BERLIN HEART REVIEW TEAM

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TWO COMPETING PROBLEMS

- Lack of effective device therapy for mechanical circulatory support (MCS) in children with acute or chronic heart failure
- Lack of monetary incentive for development of a MCS device in orphan population
SOLUTIONS

- Berlin Heart Pediatric VAD
- HDE – Humanitarian Device Exemption
  - Alternative Device Regulation Process for Pediatric/Orphan Diseases
  - To encourage the discovery and use of devices intended to benefit patients in the treatment or diagnosis of diseases or conditions that affect fewer than 4,000 individuals in the United States.
WHAT IS A BERLIN HEART?
HUMANITARIAN USE DEVICE (HUD) DESIGNATION

- Office of Development (OOPD)
- Disease manifested in, treats, or diagnoses < 4000 pts./year in US,
  - total population or
  - medically plausible subset
- No comparable devices available
- Device could not otherwise be brought to market
SIGNIFICANT RISK HUMANITARIAN USE DEVICE: HDE PROCESS

Pre-Clinical Stage
- Sufficient safety
  - Bench testing
  - Animal Studies
  - Feasibility/FIM

Pre-Submission Meeting(s)
- Scientific, clinical, regulatory strategies
- Review available pre-clinical and clinical data
- Pivotal Trial

Pivotal Trial
Safety and Probable Benefit

HDE submission

IDE submission

IDE Approval

HDE Submission

HDE Approval

MARKET
(Site with local IRB)

HUD designation

Labeling and SSED

Post Approval Study (PAS)

Valid Scientific Evidence of Safety and Probable Benefit
SAFETY

“There is reasonable assurance that a device is safe when it can be determined based on valid scientific evidence that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh the probable risks.”

PROBABLE BENEFIT

“…the device does not pose an unreasonable risk of illness or injury to patients and that the probable benefit 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. .”
REGULATORY HISTORY

1996
EXCOR Receives CE Mark

2000
First US EXCOR cases: CU/EU Provisions

2001
EXCOR Receives HUD Designation

2007
EXCOR Receives IDE Approval

2010
FDA Receives EXCOR HDE
UNIQUE PROBLEMS

- No Approved or Cleared therapy for Comparison
- Equipoise lacking for randomized comparison to available therapy
- Data for comparator - ELSO Registry (ECMO)
- Benefit–Risk Determination complicated by
  - high incidence of stroke (25-30%)
  - deterioration of results with off-label use (stroke and death)
PROSPECTIVE RCT

Performance Goals
Historical Controls
Registry based comparisons*
Objective Performance Criteria
Patient’s as their own control
Concurrent Non-Randomized Surgical Controls

* Propensity score matching with concurrent and historical ECMO controls
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.)
- Propensity Score matching – statistical difficulties
### Differences in Definitions

<table>
<thead>
<tr>
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<th><strong>EXCOR</strong></th>
<th><strong>ECMO</strong></th>
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<tbody>
<tr>
<td><strong>Endpoint</strong></td>
<td><em>Death on device or survival to transplant or recovery</em></td>
<td><em>Death or recovery</em></td>
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<tr>
<td><strong>Recovery</strong></td>
<td><em>Survival with an acceptable neurological outcome 30 days post explant or to discharge, whichever is later (i.e. successful wean)</em></td>
<td><em>Survival for 30 days after being weaned from support</em></td>
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<td><strong>Success</strong></td>
<td><em>Survival to transplant or recovery</em></td>
<td><em>Recovery</em></td>
</tr>
<tr>
<td><strong>Failure</strong></td>
<td><em>Death, or…</em></td>
<td><em>Death on device or within 30 days of being weaned from support</em></td>
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<td><strong>Failed wean</strong>:</td>
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<tr>
<td></td>
<td>• <em>Death within 30 days of explant or prior to hospital discharge, whichever is later</em></td>
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<td></td>
<td>• <em>Survival post explant with an unacceptable neurologic outcome</em></td>
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MAJOR INCLUSION/EXCLUSION CRITERIA

