Berlin Heart EXCOR® Pediatric Ventricular Assist Device

FDA Review of H100004

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Division of Cardiovascular Devices

Office of Device Evaluation

Food and Drug Administration

Circulatory System Devices Panel Meeting

July 21, 2011

FDA Team Presenters

- Shreya Mehta, MS – Lead Reviewer
  Introduction and Pre-clinical Considerations
- John Laschinger, MD – Medical Officer
  Clinical Trial Design & Outcomes
- Terri Johnson, PhD – Mathematical Statistician
  Statistical Outcomes & Challenges
- Veronica Sansing, PhD, MS – Epidemiologist
  Post-Approval Study Considerations
- Shreya Mehta, MS – Lead Reviewer
  Conclusions

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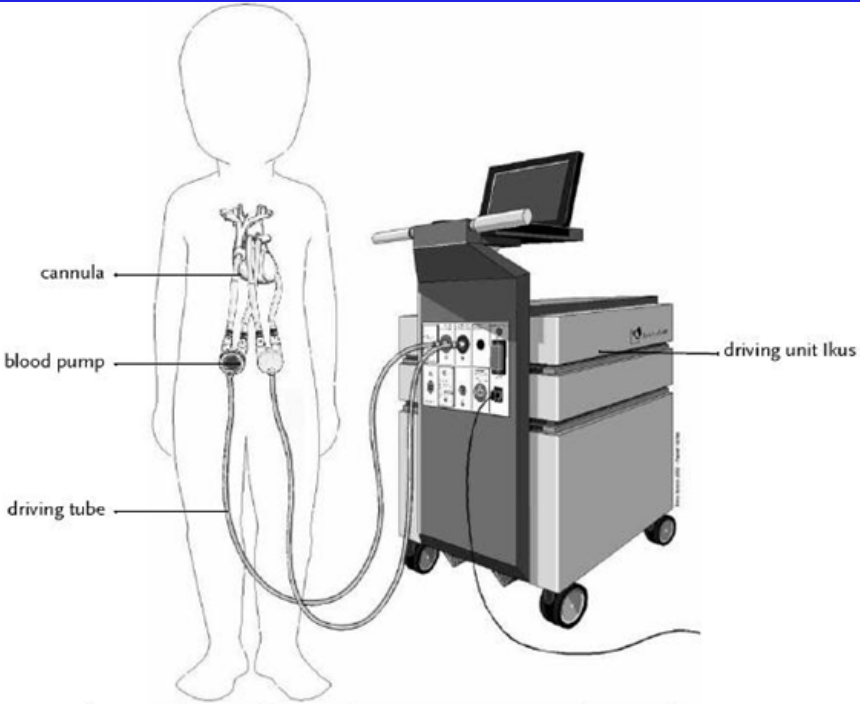
Proposed Indications for Use

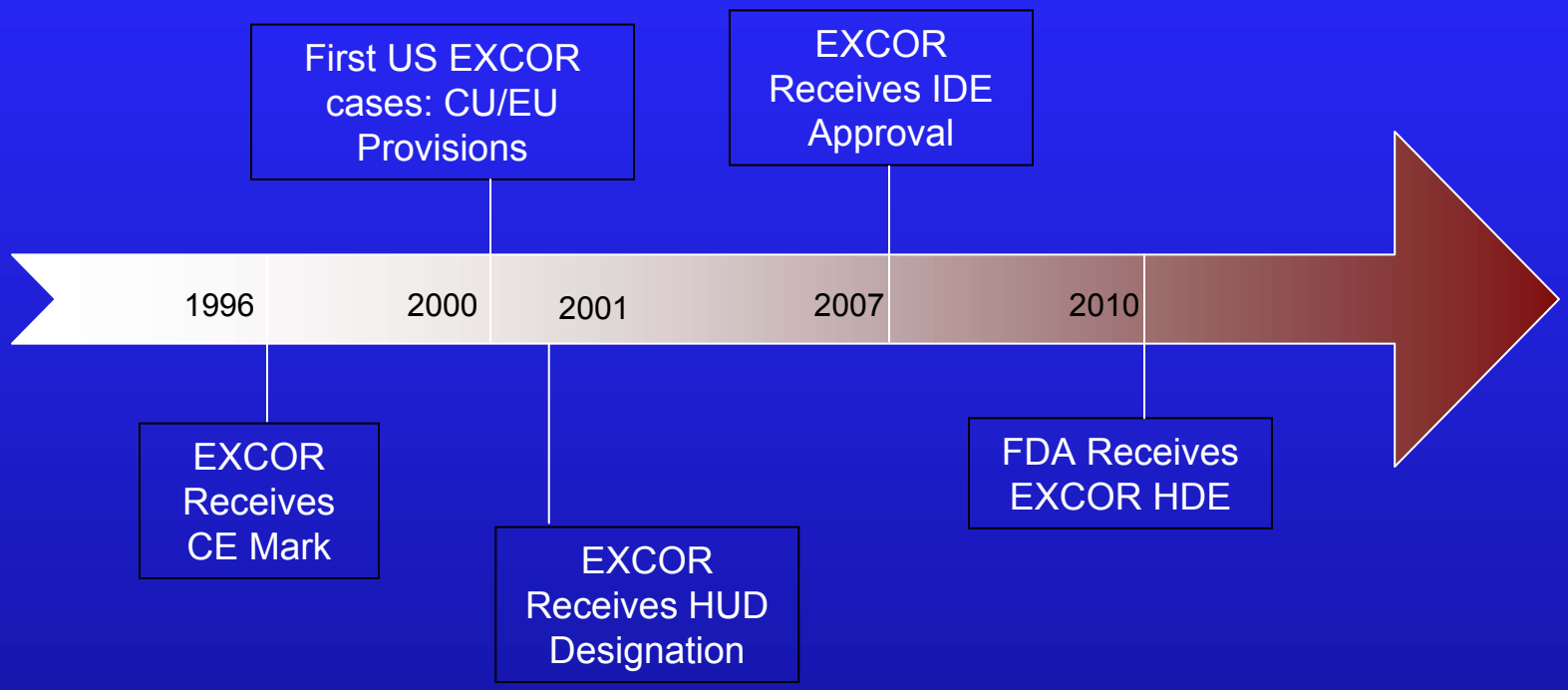
The EXCOR Pediatric Ventricular Assist Device (VAD) is intended to provide mechanical circulatory **support as a bridge to cardiac transplantation for pediatric patients**. Pediatric candidates with severe isolated left ventricular or biventricular dysfunction who are candidates for cardiac transplant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

Device Description

- 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
- IKUS driving unit



Regulatory History



FDA Pre-Clinical Review Team

- Engineering
  - Brian Fitzgerald
  - Michael Long, PhD
  - Jean Rinaldi
  - Jeffrey Silberberg
  - Changfu Wu, PhD
- Animal Review
  - Michael John, MPH
- Biocompatibility
  - Anchal Kaushiva, MS
- Sterilization, Shelf Life & Packaging
  - Lisa Kennell

Pre-Clinical Studies

- Structural integrity of the components, joints, and cannulae
- Fluid Characterization
- Biocompatibility
- Electromagnetic Compatibility (EMC) & Electrical Safety
- Software Verification & Validation

Results from the bench studies supported the anticipated/intended performance of the device in the clinical environment.

Animal Study Data

- Animal study data were not provided by the Sponsor for review
  - OUS data does not generally mitigate the need for animal studies
  - EXCOR had extensive and numerous OUS clinical experiences
  - Animal data would likely not have provided any additional information for this device

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John C. Laschinger, M.D.

Medical Officer

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Presentation Outline

- Summary of Clinical Trial
- Principal Inclusion/Exclusion Criteria
- Patient Demographics
- Enrollment and Implant Summary
- Primary and Secondary Effectiveness Endpoints
- Primary Safety Endpoint
- Additional Pre-Specified Analyses and FDA Requested Analyses
- Overall Interpretation of Safety and Probable Benefit
- Conclusions

Berlin Heart EXCOR Pediatric Ventricular Assist Device

Summary of the Clinical Trial

Clinical Study Design

- Purpose: To show that EXCOR Pediatric demonstrates reasonable assurance of safety and probable benefit for bridge-to-transplantation
- Clinical Study:
  - A prospective, multi-center, single arm study
  - Two primary study cohorts based on BSA (Cohorts 1 and 2)
    - Safety determination based on comparison to a performance goal
    - Effectiveness determination based on a survival comparison to historical ECMO controls

Additional Clinical Use

- Provided supportive data only
- Additional cohorts
  - Compassionate/Emergency (CU/EU) Use patients
    - Stratified by BSA – small and large
    - Implanted at:
      - IDE sites - subjects who failed to meet entry criteria
      - Non-IDE sites – all patients whether or not entry criteria met
  - Continued Access Protocol (CAP) – small BSA patients
    - At IDE sites
    - Strict eligibility requirements met

Berlin Heart EXCOR Pediatric Ventricular Assist Device

Principal Inclusion and Exclusion Criteria

Inclusion Criteria - Overview

- Age and weight appropriate
- Critical or worsening cardiogenic shock
  - Unresponsive to (or worsening despite) optimal medical management
  - Progressive end-organ dysfunction
  - Progressive functional deterioration – mental, ambulation
- Need for ECMO or inability to wean from bypass following corrective open heart surgery
- Two ventricle circulation
- Listed for transplant (UNOS 1A)

Exclusion Criteria - Overview

- ECMO ≥ 10 days
- Unfavorable cardiac anatomy
  - Single ventricle
  - Restrictive cardiomyopathies
  - Uncorrected hemodynamically significant CHD
  - AI/PI or mechanical aortic valve
- Intrinsic renal, hepatic or pulmonary disease
- Hematologic, clotting, immune or malignant disorders
- Stroke within 30 days

