“Portable Normothermic Ex Vivo Lung Perfusion to Reduce Warm Ischemia Time and Increase Graft Usage”

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Disclosures

- Grant support from Transmedics for involvement in EVLP clinical and translational trials
- Travel reimbursement for study related travel
- United Therapeutics grant support for translational research
- Receive grant support from Maquet for an ECMO in lung transplantation registry
End stage lung disease
Critical organ shortage

15-30% of patients die on the waitlist
Critical organ shortage

- 20% Donor lungs wasted
- 80% Donor lungs used
# Primary Graft Dysfunction

## Table 1

<table>
<thead>
<tr>
<th>PGD stage</th>
<th>P/F ratio (mmHg)</th>
<th>Chest radiography</th>
<th>Updates from 2016 Consensus Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&gt;300</td>
<td>Normal</td>
<td>Any P/F ratio</td>
</tr>
<tr>
<td>1</td>
<td>&gt;300</td>
<td>Diffuse allograft infiltration/pulmonary oedema</td>
<td>No changes</td>
</tr>
<tr>
<td>2</td>
<td>200–300</td>
<td>Diffuse allograft infiltration/pulmonary oedema</td>
<td>No changes</td>
</tr>
<tr>
<td>3</td>
<td>&lt;200</td>
<td>Diffuse allograft infiltration/pulmonary oedema</td>
<td>No changes</td>
</tr>
</tbody>
</table>

ISHLT, the International Society for Heart and Lung Transplantation; PGD, primary graft dysfunction; P/F, PaO₂/FI₀₂.
Ex Vivo Lung Perfusion

- Gas for Deoxygenation
- Reservoir
- Leukocyte Filter
- Centrifugal Pump
- Hollow-fibre oxygenator and Heat Exchanger (used for deoxygenation)
- From PV
- To PA
- Xin Vivo Chamber and Lungs
- ICU Ventilator
Static Perfusion Systems

XPS – Novel Trial

Vivo Line – Develop UK Trial
Portable Ex-vivo Lung Perfusion (EVLP) “Breathing Lung Transplantation”

- Organ Care System Lung (OCS Lung)
- Portable EVLP platform
- Normothermic, blood based perfusion, ventilation, monitoring and recruitment
- Additives – steroids, antibiotics, glucose, multivitamins, insulin
Critical Trends

Pump Flow

VR (Vascular Resistance)

SaO₂ & SvO₂

Tidal Volume

PAWP (Peak Airway Pressure)

PEEP (Positive End Expiratory Pressure)

PAP (Pulmonary Artery Pressure)

Critical Trends
Normothermic ex-vivo preservation with the portable Organ Care System Lung device for bilateral lung transplantation (INSPIRE): a randomised, open-label, non-inferiority, phase 3 study

INSPIRE trial

- Standard Criteria Donors
- PaO2:FiO2 >300mmHg
- Age < 65
- Organ suitable for either cold storage or OCS
- No active pulmonary disease
- Non DCD
370 randomly assigned before final assessment for eligibility

182 randomly assigned to control arm

13 excluded
- 8 donor screen failures (early exclusions; did not meet donor inclusion criteria) *
- 4 recipient screen failures (early exclusions; did not meet recipient inclusion criteria)
- 1 opened the wrong randomisation envelope

169 in the control intention-to-treat population

188 randomly assigned to OCS arm

37 excluded
- 26 donor screen failures (early exclusions; did not meet donor inclusion criteria) †
- 2 recipient screen failures (early exclusions; did not meet recipient inclusion criteria)
- 9 logistics screen failures (early exclusions; OCS equipment or trained personnel not available)

151 in the OCS intention-to-treat population
Total ischemic time and total cross clamp time

**Total Ischemic Time**

- 1st Lung: 4.9 [95% CI: 2.6]
- 2nd Lung: 6.6 [95% CI: 4.2]

*P*<0.0001

**Total Cross-Clamp Time**

- 1st Lung: 4.9
- 2nd Lung: 6.6

*P*<0.0001
Donor lung splitting

• Reduces ischemic exposure even further

• Increases options for size reduction and single lungs to expand the donor pool
PGD3 within 72 hours

Proportion (%)

- Control: 29.7 (n=165)
- OCS: 17.7 (n=141)
- OCS Solution Subgroup: 14.0 (n=86)

P=0.006*
P=0.015*
Resource utilization

- **Ventilation Time**
  - Control: 4.4 days (95% CI: 3.3 to 5.5)
  - OCS: 3.3 days (95% CI: 2.7 to 4.0)
  - OCS Solution Subgroup: 2.7 days (95% CI: 2.6 to 2.8)
  - P = NS