**Inclusion:**
- Severe NYHA Functional Class IV (or Ross Functional Class IV for subjects ≤ 6 years) heart failure refractory to optimal medical therapy
- Listed for Cardiac Transplant (UNOS 1A)
- INTERMACS profile status 1 or 1A (i.e. critical cardiogenic shock) or INTERMACS profile status 2 or 2A (i.e. progressive decline)
- On ECMO or unable to wean from CPB
- Two Ventricle Circulation

**Exclusion:**
- On ECMO > 10 days
- Single Ventricle
- Hepatic or renal failure (Cr > 3x ULN)
- Hemodialysis or Peritoneal Dialysis
- Coagulopathy or Platelet disorder
**OVERVIEW OF RESULTS – ALL PATIENTS (N= 209)**

**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
  - Tx n = 21
  - Weaned n = 1
  - Death n = 2
  - On Device n = 0

### IDE Cohort 3A
- **CU/EU**
  - n = 35
  - Tx n = 20
  - Weaned n = 3 (2/3 Failed)
  - Death n = 10
  - On Device n = 2

### Non-IDE Cohort 3A
- **CU/EU**
  - n = 72
  - Tx n = 31
  - Weaned n = 6*
  - Death n = 32
  - On Device n = 3

### Cohort 2
- **Primary Study Group**
  - n = 24
  - Tx n = 21
  - Weaned n = 1
  - Death n = 2
  - On Device n = 0

### IDE Cohort 3B
- **CU/EU**
  - n = 6
  - Tx n = 4
  - Weaned n = 1
  - Death n = 1
  - On Device n = 0

### Non-IDE Cohort 3B
- **CU/EU**
  - n = 23
  - Tx n = 17
  - Weaned n = 0
  - Death n = 3
  - On Device n = 3
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:

\[ H_0 : HR \geq 1 \]

\[ H_1 : HR < 1, \]

HR is the expected hazard ratio of EXCOR against ECMO for BTT*

*two-sided \( \alpha=0.05 \) using the Cox proportional hazards regression
PRIMARY EFFECTIVENESS ENDPOINT – SPONSOR REPORTED

COHORT 1

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.*

COHORT 2

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

• p=.0002 vs. ECMO control
** p=.0001 vs. ECMO control
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 conducted FDA analysis on pre-specified hypothesis test
SURVIVAL ANALYSIS - COHORT 1

Survival Analysis where Event =
Death/ Unacceptable Neuro Outcome
(censored at Transplant and at Recovery)
COMPETING OUTCOMES

COHORT 1

EXCOR

ECMO Controls

Cohort 1 - Competing Outcomes

Rates at 174 days

- Transplant 87.5%
- Weaned/Failure 4.2%
- Death 8.3%

ECMO Control Group for Cohort 1 - Competing Outcomes

Rates at 20.5 days

- Recovered 75%
- Death 25%
- Alive (on ECMO) 0%

Alive (device in place) 0%
Survival Analysis where Event = Death (censored at Transplant and at Recovery)

Time (days post implant)

% Survival

Cohort 2
ECMO Control
COMPETING OUTCOMES
COHORT 2

EXCOR

ECMO Controls

Cohort 2 - Competing Outcomes

- Rates at 192 days
- Transplant 87.5%
- Death 8.3%
- Weaned/Recovered 4.2%
- Alive (device in place) 0%

ECMO Control Group - Competing Outcomes

- Rates at 27.5 days
- Recovered 66.7%
- Death 33.3%
- Alive (on ECMO) 0.0%
SECONDARY EFFECTIVENESS ENDPOINT

CONCLUSIONS

• 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
• Use of historical controls - problematic