Berlin Heart EXCOR Pediatric Ventricular Assist Device

Patient Demographics

Patient Demographics

Variable	Category	Cohort 1 n=24	Cohort 2 n=24
Gender	Female	12 (50.0%)	11 (45.8%)
	Male	12 (50.0%)	13 (54.2%)
Age (months)	Mean ± Std (N)	15.4 ± 12.4 (24)	113.2 ± 37.6 (24)
	Median	11.7	111.2
	Min – Max	2.6 - 45.6	50.8 - 191.8
Age Group	0 - 30 days	0 (0.0%)	0 (0.0%)
	30 days – 2 Years	20 (83.3%)	0 (0.0%)
	2 to 10 years	4 (16.7%)	14 (58.3%)
	10 to 16 years	0 (0.0%)	10 (41.7%)
BSA (m^2)	Mean ± Std (N)	0.43 ± 0.10 (24)	1.09 ± 0.29 (24)
	Median	0.44	1.08
	Min – Max	0.23 - 0.62	0.71 - 1.66 [vii]
Height (cm)	Mean ± Std (N)	75.0 ± 12.0 (24)	135.5 ± 19.7 (24)
	Median	73.0	137.5
	Min – Max	51.0 - 103.0	104.0 - 171.0
Weight (kg)	Mean ± Std (N)	9.1 ± 2.7 (24)	32.2 ± 12.5 (24)
	Median	9.2	30.7
	Min – Max	3.6 - 13.6	16.0 – 58.1
Patient Profile/Status	1 Critical Cardiogenic Shock	11 (45.8%)	13 (54.2%)
	2 Progressive decline	13 (54.2%)	11 (45.8%)
	3 Stable but Inotrope dependent	0 (0.0%)	0 (0.0%)
	4 Recurrent advanced heart failure	0 (0.0%)	0 (0.0%)
	7 Advanced NYHA Class 3	0 (0.0%)	0 (0.0%)

Berlin Heart EXCOR Pediatric Ventricular Assist Device

Implantation Summary and Cohorts

Overall Number of Implants

Total Implants

June 21, 2007 – December 20, 2010

n = 204

BSA < 0.7m²				0.7m² ≤ BSA < 1.5m²		
n = 151				n = 53		
Cohort 1 **Primary Study Group** **n=24**	Cohort 1 CAP n=20	IDE Cohort 3A CU/EU n=35	Non-IDE Cohort 3A CU/EU n=72	**Cohort 2** **Primary Study Group** **n=24**	IDE Cohort 3B CU/EU n=6	Non-IDE Cohort 3B CU/EU n=23
Tx n = 21	Tx n = 16	Tx n = 20	Tx n = 31	Tx n = 21	Tx n= 4	Tx n = 17
Weaned n=1	Weaned n=0	Weaned n=3 (2/3 Failed)	Weaned n=6*	Weaned n=1	Weaned n=1	Weaned n=0
Death n=2	Death n=1	Death n=10	Death n=32	Death n=2	Death n=1	Death n=3
On Device n=0	On Device n=3	On Device n=2	On Device n=3	On Device n=0	On Device n=0	On Device n=3

Total Number of Implants
Small BSA

Total Implants

June 21, 2007 – December 20, 2010

n = 204

BSA < 0.7m²

n = 151

0.7m² ≤ BSA < 1.5m²

n = 53

Cohort 1 Primary Study Group n=24	Cohort 1 CAP n=20	IDE Cohort 3A CU/EU n=35	Non-IDE Cohort 3A CU/EU n=72	Cohort 2 Primary Study Group n=24	IDE Cohort 3B CU/EU n=6	Non-IDE Cohort 3B CU/EU n=23
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Death n=2	Death n=1	Death n=10	Death n=32	Death n=2	Death n=1	Death n=3
On Device n=0	On Device n=3	On Device n=2	On Device n=3	On Device n=0	On Device n=0	On Device n=3

Total Number of Implants
Large BSA

Total Implants

June 21, 2007 – December 20, 2010

n = 204

BSA < $0.7m^2$	$0.7m^2 \leq$ BSA < $1.5m^2$
n = 151	n = 53

Cohort 1 Primary Study Group n=24	Cohort 1 CAP n=20	IDE Cohort 3A CU/EU n=35	Non-IDE Cohort 3A CU/EU n=72	Cohort 2 Primary Study Group n=24	IDE Cohort 3B CU/EU n=6	Non-IDE Cohort 3B CU/EU n=23
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Death n=2	Death n=1	Death n=10	Death n=32	Death n=2	Death n=1	Death n=3
On Device n=0	On Device n=3	On Device n=2	On Device n=3	On Device n=0	On Device n=0	On Device n=3

Primary Study Group Enrollment

Total Implants

June 21, 2007 – December 20, 2010

n = 204

BSA < $0.7m^2$				$0.7m^2 \leq$ BSA < $1.5m^2$		
n = 151				n = 53		
Cohort 1 **Primary Study Group** **n=24**	Cohort 1 CAP n=20	IDE Cohort 3A CU/EU n=35	Non-IDE Cohort 3A CU/EU n=72	**Cohort 2** **Primary Study Group** **n=24**	IDE Cohort 3B CU/EU n=6	Non-IDE Cohort 3B CU/EU n=23
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Death n=2	Death n=1	Death n=10	Death n=32	Death n=2	Death n=1	Death n=3
On Device n=0	On Device n=3	On Device n=2	On Device n=3	On Device n=0	On Device n=0	On Device n=3

Total Number of Implants
All IDE Sites

Total Implants

Total IDE Site
n=109

BSA <
n =

≤ BSA < 1.5m²
n = 53

Cohort 1 Primary Study Group n=24	Cohort 1 CAP n=20	IDE Cohort 3A CU/EU n=35	Non-IDE Cohort 3A CU/EU n=72	Cohort 2 Primary Study Group n=24	IDE Cohort 3B CU/EU n=6	Non-IDE Cohort 3B CU/EU n=23
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Death n=2	Death n=1	Death n=10	Death n=32	Death n=2	Death n=1	Death n=3
On Device n=0	On Device n=3	On Device n=2	On Device n=3	On Device n=0	On Device n=0	On Device n=3

Total Number of Implants
All Non- IDE Sites

Total Implants

June 21, 200

Total Non-IDE Site
n=95

BSA < 0.7m^2

n = 151

n = 53

Cohort 1 Primary Study Group n=24	Cohort 1 CAP n=20	IDE Cohort 3A CU/EU n=35	Non-IDE Cohort 3A CU/EU n=72	Cohort 2 Primary Study Group n=24	IDE Cohort 3B CU/EU n=6	Non-IDE Cohort 3B CU/EU n=23
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Death n=2	Death n=1	Death n=10	Death n=32	Death n=2	Death n=1	Death n=3
On Device n=0	On Device n=3	On Device n=2	On Device n=3	On Device n=0	On Device n=0	On Device n=3

Berlin Heart EXCOR Pediatric Ventricular Assist Device

Primary and Secondary Effectiveness Endpoints

Primary Effectiveness Endpoint

Effectiveness – Overall Survival:

- The objective of the study was to demonstrate that the **survival** in subjects treated with the EXCOR Pediatric was different from the survival in the historical control subjects treated with ECMO as a means of mechanical circulatory support (MCS)

Pre-Specified Hypothesis Test:

$$H_0 : HR \geq 1$$

$$\text{vs.}$$

$$H_1 : HR < 1,$$

HR is the expected hazard ratio of EXCOR against ECMO

Comparator for Effectiveness: Why ECMO (ELSO) Historical Controls?

- No approved or cleared pediatric VADs
- ECMO: Current standard of care for pediatric MCS
  - Not approved or cleared for BTT
  - ELSO Registry – Historical Controls
    - Determination of Survival
    - Propensity matching (n=48 per Cohort, 2:1 matching)
    - Patients treated after 2000
- Limitations of ELSO registry use:
  - Patients may not be appropriately matched
  - Definition of outcome/recovery/success different for EXCOR and ECMO
  - ELSO does not capture events after explant (transplantation, neurologic status, etc.)
- Details of the PSA matching to be discussed in the statistical review presentation

