump change was not considered an adverse event for this study, 52.3% of patients implanted at IDE sites and 45.6% of all patients implanted at any site required one or more pump changes due to visible thrombus in the pump circuit. There was also a higher incidence of ischemic neurologic events in patients requiring a pump change (31.6%) compared to patients who did not receive a pump change (13.5%). A detailed examination of the available data did not reveal any specific events, anticoagulation deficiencies, or co-morbidities as contributing to the incidence of pump thrombus.

Q2b. Please comment on the clinical significance of pump changes including the high stroke rate that was observed in patients treated with the EXCOR® who required pump change for visible thrombus.

3. Labeling

The Sponsor has provided the following mortality information regarding patients who received pre-implant ECMO and those with single ventricle circulation:

Variable	Deaths for those who Passed Criterion	Deaths for those who Failed Criterion
	n/N (%)	n/N (%)
Two-ventricle Circulation (failed means single ventricle)	10/96 (10.4%)	6/13 (46.2%)
Pre-implant ECMO (failed means ECMO pre-implant)	669 (8.7%)	10/40 (25.0%)

These data show that the incidence of mortality increased in patients receiving pre-implant ECMO and in patients with single ventricle circulation.

Q3a. Please discuss whether additional language should be included in the labeling regarding patients with single ventricle circulation and those who have had use of pre-implant ECMO. Such language may include data regarding increased mortality in these patients.

In addition to the survival data for IDE study patients, the Sponsor also provided the overall mortality rates, summarized by cohort and site of implant in the table below. FDA has noted several observations regarding the mortality data related to each of the subgroups at IDE and non-IDE sites.

- Subjects enrolled at IDE sites according to strict eligibility criteria (Cohorts 1 and 2, and Cohort 1 CAP) had the lowest observed mortality rate.
- Subjects enrolled into CU/EU cohorts 3A or 3B at any site had higher observed mortality rate compared to the primary study populations of Cohorts 1, 1 CAP, and 2.
- Total mortality rates in CU/EU patients may have been affected by the IDE versus non-IDE status of each site of implantation.
- Total mortality rates in CU/EU patients may also have been affected by whether subjects met or did not meet all protocol eligibility criteria.

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

Q3b. Please comment on how these data should be incorporated into the labeling, including your recommendations regarding the scope of any training program with regard to implant techniques, patient selection, recognition, treatment, and minimization of adverse events, etc.

4. Post-Approval Study (PAS)

The current post-approval study proposes following participants (n=24) until transplant or recovery. The longer-term (~5 year) clinical outcomes of the participants following explant of the device are not captured. According to the clinical study, the median time on device for Cohorts 1 and 2 was 27.5 and 42.5 days (respectively).

Q4a. Please comment on an appropriate comparator for this study given the limitations of the ELSO registry. For example, please discuss whether the current IDE EXCOR cohort would be appropriate.

Q4b. Given the high rate of neurologic dysfunction in patients treated with the EXCOR device, please comment on the need for data regarding longer-term neurologic and health related quality of life (HRQOL) outcomes.

Q4c. Please discuss the need for longer-term evaluation of the causes and incidence of pump thrombus and its effects on central nervous system (CNS) morbidity.

Q4d. Please discuss whether an overall AE rate of less than 0.25 SAEs per patient day on support remains appropriate given that the new proposed comparator may be SAE rates derived from patients in the EXCOR IDE study.

Q4e. Please discuss any other additional topics you believe are pertinent to the continued evaluation of risk and benefit for this device.

5. Safety and Probable Benefit

Q5. Based upon the study results, please discuss whether you believe the overall data demonstrate a reasonable assurance of safety and probable benefit for the EXCOR in the intended patient population. Please discuss all of the key factors that influence your assessment.