- **Initial ICU Stay**
  - Control: 9.7 days (95% CI: 8.9 to 10.5)
  - OCS: 8.9 days (95% CI: 8.2 to 9.6)
  - OCS Solution Subgroup: 8.2 days (95% CI: 7.8 to 8.6)
  - P = NS

- **Transplant Hospital Stay**
  - Control: 31.7 days (95% CI: 30.0 to 33.4)
  - OCS: 27.4 days (95% CI: 27.0 to 27.8)
  - OCS Solution Subgroup: 27.0 days (95% CI: 27.0 to 27.0)
  - P = NS
Survival

Log-rank p=0.724

Control

OCS

Number at risk

Follow-up (months)

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCS</td>
<td>141</td>
<td>133</td>
<td>126</td>
<td>123</td>
<td>121</td>
</tr>
<tr>
<td>Control</td>
<td>165</td>
<td>150</td>
<td>146</td>
<td>143</td>
<td>139</td>
</tr>
</tbody>
</table>
Summary of portable EVLP in standard donors

- Safe, FDA approved
- Mean clamp times of 8 hours, despite lower ischemic times
- Less PGD 3 – better graft function
- Trends towards decreased resource utilization
- Costs include modules and stationary console
- Survival at 12 months and 24 months are similar to ice storage
- CLAD data is not yet available
Can we extrapolate this to extended criteria lungs?
Critical organ shortage

- Donor lungs wasted: 20%
- Donor lungs used: 80%
The OCS Lung EXPANDI International Trial Results


U. Minnesota, Minneapolis, USA; Hannover Medical School, Germany; Massachusetts General Hospital, Boston, USA; St. Joseph’s Medical Center, Phoenix, USA; University of California San Francisco, USA; University Hospital Puerta de Hierro, Madrid, Spain; Ronald Reagan UCLA Medical Center, Los Angeles, USA; University Hospital Leuven, Leuven, Belgium
Objective: To evaluate the safety and effectiveness of the OCS™ Lung System to recruit, preserve and assess non-standard donor lungs that may not meet current standard donor lung acceptance criteria for transplantation.

Trial Design: Prospective single arm multi-center international pivotal trial focusing on improving utilization of non-ideal donor lungs for double lung transplantation.
# EXPAND Lung Donor Eligibility

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor PaO2/FiO2 ≤ 300 mmHg</td>
<td>Moderate/Severe Lung Injury</td>
</tr>
<tr>
<td>Expected Ischemic time &gt; 6 hours</td>
<td>Presence of Active Pneumonia</td>
</tr>
<tr>
<td>DCD Donors</td>
<td>History of Active Lung Disease</td>
</tr>
<tr>
<td>Donor Age ≥ 55 years</td>
<td>Blood Transfusion &gt;10 pRBCs</td>
</tr>
<tr>
<td></td>
<td>ABO Incompatibility</td>
</tr>
<tr>
<td></td>
<td>Tobacco history &gt;20 pack years</td>
</tr>
</tbody>
</table>
EXPAND I Trial

OCS Perfused Donor Lungs N=93

Did Not Meet Tx Criteria on OCS N=12

Met Transplant Criteria on OCS N=81

87% Yield Rate

Not Transplanted
N=1 Recipient dx. lung Ca
N=1 No surgeon available

Recipient Txed. with OCS Lungs N=79
Lungs screened out on OCS

Anticipated ischemic time > 6 hrs (N=1, 8%)

Age > 55 yo (N=4, 33%)

DCD isolated (N=1, 8%)

DCD + other (N=6, 50%)
## Donor lung inclusion characteristics

<table>
<thead>
<tr>
<th>Donor lung inclusion characteristic(s)</th>
<th>Percentage of donor entries</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF &lt; 300</td>
<td>25%</td>
</tr>
<tr>
<td>DCD</td>
<td>33%</td>
</tr>
<tr>
<td>Anticipated ischemic time &gt; 6 hours</td>
<td>32%</td>
</tr>
<tr>
<td>Age &gt; 55 yo</td>
<td>39%</td>
</tr>
<tr>
<td>&gt; 1 inclusion</td>
<td>27%</td>
</tr>
</tbody>
</table>

52 U.S. Transplanted Donors in EXPAND had an Avg. of 39 Declines by other U.S. Centers in UNOS Match Run
# Recipient characteristics