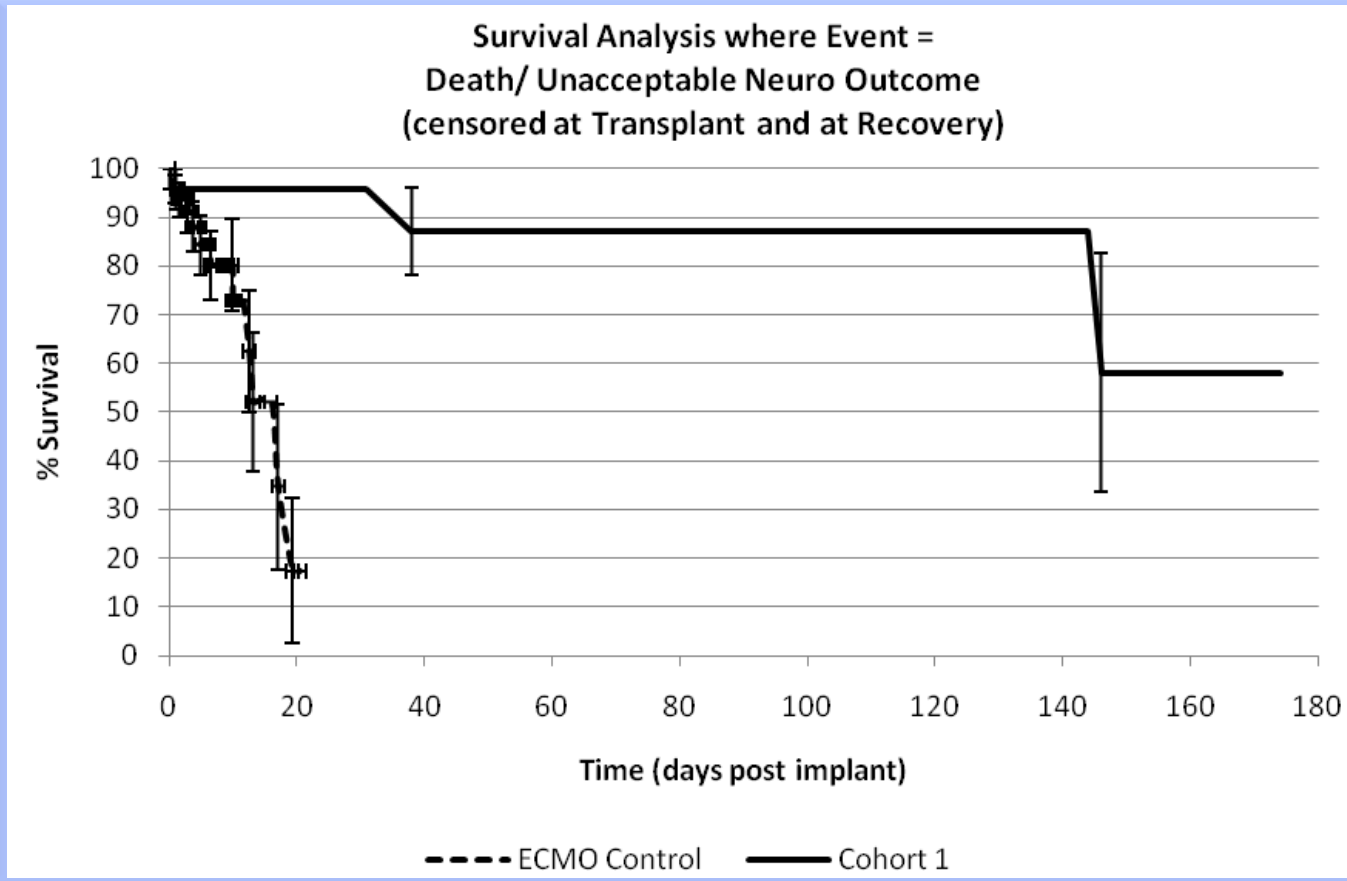
Differences in Definitions

	EXCOR	ECMO
Endpoint	*Death on device or survival to transplant or recovery*	*Death or recovery*
Recovery	*Survival with an acceptable neurological outcome 30 days post explant or to discharge, whichever is later (i.e.* ***successful wean****)*	*Survival for 30 days after being weaned from support*
Success	*Survival to transplant or recovery*	*Recovery*
Failure	*Death, or…* ***Failed wean****:* *•Death within 30 days of explant or prior to hospital discharge, whichever is later* *•Survival post explant with an unacceptable neurologic outcome*	*Death on device or within 30 days of being weaned from support*

Primary Effectiveness Endpoint

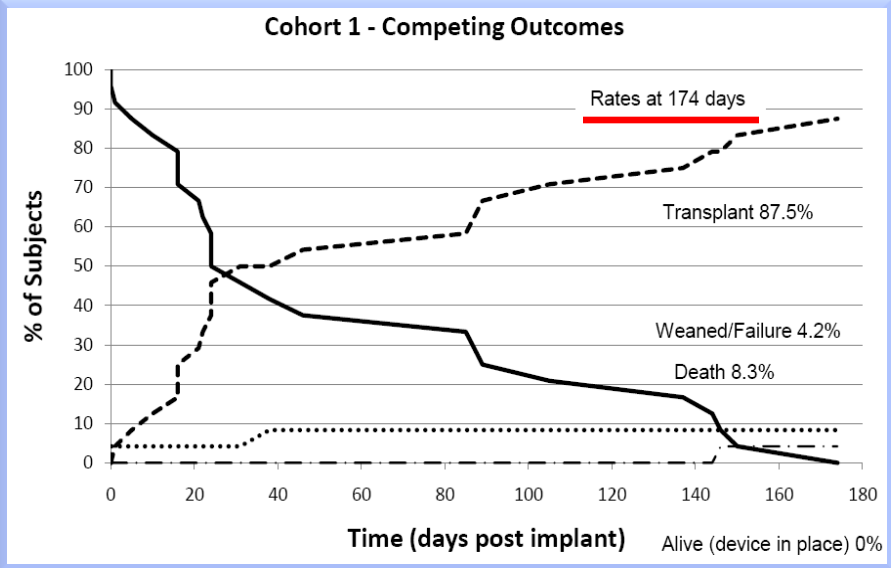
- Clinical survival and outcome data reviewed:
  - Kaplan-Meier Survival Curves, Competing Outcomes data
    - Pre-specified cohorts – separated by BSA
    - *Post hoc* cohorts – separated by age (<, or ≥ 4 yrs)
      - Did not change composition of primary study groups
      - New ECMO comparator groups
      - Provided further information to judge clinical benefit
      - Data presented by sponsor
- Pre-specified hazard ratio comparison not submitted by the Sponsor
  - FDA conducted independent analysis
  - FDA Statistical Reviewer will present FDA analysis on pre-specified hypothesis test