• Based upon clinically relevant data
  ▪ EXCOR provided clinically important benefits for both survival rate and time vs. ECMO
  ▪ These survival differences are critical for use for a BTT indication

• Essential Features of Mechanical Support Device for BTT met:
  ▪ Survival
  ▪ Prolonged support
  ▪ Preservation of transplant eligibility
  ▪ Ability to de-intensify concomitant support
PRIMARY SAFETY ENDPOINT: ALL IDE PATIENTS

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

\[ H_0: \text{SAE} \geq 0.25 \]
\[ H_A: \text{SAE} < 0.25 \]
### PRIMARY SAFETY ENDPOINT: ALL IDE PATIENTS

* < 0.25 SAEs per patient day of support

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Events</th>
<th>Total Time on Support (Days)</th>
<th>Rates Success Criterion &lt;0.25</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Events per Patient-Day</td>
</tr>
<tr>
<td>Cohort 1</td>
<td>24</td>
<td>96</td>
<td>1411</td>
<td>0.068</td>
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<tr>
<td>Cohort 1 CAP</td>
<td>20</td>
<td>74</td>
<td>1330</td>
<td>0.056</td>
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<tr>
<td>Cohort 3A</td>
<td>35</td>
<td>135</td>
<td>1993</td>
<td>0.068</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>24</td>
<td>107</td>
<td>1376</td>
<td>0.078</td>
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<tr>
<td>Cohort 3B</td>
<td>6</td>
<td>40</td>
<td>240</td>
<td>0.167</td>
</tr>
</tbody>
</table>

* < 0.25 SAEs per patient day of support
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 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 – not an AE but common
Mortality

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

• Pre-Implant Predictors of mortality included:
  • Single ventricle circulation
  • Any pre-implant use of ECMO

• For all CU/EU patients
  • Total mortality and failed wean:
    - Was high
    - Was not affected by the site of implantation (IDE vs. non-IDE)
SURVIVAL AND NEUROLOGIC OUTCOME: COHORT 1

Cohort 1 (n=24)

21 Transplanted (87.5%)
  2 deaths
  1 Failed Wean

Alive and Transplanted with Good* Neurologic Outcome (70.8%)
  Normal n=15
  No/Mild n=2

Alive and Transplanted with Poor** Neurologic Outcome (16.7%)
  n=4

Death or Failed Wean (12.5%)
  Neuro Injury n=2
  Other Cause n=1

* Good = PSOM < 1; **Poor = PSOM ≥ 1
Survival and Neurologic Outcome: Cohort 2

Cohort 2 (n=24)

22 Transplanted or Weaned (91.7%)
2 deaths

Alive and Transplanted or Weaned with Good* Neurologic Outcome (75%)
- Normal n=16
- No/Mild n=2

Alive and Transplanted with Poor** Neurologic Outcome (16.7%)
- n=4

Death (8.3%)
- Neuro Injury n=2
- Other Cause n=0

* Good = PSOM <1; **Poor = PSOM ≥ 1
SUMMARY OF NEUROLOGIC OUTCOMES IN STUDY COHORTS

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

• Survived to transplant or were 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)

\[
\frac{35}{48} = 72.9\% 
\]
SUMMARY OF CLINICAL REVIEW

• Primary safety was met based upon pre-specified hypothesis

• EXCOR showed probable benefit 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
  ▪ Prone to thrombus formation – inlet and outlet valves

• 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
**AREAS REQUIRING ADDITIONAL STUDY - PAS**

- **Neurologic Events and Outcome**
  - Risk of ischemic neurologic events is uniformly high (25-30%)
  - Almost all deaths/failed weans or poor outcomes – Neuro Events
  - Long term effects on neurocognitive function unknown
  - Overwhelming majority (72.9%) - transplant or successful weaning with either no neurologic events or good neurologic outcome

- **Health related quality of life**
  - Worse than levels typically observed in chronic disease states
  - Only measured on device

- **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
THANK YOU!

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