<table>
<thead>
<tr>
<th>Transplanted Recipients with OCS Lungs N=79</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years) (Mean ± SD)</strong></td>
</tr>
<tr>
<td><strong>Female Gender</strong></td>
</tr>
<tr>
<td><strong>Male Gender</strong></td>
</tr>
<tr>
<td><strong>LAS Score (Range)</strong></td>
</tr>
<tr>
<td><strong>Primary Diagnosis</strong></td>
</tr>
<tr>
<td><strong>COPD</strong></td>
</tr>
<tr>
<td><strong>IPF</strong></td>
</tr>
<tr>
<td><strong>CF</strong></td>
</tr>
<tr>
<td><strong>Sarcoidosis</strong></td>
</tr>
<tr>
<td><strong>Other</strong></td>
</tr>
<tr>
<td><strong>Secondary Pulmonary Hypertension</strong></td>
</tr>
<tr>
<td><strong>Transplanted on CPB</strong></td>
</tr>
</tbody>
</table>
Reduced Cold Ischemic Times Despite Extended Total Clamp Times

<table>
<thead>
<tr>
<th></th>
<th>1st Lung</th>
<th>2nd Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Out of Body Time</td>
<td>8.5</td>
<td>10.1</td>
</tr>
<tr>
<td>Total Ischemic Time</td>
<td>2.6</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Mean Time (Hours)
EXPAND Lung Trial – EVLP Physiology

**Vascular Resistance (dyn·s/cm²)**
- Initial OCS Assessment: 351
- Final OCS Assessment: 320

**Peak Airway Pressures (CmH₂O)**
- Initial OCS Assessment: 12
- Final OCS Assessment: 11

**PaO₂/FiO₂ Ratio**
- Donor Assessment: 378
- Final OCS Assessment: 409
EXPAND I Trial

Post-Transplant Patient Survival
Patient Survival 1, 6 and 12 months

- 1 month: 98.7%
- 6 months: 93.7%
- 12 months: 91.1%
Patient Survival EXPANDI vs INSPIRE Cohorts

EXPAND Trial (Extended Criteria Donors) vs INSPIRE Trial Control (Standard Criteria Donors)

- **30 Days**: 98.7% (EXPAND) vs 99.5% (INSPIRE)
- **6 Months**: 93.7% (EXPAND) vs 90.8% (INSPIRE)
- **12 Months**: 91.1% (EXPAND) vs 87% (INSPIRE)

Proportion (%)
EXPAND Patient Survival vs Standard of Care

<table>
<thead>
<tr>
<th>Time</th>
<th>EXPAND Trial (Extended Criteria)</th>
<th>INSPIRE Trial Control (Standard Criteria)</th>
<th>US National UNOS Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 Days</td>
<td>98.7</td>
<td>99.5</td>
<td>96.2</td>
</tr>
<tr>
<td>6 Months</td>
<td>93.7</td>
<td>90.8</td>
<td>90.2</td>
</tr>
<tr>
<td>12 Months</td>
<td>91.1</td>
<td>90.2</td>
<td>85</td>
</tr>
</tbody>
</table>

Proportion (%)
Primary Graft Dysfunction Grade 3
EXPAND I Trial PGD3 Rates

Proportion (%)

PGD3 Within Initial 72 Hours

44.30%

T0 T24 T48 T72

40.5% 16.5% 9.0% 6.4%
PGD3 Rates EXPAND (ECD) vs INSPIRE (SOC)

Incidence of PGD3 Within 72 hours

- EXPAND Trial: 44.3%
- INSPIRE Trial Control: 28.8%

Incidence of PGD3 At Each Timepoint

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>EXPAND Trial</th>
<th>INSPIRE Trial Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>40.5</td>
<td>20.7</td>
</tr>
<tr>
<td>T24</td>
<td>16.5</td>
<td>10.9</td>
</tr>
<tr>
<td>T48</td>
<td>9</td>
<td>6.6</td>
</tr>
<tr>
<td>T72</td>
<td>6.4</td>
<td>5.5</td>
</tr>
</tbody>
</table>
PGD3 in EXPAND (OCS) and DEVELOP UK Trial (Static)

PGD3 Stratified by Donor Inclusion Criteria

- PF Ratio <300 mmHg: 40%
- Age > 55 YO: 41%
- Ischemic Time >6 hours: 48%
- DCD Donors: 61%
Portable EVLP in Extended Criteria Donors

• Excellent survival with Extended Criteria Donors (EXPAND)

• But still have a burden of PGD with Extended Criteria Donors

• Static platform also FDA approved – need to further understand options.
Effects of time on portable EVLP on incidence of PGD remain unknown

Does this curve change if the parameters are excellent on EVLP??
THANK YOU!

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Visible Heart Lab
OCS Investigators collaborators

Transforming Healthcare

CHI St. Luke’s Health
Baylor St. Luke’s Medical Medical Center

McNair Campus