Survival Analysis - Cohort 1

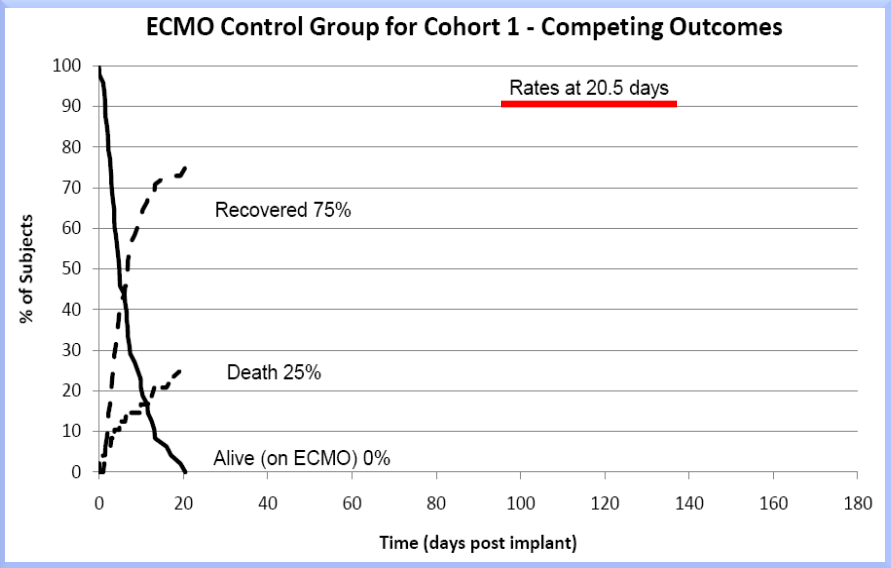


Competing Outcomes - Cohort 1

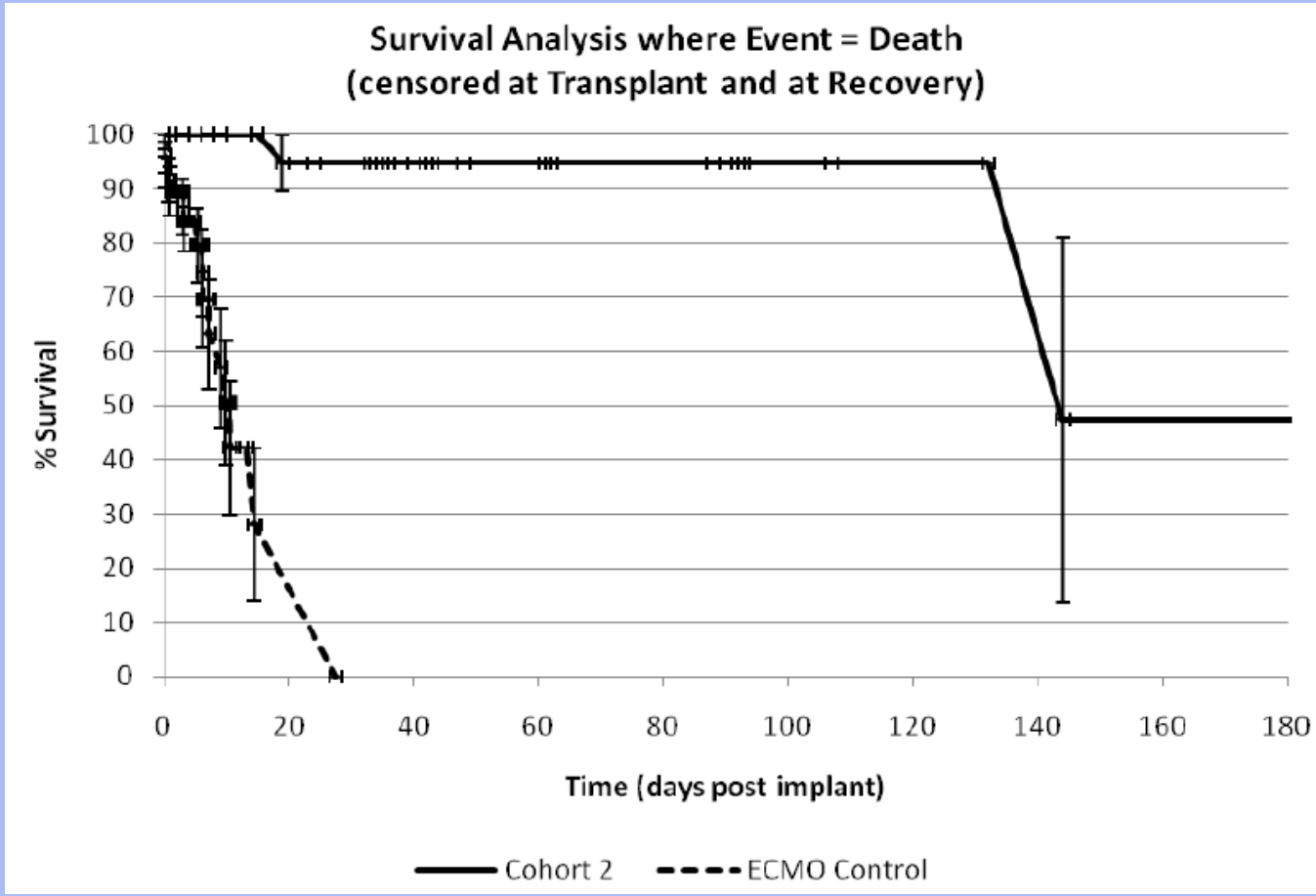
EXCOR



ECMO Controls

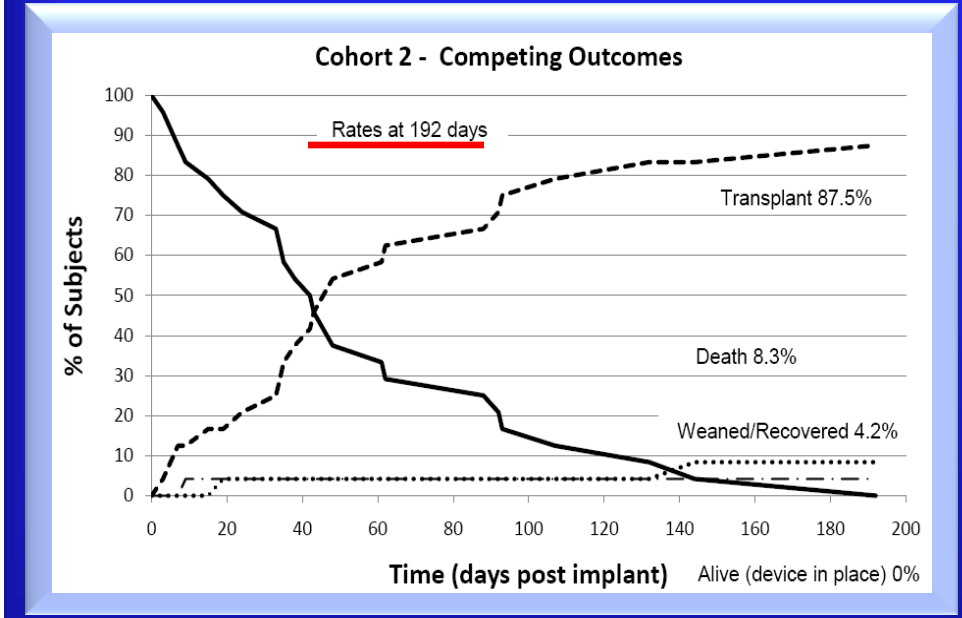


Survival Analysis - Cohort 2

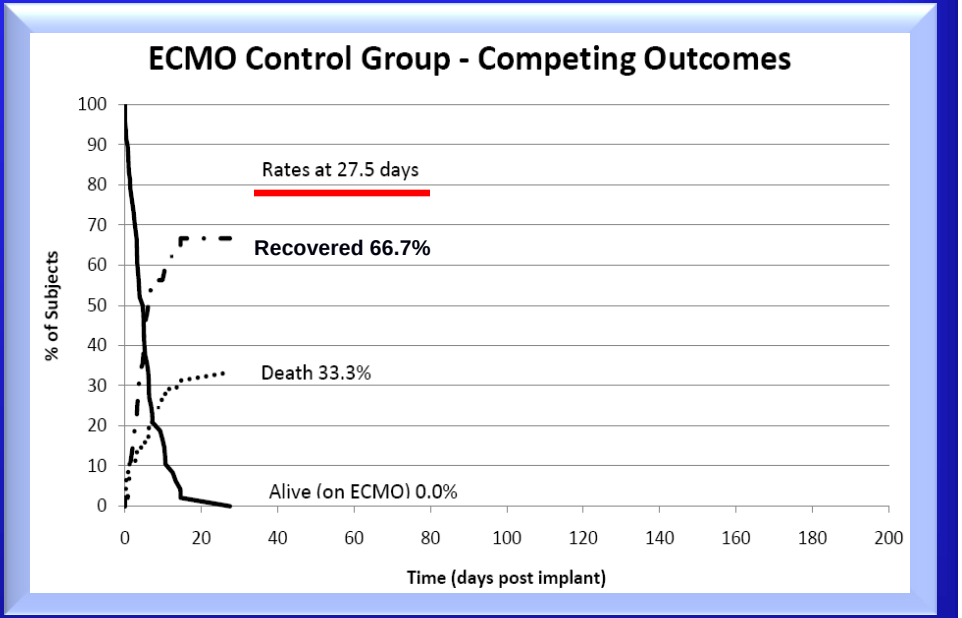


Competing Outcomes - Cohort 2

EXCOR



ECMO Controls



Primary Effectiveness Endpoint Conclusion

Primary Effectiveness Determination:

- Use of historical controls - problematic
- Based upon clinically relevant data
  - EXCOR provided clinically important benefits in survival rate and time vs. ECMO
  - These survival differences are critical for use for a BTT indication

Pre-Specified Secondary Effectiveness Endpoints

- Days of transplant-eligible support
- Ability to de-intensify concomitant hemodynamic support by analyzing the subjects status with respect to whether the subject is:
  - Awake
  - Ambulating
  - Sedated
  - Intubated
  - On ECMO or another assist device
  - Eating

* Descriptive Statistics Only

Secondary Effectiveness Endpoints

- Days of transplant eligible support (99.3%)
  - No accounting for real or potential organ refusal due to temporary clinical status
  - Ability to de-intensify concomitant hemodynamic support
    - Trend towards decreased levels of support over time was noted
- Sponsor has met secondary effectiveness endpoints

Essential Features of Mechanical Support Devices Used for BTT

- Survival
- Prolonged support
- Preservation of transplant eligibility
- Ability to de-intensify concomitant support

The Panel will be asked whether the data submitted and reviewed regarding these 4 key features of primary and secondary effectiveness are sufficient for demonstration of probable benefit for use of the EXCOR device for a BTT indication in children

Berlin Heart EXCOR Pediatric Ventricular Assist Device

Primary Safety Endpoint

Primary Safety Endpoint

Safety:

- The primary objective of the study was to summarize the serious adverse events rate calculated as the number of SAEs per patient-day of support on EXCOR Pediatric.

SAE Rate Performance Goal:

- The objective of the primary safety was to compare the SAE rate in EXCOR treated patients to a performance goal of 0.25 events per patient-day of support

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

Safety Endpoint Considerations

- No approved or cleared pediatric VADs for comparison
- ECMO
  - No approved or cleared devices
  - ELSO Registry - direct comparison of serious adverse events (SAEs) not possible
    - Non-monitored/adjudicated
    - Voluntary
    - Discordant definitions for SAEs
- INTERMACS
    - Adult VAD registry
    - Basis for standardized SAE definitions in study subjects

Primary Safety Endpoint: All IDE Patients

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

* < 0.25 SAEs per patient day of support

Does Pre-Implant ECMO Effect on SAE Event Rate?

Group	ECMO Pre-implant	N	Events per day on device
Cohort 1	Yes	6	0.11 events per day (38 SAEs/345 total days)
	No	18	0.05 events per day (58 SAEs/1066 total days)
Cohort 2	Yes	8	0.10 events per day (43 SAEs/450 total days)
	No	16	0.07 events per day (64 SAEs/926 total days)

2.2 X

Does Pre-Implant ECMO Effect on SAE Event Rate?

Group	ECMO Pre-implant	N	Events per day on device
Cohort 1	Yes	6	0.11 events per day (38 SAEs/345 total days)
	No	18	0.05 events per day (58 SAEs/1066 total days)
Cohort 2	Yes	8	0.10 events per day (43 SAEs/450 total days)
	No	16	0.07 events per day (64 SAEs/926 total days)

1.4 X

Primary Safety Endpoint

- Sponsor has met primary safety endpoint
  - Total SAE rate < 0.25 events per day of support
  - Upper bound of 95% CI < 0.25 events per day

The Panel will be asked whether safety sufficient for approval for use of the EXCOR device for a BTT indication in children has been demonstrated

Berlin Heart EXCOR Pediatric Ventricular Assist Device

Additional Supportive Analyses
(Pre-Specified)
and
FDA Requested Analyses

Supportive Analyses

- Transfusion Requirements – The total number and amount of transfusions that a subject received
- EXCOR Performance
  - System parameters including the rate, systolic pressure, diastolic pressure, and systolic percent
  - Filling and emptying of the blood pumps according to defined states (complete/almost complete, incomplete, poor, or unknown) on a regular basis
- Neurological Status – Assessed using the Pediatric Stroke Outcomes Measure (PSOM).
- Quality of Life / Neurodevelopmental Assessment – Assessed with the Pediatric Quality of Life Generic Module (PedsQL).

* Descriptive Statistics Only

Supportive Analyses: Pump Performance and Transfusion Requirements

- Transfusion requirements within expected ranges for all blood products
- Pump performed well
  - No failures or unanticipated adverse events
  - Hemodynamics remained within expected ranges
  - Pump filling and emptying as expected

FDA Requested Analyses

- FDA requested additional data from the Sponsor in four key areas to further understand risk/benefit profile

  I. Mortality in Non-Primary Implant Groups
  II. Stroke and Neurologic Status and Outcomes
  III. Health Related Quality of Life Data
  IV. Pump Thrombus

FDA will be seeking panel input regarding each of these four areas and their implications for:

- Approval
- Labeling for a broader BTT indication
- Requirements for training programs
- Post-approval study goals

Berlin Heart EXCOR Pediatric Ventricular Assist Device

I. Mortality Data

Total Mortality: All Patients

Total Implants

June 21, 2007 – December 20, 2010

n = 204

BSA < 0.7m²				BSA ≥ 0.7m² < 1.5m²		
n = 151				n = 53		
Cohort 1 Primary Study Group n=24	Cohort 1 CAP n=20	IDE Cohort 3A CU/EU n=35	Non-IDE Cohort 3A CU/EU n=72	Cohort 2 Primary Study Group n=24	IDE Cohort 3B CU/EU n=6	Non-IDE Cohort 3B CU/EU n=23
Tx n = 21	Tx n = 16	Tx n = 20	Tx n = 31	Tx n = 21	Tx n= 4	Tx n = 17
Weaned n=1	Weaned n=0	Weaned n=3 (2/3 Failed)	Weaned n=6	Weaned n=1	Weaned n=1	Weaned n=0
Death n=2	**Death n=1**	**Death n=10**	**Death n=32**	**Death n=2**	**Death n=1**	**Death n=3**
On Device n=0	On Device n=3	On Device n=2	On Device n=3	On Device n=0	On Device n=0	On Device n=3

Total Mortality and Failed Weans: All Patients

Total Mortality: 51/204 = 25.0%

- Total Death or Failure (includes failed weans): 55/204 = **26.9%**

* Status of 6 weans unknown

Cohort 1 Primary Study Group n=24	Cohort 1 CAP n=20	IDE Cohort 3A CU/EU n=35	Non-IDE Cohort 3A CU/EU n=72	Cohort 2 Primary Study Group n=24	IDE Cohort 3B CU/EU n=6	Non-IDE Cohort 3B CU/EU n=23
Tx n = 21	Tx n = 16	Tx n = 20	Tx n = 31	Tx n = 21	Tx n= 4	Tx n = 17
Weaned n=1	Weaned n=0	Weaned n=3 **(2/3 Failed)**	Weaned n=6*	Weaned n=1	**Weaned n=1**	Weaned n=0
Death n=2	**Death n=1**	**eath n=10**	**Death n=32**	**Death n=2**	**Death n=1**	**Death n=3**
On Device n=0	On Device n=3	D On Device n=2	On Device n=3	On Device n=0	On Device n=0	On Device n=3

Mortality in EXCOR Patients: Observation 1

- Low mortality is observed when:
  - Device is implanted at experienced centers and
  - Requirements for use include strict inclusion/exclusion criteria

Total Mortality and Failed Weans: Strict Entry Criteria IDE Site Patients

Total: 6/68 = 8.8%

- Cohort 1 12.5%
- Cohort 1 CAP 5.0%
- Cohort 2 8.3%

0

B A ≥ 0.7m² < 1.5m²

n = 53

Cohort 1 Primary Study Group n=24	Cohort 1 CAP n=20	IDE Cohort 3A CU/EU n=35	Non-IDE Cohort 3A CU/EU n=72	Cohort 2 Primary Study Group n=24	IDE Cohort 3B CU/EU n=6	Non-IDE Cohort 3B CU/EU n=23
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Death n=2	Death n=1	Death n=10	Death n=32	Death n=2	Death n=1	Death n=3
On Device n=0	On Device n=3	On Device n=2	On Device n=3	On Device n=0	On Device n=0	On Device n=3

Mortality in EXCOR Patients: Observation 2

- At experienced centers (all-IDE sites), the rate of death or failure was substantially higher in patients not meeting strict eligibility criteria when compared to patients who did
- Predictors of mortality included:
  - Single ventricle circulation
  - Any pre-implant use of ECMO

Total Mortality and Failed Weans: IDE Site Patients

Total Implants

Total: 20/109 = 18.3%

- Eligibility Criteria Met (All Cohorts): (8/81), **9.9%**
- Criteria not met – CU and EU (3A and 3B): (12/28), **42.3%**

5m²

Cohort 1 Primary Study Group n=24	Cohort 1 CAP n=20	IDE Cohort 3A CU/EU n=35	Non-IDE Cohort 3A CU/EU n=72	Cohort 2 Primary Study Group n=24	IDE Cohort 3B CU/EU n=6	Non-IDE Cohort 3B CU/EU n=23
Tx n = 21	Tx n = 16	Tx n = 20	Tx n = 31	Tx n = 21	Tx n= 4	Tx n = 17
Weaned n=1	Weaned n=0	Weaned n=3 (2/3 Failed)	Weaned n=6*	Weaned n=1	Weaned n=1	Weaned n=0
Death n=2	Death n=1	Death n=10	Death n=32	Death n=2	Death n=1	Death n=3
On Device n=0	On Device n=3	On Device n=2	On Device n=3	On Device n=0	On Device n=0	On Device n=3

What Pre-Implant Factors Increase the Risk of Mortality? IDE Site Analysis

Variable	Deaths for those who Passed Criterion n/N (%)	Deaths for those who Failed Criterion 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)	6/69 (8.7%) →	10/40 (25.0%)

Mortality in EXCOR Patients: Observation 3

- For all CU/EU patients
  - Total mortality and failed wean:
    - Was high
    - Was not affected by the site of implantation (IDE vs. non-IDE)
  - For patients implanted at non-IDE sites, meeting all eligibility criteria did not result in a lower mortality

Mortality and Known Failed Weans
All CU/EU Patients

Total Implants

BSA < 0. … 1.5m²

n = 151 …

Total: 49/136 = 36.0%

- IDE (14/41) **34.1%**
- Non-IDE (35/95) **36.8%**

Cohort 1 Primary Study Group n=24	Cohort 1 CAP n=20	**IDE Cohort 3A CU/EU n=35**	**Non-IDE Cohort 3A CU/EU n=72**	Cohort 2 Primary Study Group n=24	**IDE Cohort 3B CU/EU n=6**	**Non-IDE Cohort 3B CU/EU n=23**
Tx n = 21	Tx n = 16	Tx n = 20	Tx n = 31	Tx n = 21	Tx n= 4	Tx n = 17
Weaned n=1	Weaned n=0	Weaned n=3 **(2/3 Failed)**	Weaned n=6*	Weaned n=1	**Weaned n=1**	Weaned n=0
Death n=2	**Death n=1**	**Death n=10**	**Death n=32**	**Death n=2**	**Death n=1**	**Death n=3**
On Device n=0	On Device n=3	On Device n=2	On Device n=3	On Device n=0	On Device n=0	On Device n=3

Mortality and Known Failed Weans All CU/EU Patients

Total: 49/136 = 36.0%

Eligibility criteria met:

- Yes (16/48) **33.3%**
- No (33/88) **37.5%**

Ju

BSA < 0.7 … 5m²

n = 151

Cohort 1 Primary Study Group n=24	Cohort 1 CAP n=20	IDE Cohort 3A CU/EU n=35	Non-IDE Cohort 3A CU/EU n=72	Cohort 2 Primary Study Group n=24	IDE Cohort 3B CU/EU n=6	Non-IDE Cohort 3B CU/EU n=23
Tx n = 21	Tx n = 16	Tx n = 20	Tx n = 31	Tx n = 21	Tx n= 4	Tx n = 17
Weaned n=1	Weaned n=0	Weaned n=3 **(2/3 Failed)**	Weaned n=6*	Weaned n=1	**Weaned n=1**	Weaned n=0
Death n=2	**Death n=1**	**Death n=10**	**Death n=32**	**Death n=2**	**Death n=1**	**Death n=3**
On Device n=0	On Device n=3	On Device n=2	On Device n=3	On Device n=0	On Device n=0	On Device n=3

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II. Stroke, Neurologic Function, and Outcomes

SAE Rates for Ischemic Neurologic Events (CVA or TIA)

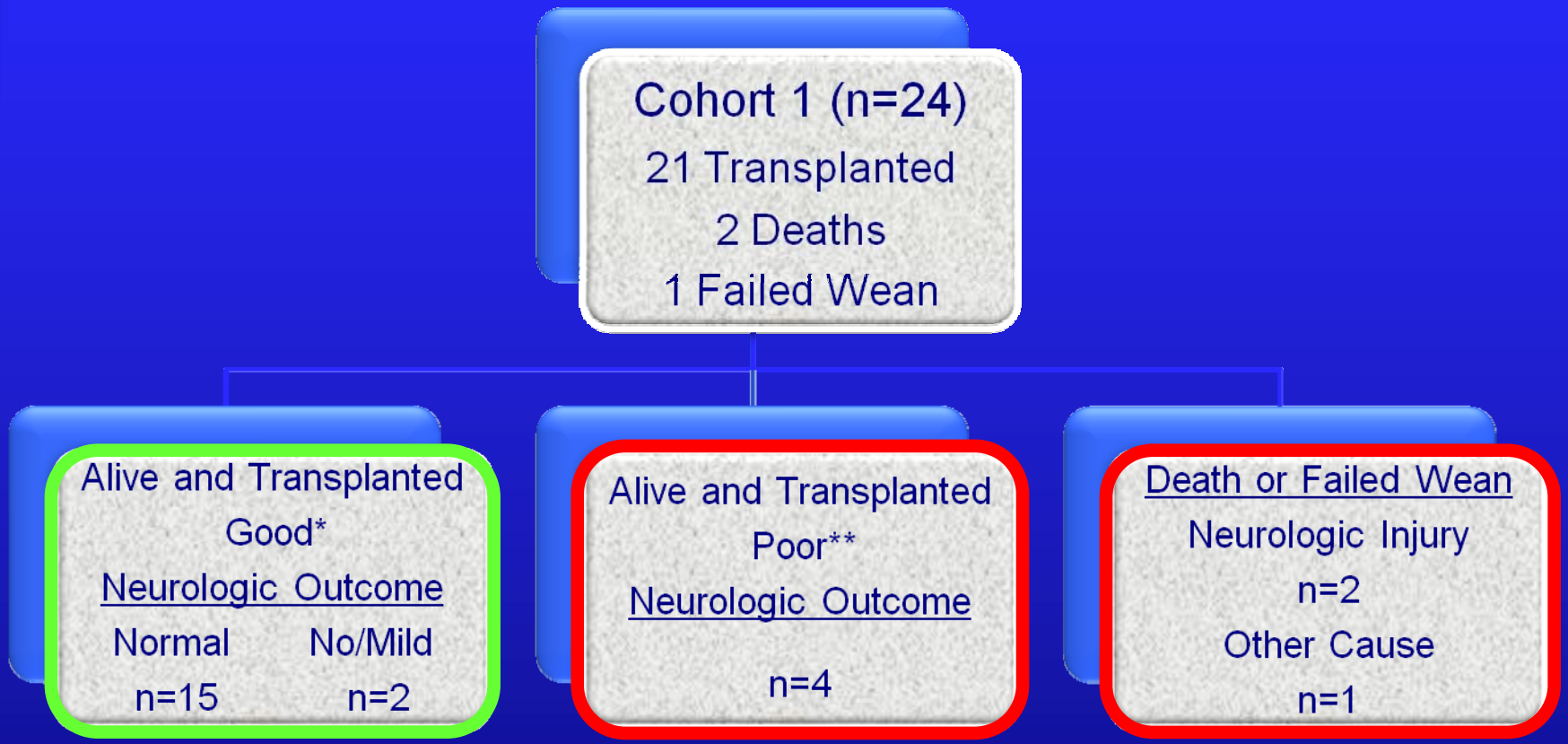
- Cohort 1:
  - 7 / 24 patients - 29.2%
  - 1 additional patient with global ischemic neurologic insult
  - 0.57 events per 100 days of support

  Total Rate: 33.3%
- Cohort 2:
  - 7 / 24 patients - 29.2%
  - 1 additional patient with global thromboembolic neurologic insult
  - 0.65 events per 100 days of support

  Total Rate: 33.3%
- All other IDE site patients (1CAP, 3A and 3B)
  - 12 / 61 patients – 19.6%
- All non-IDE site patients
  - 32 / 95 patients – 33.7%

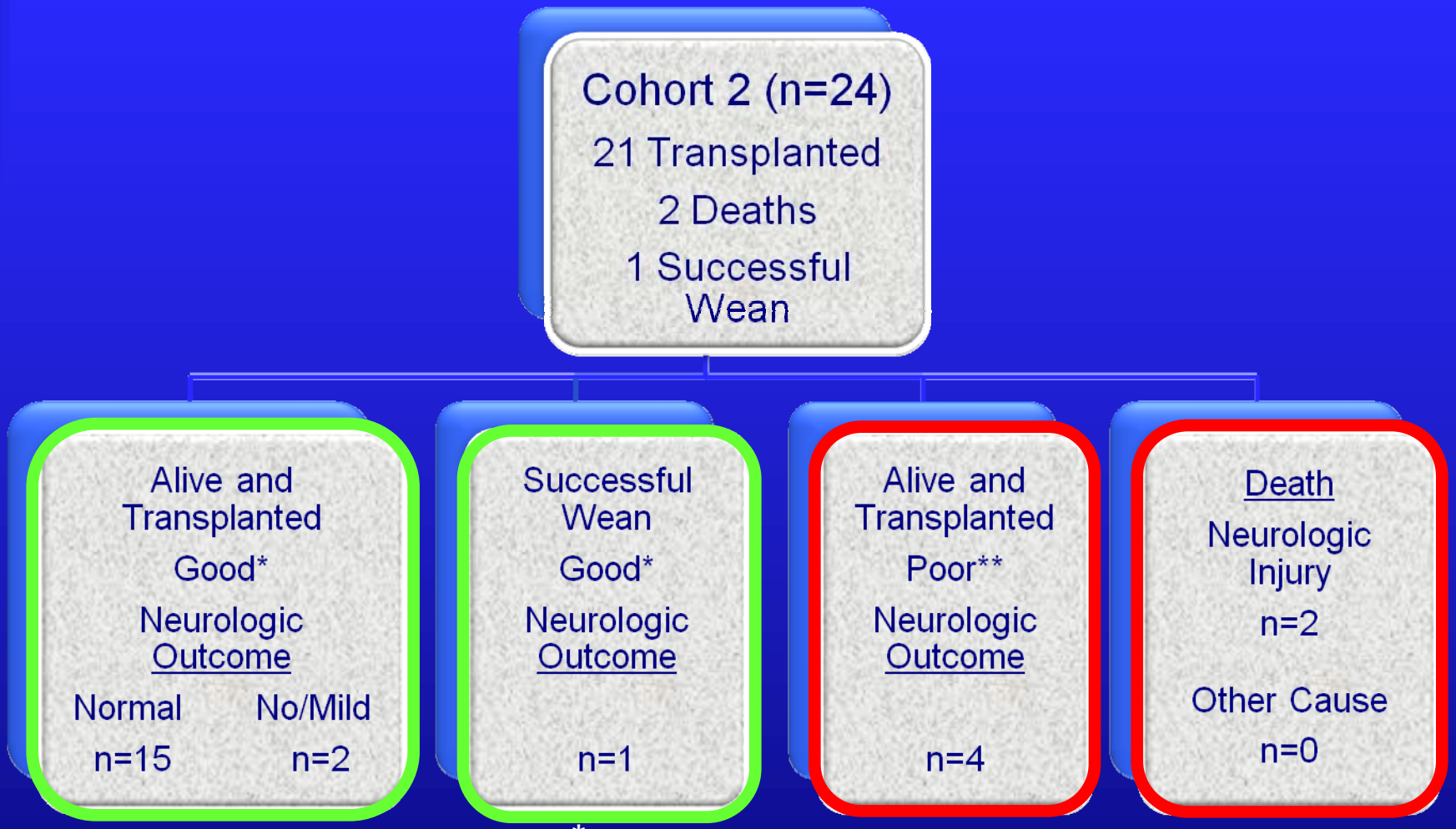
Total Rate (44 / 156) = 28.2%

Cohort 1 - Outcome by Neurologic Function



*Good = no or mild neurologic deficit, PSOM < 1
** Poor = moderate or severe neurologic deficit, PSOM ≥ 1

Cohort 2 - Outcome by Neurologic Function



*Good = no or mild neurologic deficit, PSOM < 1

** Poor = moderate or severe neurologic deficit, PSOM ≥ 1

Survival: Stroke Free and Good Neurologic Outcome in Primary Study Groups

- Survived to transplant or successfully weaned with no neurologic events
  - 64.5% (15/24) of Cohort 1
  - 66.7% (16/24) of Cohort 2

  } **31/48 = 64.6%**
- Survived to transplant or successfully weaned with either no neurologic events or a good neurologic outcome (PSOM <1).
  - 70.8% of Cohort 1 (17/24)
  - 75% of Cohort 2 (18/24)

  } **35/48 = 72.9%**
- 12 of the 13 adverse outcomes (92.3%) resulted from Ischemic/thrombotic events → Death, failed wean or "poor" neurologic outcome

Berlin Heart EXCOR® Pediatric Ventricular Assist Device

III. Health Related Quality of Life (PedsQL)

PedsQL in EXCOR Patients

- Results
  - Range of PedsQL scores for EXCOR study patients:
    - Patient reported: from 34-60 points
    - Parent/Proxy reported: from 20-65 points
  - Patient and parent/proxy reported QOL are significantly lower than QOL assessments typically reported for patient with chronic health conditions

PedsQL scores in EXCOR supported patients are observed to be several multiples of the standard error of the mean (SEM) lower than levels associated with chronic disease states in children

Berlin Heart EXCOR® Pediatric Ventricular Assist Device

IV. Pump Change Due to Thrombus

Pump Thrombus: The Problem

- Not regarded as an SAE
- Detected by visualization, requires vigilance
- Detection requires pump change
- Localized primarily to inflow/outflow valves
- Pump change due to thrombus was common
  - 45.6% of all implants
  - 52.6% of Primary study patients
  - 1.1 pump changes per patient at IDE sites
  - 0.02 ± 0.03 pump changes per day of support

Pump Thrombus: What does it mean?

- Noting the high incidence of the need for pump change due to thrombus, FDA requested further analysis of the data to determine:
- Potential contributory factors
- Effect on the incidence of SAEs
  - Thromboembolic complications
  - Stroke
- Effect on late neurologic outcome

Pump Thrombus: Potential Causes for an Ongoing Risk

- Pump size
- Adherence to pump sizing recommendations
- Initiation or weaning of support
- Adherence to anticoagulation regime
- Any specific clinical risk factor
- Implant site (IDE vs. non-IDE)

Pump Thrombus: Effect on SAEs

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%)

Pump Thrombus: Effect on SAEs (continued)

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%)

Neurologic Outcome (PSOM Scores) In Patients Requiring Pump Change

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 ≥ 1.0 (Average score)
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)

* excludes 2 patients with missing data – deaths

** excludes 1 patient with missing data – successful wean

Neurologic Outcome (PSOM Scores) In Patients Requiring Pump Change

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 ≥ 1.0 (Average score)
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)

*excludes 2 patients with missing data – deaths

** excludes 1 patient with missing data – successful wean

Pump Thrombus - Conclusions

- Is a frequent occurrence
- Data suggest that pump change due to thrombus is associated with:
  - A substantially higher incidence of ischemic neurologic events
  - Poorer neurologic outcome as measured by PSOM
- Contributory Factors:
  - No clinical events, anticoagulation abnormalities, or co-morbidities identified as contributory
  - Pump materials and/or its design – a potential suspect?

Overwhelming majority of patients (72.9%) were able to undergo transplant or successful weaning with either no neurologic events or good neurologic outcome

Summary of Clinical Review

- Primary safety was met based upon pre-specified hypothesis
- EXCOR showed superior effectiveness based on submitted data with clinically important improvements in the ability to provide prolonged support
- Pump performance:
  - No device failures
  - Excellent long-term hemodynamic support allows use as BTT
  - Concomitant support able to be weaned in selected patients
- Results indicate increased mortality can be expected in certain situations:
  - Broader clinical use for BTT indication
  - Relatively less-experienced centers
  - Patients with single ventricle physiology
  - Patients requiring pre-implant ECMO support

Summary of Clinical Review

Areas requiring further study

- Neurologic Events and Outcome
  - Risk of ischemic neurologic events is uniformly high
  - 92.3% (12/13) “poor” neurologic outcomes, failed weans, and deaths were a result of ischemic neurologic events
- Health related quality of life
  - Worse than levels typically observed in chronic disease states
- Pump thrombus is a significant problem
  - Likely related to pump materials and/or design
  - Acute effects include:
    - Higher incidence of ischemic stroke
    - “Poorer” neurologic outcome
    - Lower HRQoL assessments

FDA Team Presenters

- Shreya Mehta, MS – Lead Reviewer
  Introduction and Pre-clinical Considerations
- John Laschinger, MD – Medical Officer
  Clinical Trial Design & Outcomes
- Terri Johnson, PhD – Mathematical Statistician
  Statistical Outcomes & Challenges
- Veronica Sansing, PhD, MS – Epidemiologist
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  Conclusions

Berlin Heart EXCOR® Pediatric Ventricular Assist Device

FDA Review of H100004

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Division of Biostatistics

Office of Surveillance and Biometrics

Food and Drug Administration

Outline

I. Sample Size Calculation

II. Analysis and Results

   a) Primary Safety Endpoint

   b) Primary Effectiveness Endpoint

III. Summary

Sample Size Calculation

- Sample size is driven by the primary safety endpoint (SAE):

$$H_0: \lambda \geq 0.25 \text{ vs. } H_1: \lambda < 0.25$$

  λ is the expected SAE rate for the population treated with the EXCOR VAD

- A sample of 24 subjects followed for approximately 100 days each would provide a power of 80% using Poisson exact test assuming SAE of 0.21 per patient-day at a one-sided significance level of 2.5%

Power for Effectiveness Evaluation

- Primary effectiveness endpoint:

$$H_0: HR \geq 1 \text{ vs. } H_1: HR < 1$$

  HR is the expected hazard ratio of EXCOR VAD against ECMO for the target population

- The study would provide a power of 99% using Cox-proportional hazards regression, assuming median time to death or recovery is 100 days for the EXCOR group and 4.833 days for the ECMO group at a two-sided significance level of 5%.

Primary Safety Endpoint

- To show that the SAE rate calculated as the number events per patient-day is less than 0.25 tested at one-sided significant level of 0.025 (using Poisson exact method)

$$H_0: \lambda \geq 0.25$$

$$H_1: \lambda < 0.25$$

Statistical Results: Primary Safety Endpoint (Cohort 1)

- Primary safety endpoint:
  - The total time on device of the Cohort 1 subjects was 1,411 days.
  - There were 96 SAEs for Cohort 1 yielding a rate of 0.068 events per patient-day.
  - The two-sided upper 95% Poisson confidence interval was 0.083 (< PG of 0.25)
  - ***The safety objective seems to be met.***

Statistical Results: Primary Safety Endpoint (Cohort 2)

- Primary safety endpoint:
  - The total time on support of the Cohort 2 subjects was 1,376 days.
  - There were 107 SAEs for this cohort yielding a rate of 0.078 events per patient-day.
  - The two-sided upper 95% Poisson confidence interval was 0.094 (< PG of 0.25).
  - ***The safety objective seems to be met.***

Statistical Issue: Primary Safety Endpoint

- Poisson model assumes that
  1) within a subject, the AE rate is constant over time, and
  2) among subjects in the study, the AE rate is same

- If AE rates are different between patients, the upper limit of the CI would be underestimated

Statistical Issue: Primary Safety Endpoint (cont'd)

- Significant overdispersion detected: additional variation exists beyond the Poisson model
- Negative binomial method:
  - Cohort 1: Upper 95% CI is 0.144
  - Cohort 2: Upper 95% CI is 0.168
- Bootstrap method:
  - Cohort 1: Upper 95% CI is 0.16
  - Cohort 2: Upper 95% CI is 0.15

Primary Effectiveness Endpoint: Propensity Score Analysis

- Propensity score is a probability of a patient receiving one treatment over another treatment given certain baseline and demographic characteristics
  - Mimics randomization setting
- Propensity score methods could NOT adjust for imbalances in unobserved covariates.
- Pre-specification of ALL relevant covariates

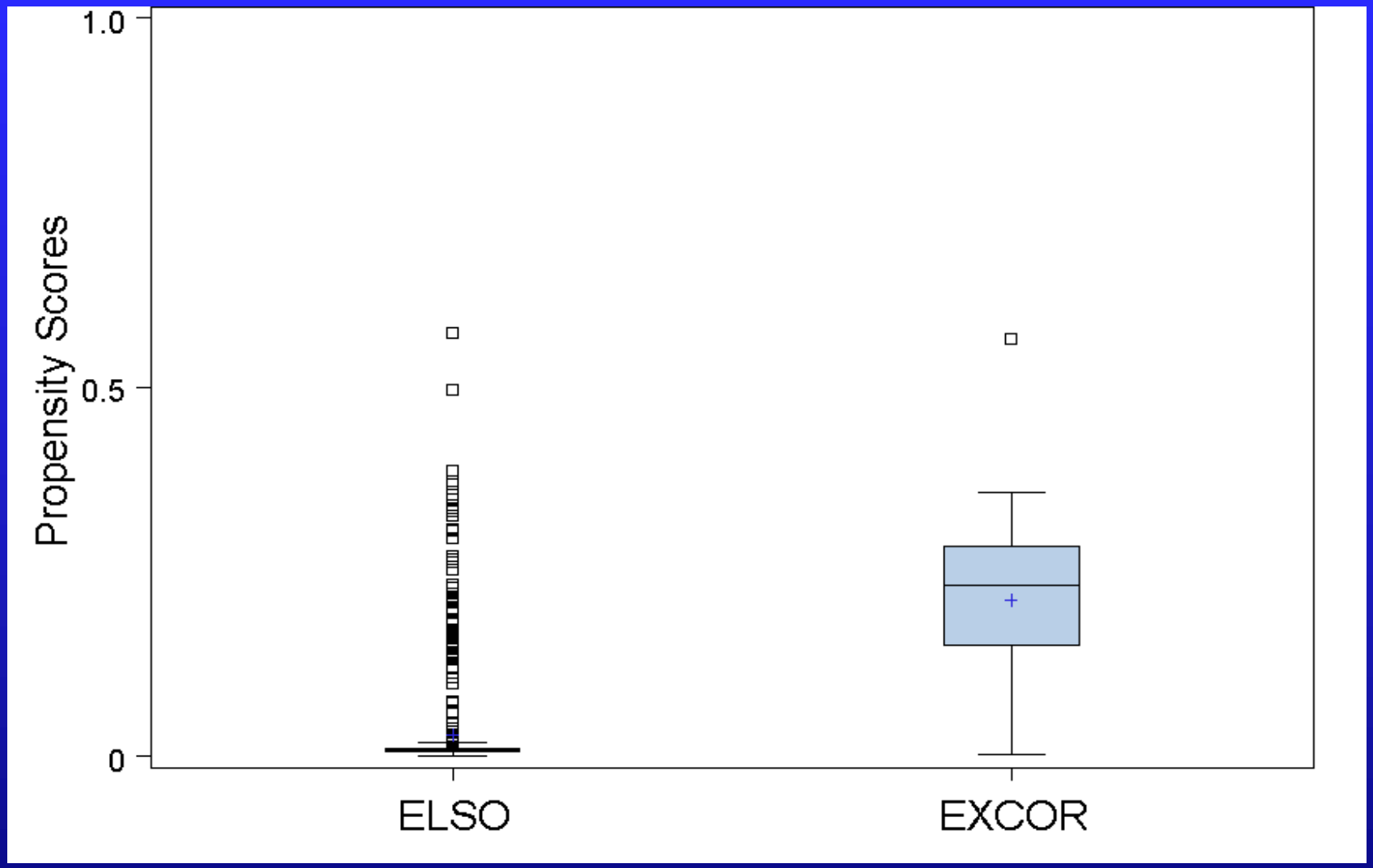
Primary Effectiveness Endpoint: Propensity Score Analysis (cont'd)

- Propensity score: probability of receiving EXCOR
- Covariates built in to the propensity score model: age, weight, diagnosis, ventilator status, inotrope use, and prior cardiac arrest
- BSA is an important covariate not included in the propensity score model since it is not available in the ELSO registry

Primary Effectiveness Endpoint: Propensity Score Analysis (cont'd)

- Historical control: ELSO registry (N=747)
  - Eligible Controls for Cohort 1 (n=640)
    - Excluded 10-16 years old and > 40 kg
  - 48 controls were selected (2 ECMO patients for each EXCOR patient)

Primary Effectiveness Endpoint: Propensity Score Analysis (Cohort 1)



Primary Effectiveness Endpoint: Propensity Score Analysis (Cohort 1)

Variable	Category	Cohort 1 n=24	ELSO matches N=48	P-value*
Age Group	0-30 days 30 days – 2 years 2 to 10 years 10 to 16 years	0 (0.0%) 20 (83.0%) 4 (17.0%) 0 (0.0%)	4 (8.3%) 32 (66.7%) 12 (25.0%) 0 (0.0%)	0.24
Weight Group	3-10 kg 10-30 kg 30-60 kg	16 (67.0%) 8 (33.0%) 0 (0. 0%)	34 (70.8%) 14 (29.2%) 0 (0.0%)	0.79
Primary Diagnosis	Cancer Congenital Heart Disease Coronary Artery Disease Dilated Myopathy Hypertrophic Cardiomyopathy Restrictive Myopathy Valvular Heart Disease	0 (0.0%) 3 (12.5%) 0 (0.0%) 19 (79.2%) 1 (4.2%) 1(4.2%) 0 (0%)	0 (0.0%) 8 (16.7%) 0 (0.0%) 39 (81.3%) 0 (0.0%) 0 (0.0%) 1 (2.1%)	0.36
Ventilator Use (pre-implant)	Yes	20 (83.3%)	36 (75.0%)	0.55
Inotrope Use (pre-implant)	Yes	22 (91.7%)	43 (89.6%)	>0.99
Cardiac Arrest (pre-implant)	Yes	7 (29.2%)	14 (29.2%)	>0.99

* Fisher's exact test

Primary Effectiveness Endpoint

- To show that the survival in subjects treated with the EXCOR is different from the historical controls treated with ECMO as a BTT, tested at two-sided $\alpha=0.05$ using the Cox proportional hazards regression

$$H_0: HR \geq 1$$

$$H_1: HR < 1$$

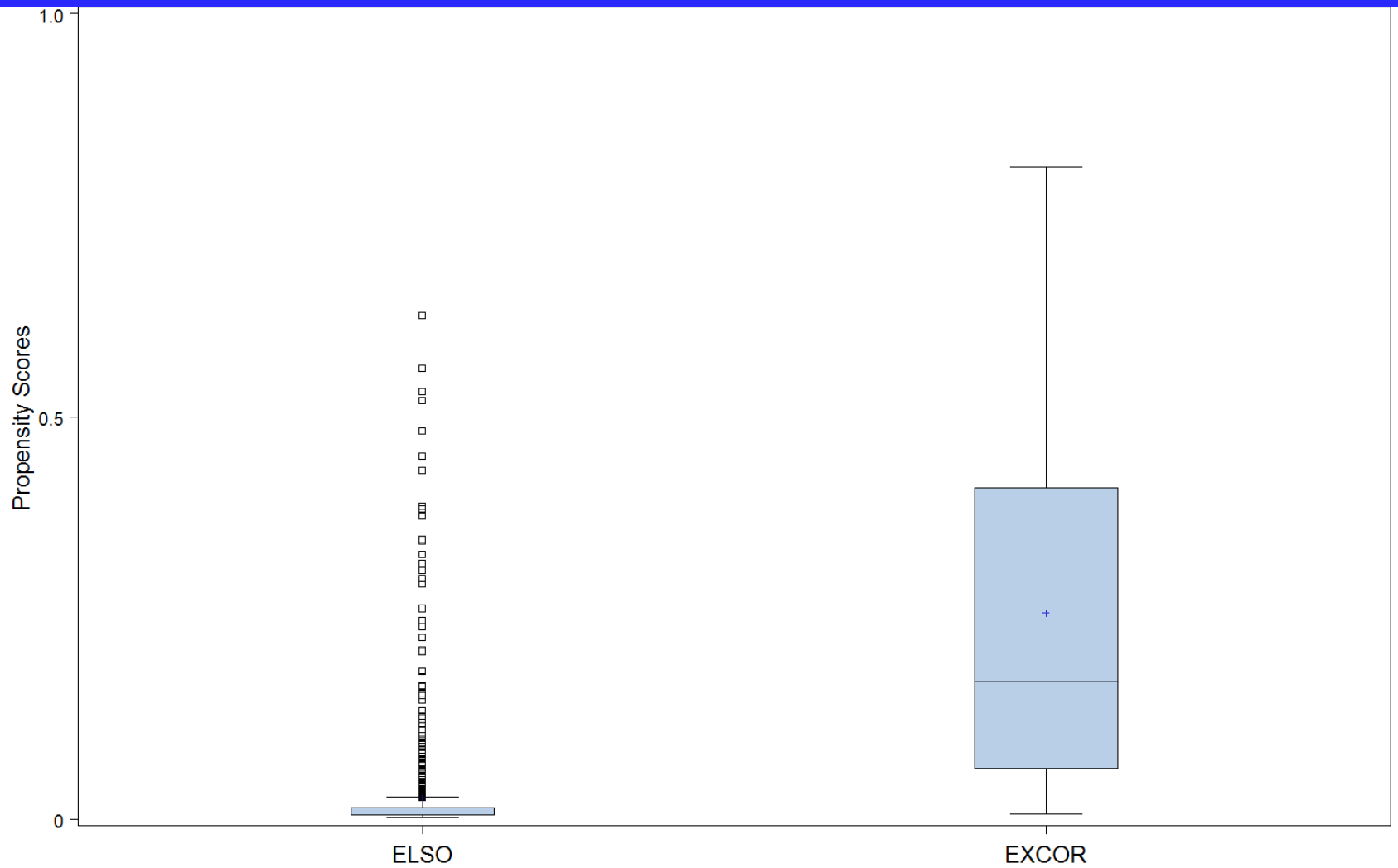
Statistical Results (Cohort 1): Primary Effectiveness Endpoint

- Unadjusted hazard ratio = 0.043 (*P-value*=0.004)
- Adjusted hazard ratio = 0.099 (*P-value* = 0.03)
- *The objective for Cohort 1 seems to be met.*

Primary Effectiveness Endpoint: Propensity Score Analysis

- Historical control: ELSO registry (N=747)
  - Eligible controls for Cohort 2 (n=682)
    - All patients including those who were young and small were included
    - Appropriate selection of the 48 controls cannot be verified

Primary Effectiveness Endpoint: Propensity Score Analysis (Cohort 2)



Primary Effectiveness Endpoint: Propensity Score Analysis (Cohort 2)

Variable	Category	Cohort 2 n=24	ELSO matches N=48	P-value*
Age Group	0-30 days	0 (0.0%)	0 (0.0%)	**<0.0001**
	30 days – 2 years	**0 (0.0%)**	**9 (18.8%)**	
	2 to 10 years	14 (58.3%)	9 (18.8%)	
	10 to 16 years	10 (41.7%)	30 (62.5%)	
Weight Group	3-10 kg	**0 (0.0%)**	**9 (18.8%)**	**0.02**
	10-30 kg	12 (50.0%)	12 (25.0%)	
	30-60 kg	12 (50.0%)	27 (56.3%)	
Primary Diagnosis	Cancer	0 (0.0%)	0 (0.0%)	0.66
	Congenital Heart Disease	6 (25.0%)	15 (31.3%)	
	Coronary Artery Disease	0 (0.0%)	1 (2.1%)	
	Dilated Myopathy	17 (70.8%)	31 (64.6%)	
	Hypertrophic Cardiomyopathy	0 (0.0%)	0 (0.0%)	
	Restrictive Myopathy	1 (4.2%)	0 (0.0%)	
	Valvular Heart Disease	0 (0.0%)	1 (2.1%)	
Ventilator Use (pre-implant)	Yes	12 (50.0%)	26 (54.2%)	0.62
Inotrope Use (pre-implant)	Yes	21 (87.5%)	40 (83.3%)	0.79
Cardiac Arrest (pre-implant)	Yes	5 (20.8%)	13 (27.1%)	0.77

Statistical Results (Cohort 2): Primary Effectiveness Endpoint

- Primary effectiveness endpoint HR for Cohort 2 cannot be evaluated
  - Analysis that appropriately adjusts for matching design cannot be performed since matched controls cannot be identified
  - The results for the primary effectiveness endpoint in the HDE may be biased since imbalances in the observed propensity score covariates exist

Statistical Summary

- Primary safety objective was met
- Primary effectiveness objective
  - Cohort 1: seems to be met; *however*, results may still be biased due to imbalances in omitted covariates from the propensity score model (BSA)
  - Cohort 2: statistically inconclusive; in addition to imbalance in omitted covariates, imbalances in observed covariates still exist
  - Clinical judgment is needed

FDA Team Presenters

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Berlin Heart EXCOR® Pediatric Ventricular Assist Device

FDA Review of H100004

Veronica Sansing, Ph.D., M.S.

Epidemiologist

Division of Epidemiology

Office of Surveillance and Biometrics

Food and Drug Administration

Reminder

- The discussion of a PAS prior to FDA determination of device approvability should not be interpreted to mean FDA is suggesting the device's safety and probable benefit have been established.
- The plan to conduct a PAS does not decrease the threshold of evidence required by FDA for device approval.
- The premarket HDE data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and probable benefit.

Need for Post-Approval Studies for HDEs

- Gather postmarket information
  - Long-term performance including effects of re-treatments & device changes
  - Broader device performance (patients and clinicians)
  - Effectiveness of training programs
  - Sub-group performance
  - Outcomes of concern (safety and probable benefit)
- Account for Panel recommendations

Post-Approval Study Components

- Fundamental study question or hypothesis
- Safety endpoints and methods of assessment
- Acute and chronic effectiveness endpoints and methods of assessment
- Duration of follow-up

Important Postmarket Issues for Berlin EXCOR Pediatric VAD

- Learning curve
  - AEs associated with patient selection, procedures, and postoperative care. [1]
- Long term effects of device exposure
  - IDE study followed patients to transplant/recovery and 1 year post explant
    - Clinical, neurological, and QoL status
  - Studies have followed pediatric patients for avg. 5-10 yrs post-explant. [2-4]

1. McCarthy et al., J Heart Lung Transplant . 2000;19(8, Supplement 1):S64-S67
2. Januszewska et al., Interactive CardioVascular and Thoracic Surgery 9 (2009) 807–810
3. Blume et al., Circulation 2006;113:2313-2319
4. Davies et al., J Thorac Cardiovasc Surg 2008;135:421-427

Outline for Sponsor's Proposed PAS

Title	EXCOR Pediatric VAD Post Approval Study
Study Design	Prospective registry of patients implanted with the EXCOR Pediatric VAD
Sample Size	First 24 patients implanted per device labeling Safety endpoint: >80% power, one-sided α=0.025 Enroll 3 sites per month
Follow-up Duration	From implant until transplant/recovery
Scheduled Contacts	2, 4, and 6 weeks, 3 and 6 months, every 3 months while on device support

Outline for Sponsor's Proposed PAS

Primary Effectiveness Hypothesis	Survival to transplant/recovery rate for EXCOR post-market ≠ EXCOR pre-market
Primary Safety Hypothesis	Composite serious adverse event rate <0.25 (as defined in the IDE study)
Secondary Endpoints	Device malfunctions - Pump failure and non-pump failure

Review Team Assessment

- The PAS includes a training program, but does not assess a possible learning curve associated with the implant and explant of the device

- The FDA would like the PAS to include a formal evaluation of a potential learning curve

Review Team Assessment (cont'd)

- Current PAS proposal does not include follow-up of patients beyond recovery or transplant.

- The FDA would like PAS patients to be followed post recovery/transplant
  - Appropriate length of follow up (>5 yrs)
  - Assessment of QoL metrics

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  Conclusions

HUD/HDE Requirements

- Office of Orphan Products
  - Reviews application for HUD designation
    - < 4000 US patients per year
    - Not an assessment of device's safety or probable benefit
- Center for Devices and Radiological Health
  - Reviews HDE and considers totality of data
  - HDE exempt from statutory effectiveness requirements
  - Considering other alternatives, device's probable benefit should outweigh its known risks

Conclusions

- Pre-clinical data adequately demonstrates safe use of the device for the clinical environment
- Primary safety endpoint was met demonstrating less than 0.25 SAEs per patient day of support
- Primary effectiveness objective was met based on clinical interpretation of the data
  - Date demonstrated that overall survival of EXCOR likely to be superior to ECMO

Conclusions (cont'd)

- Secondary effectiveness endpoints
  - Days of transplant eligible support
  - Ability to de-intensify concomitant hemodynamic support
  - Results were supportive of clinical conclusions
- Additional Supportive Analyses
  - Eligibility criteria
    - Single ventricle physiology
    - Pre-implant ECMO
    - Implantation at relatively less experienced centers
  - Neurologic dysfunction: incidence and its effect on outcome
  - HRQoL data
  - Pump thrombus: incidence and its effects on neurologic injury and outcome

Conclusions (cont'd)

- Panel input regarding PAS:
  - Statistical challenges exist when using historical control data from ELSO as a comparator
  - Long-term neurologic and health-related quality of life outcomes remain unknown
  - CU, EU, and CAP patients represent broader BTT outcomes
    - Learning curve & training protocols

Questions?