Results of the Fontan Udenafil Exercise Longitudinal (FUEL) Trial

David J. Goldberg, MD
Presenting on behalf of the FUEL Writing Committee and the Investigators of the Pediatric Heart Network

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Disclosure

• This trial was conducted by the Pediatric Heart Network, funded by NIH / NHLBI, with financial support from the sponsor, Mezzion Pharma Co. Ltd.

• The contents of this work are solely the responsibility of the authors and do not necessarily represent the official views of NHLBI, NIH, DHHS, or Mezzion

• Dr. Goldberg and Dr. Paridon receive grant support from Mezzion and are co-inventors of patent US10137128B2
Background

• The Fontan operation is the final step in the staged palliation of the heterogeneous forms of congenital heart disease characterized by a functional single ventricle
  • Hypoplastic left heart syndrome, tricuspid atresia, double inlet left ventricle, pulmonary atresia with intact ventricular septum
• This procedure creates a total cavopulmonary connection, allowing for systemic venous return to bypass the heart and flow passively into the pulmonary arteries
Background

• The circulation created by Fontan palliation is characterized by elevated central venous pressure and low cardiac output.

• In this physiology, pulmonary vascular resistance plays a critical role in allowing for the efficient flow of blood through the lungs without the benefit of a ventricular pump.

• While this circulation is typically stable through childhood, cardiovascular efficiency deteriorates over time, associated with a decline in exercise performance.
Background

• Given the importance of pulmonary vascular resistance, modulators of PVR make sense as potential therapies

• Udenafil is a novel PDE5 inhibitor that has undergone Phase I/II testing in adolescents after Fontan (PHN / Mezzion)

• 87.5 mg twice daily was associated with the highest average serum concentration, with no dose-limiting adverse events

• In the FUEL Trial, we evaluate the effect of 87.5 mg of udenafil, given twice daily, on exercise performance in adolescents who have undergone Fontan palliation
Inclusion:
1. Currently on anticoagulation
2. Fluent in English, Spanish, Korean

Exclusion:
1. Small body size
2. Significant co-morbidities
3. Current therapy with a pulmonary vasodilator
4. Peak VO₂ <50% predicted on a recent clinical exercise test

30 sites in North America and Republic of Korea

Adolescents 12 to <19 y with Fontan physiology

Baseline exercise test: max effort (RER ≥1.1)?

No → Ineligible

Yes → Randomize

Udenafil, 87.5 mg BID

Matching placebo

Primary Endpoint: Change in Peak VO₂ from baseline to 26 weeks

Key secondary endpoints:
1. Exercise measures at VAT
2. Myocardial performance index
3. Reactive hyperemia index
4. Brain natriuretic peptide
Statistical Analyses

• Primary efficacy endpoint: Between group difference in change in peak VO$_2$ from baseline to 26-weeks

• Sample size determined by number of participants needed to detect a 10% between-group difference with 90% power, assuming within-patient correlation of 0.33 and 15% dropout

• For primary outcome, missing data imputed as equal to baseline

• ANCOVA with fixed factors for ventricular morphology and continuous covariate of baseline peak VO$_2$
Results

1376 patients screened

400 randomized

200 udenafil
- 2 unable to generate 26-week maximal exercise test
- 9 did not complete testing

189 completed testing

200 placebo
- 5 unable to generate 26-week maximal exercise test
- 5 did not complete testing

190 completed testing
## Baseline Characteristics, Mean ± SD / n (%)

<table>
<thead>
<tr>
<th></th>
<th>Udenafil (n=200)</th>
<th>Placebo (n=200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>15.4 ± 2.0</td>
<td>15.6 ± 2.0</td>
</tr>
<tr>
<td>Female</td>
<td>89 (44%)</td>
<td>72 (36%)</td>
</tr>
<tr>
<td>White</td>
<td>169 (84%)</td>
<td>155 (78%)</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>94 (47%)</td>
<td>95 (48%)</td>
</tr>
<tr>
<td>Fenestration</td>
<td>73 (36%)</td>
<td>58 (29%)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>162 ± 10</td>
<td>165 ± 9</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>57 ± 14</td>
<td>59 ± 13</td>
</tr>
<tr>
<td>BMI</td>
<td>22 ± 4</td>
<td>22 ± 4</td>
</tr>
</tbody>
</table>
### Exercise Data, Mean ± SD (n)

<table>
<thead>
<tr>
<th></th>
<th>Udenafil</th>
<th>Placebo</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Change</td>
<td>Baseline</td>
</tr>
<tr>
<td>Peak VO₂ (ml/kg/min)</td>
<td>27.8±6.9 (200)</td>
<td>-0.23±4.1 (200)</td>
<td>28.0±6.6 (200)</td>
</tr>
<tr>
<td>Peak VO₂ (ml/min)</td>
<td>1562±437 (200)</td>
<td>44±245 (200)</td>
<td>1627±414 (200)</td>
</tr>
<tr>
<td>Peak heart rate (bpm)</td>
<td>165±20 (200)</td>
<td>-1.4±11 (189)</td>
<td>168±22 (199)</td>
</tr>
<tr>
<td>O₂ sat at peak (%)</td>
<td>89.2±5.3 (195)</td>
<td>0.4±3.4 (186)</td>
<td>89.8±5.0 (197)</td>
</tr>
<tr>
<td>VO₂ at VAT (ml/min)</td>
<td>1039±301 (170)</td>
<td>33±185 (155)</td>
<td>1021±280 (181)</td>
</tr>
<tr>
<td>Work rate at VAT (W)</td>
<td>66.2±26 (167)</td>
<td>3.8±16 (152)</td>
<td>66.1±23 (177)</td>
</tr>
<tr>
<td>VE/VCO₂ at VAT</td>
<td>34.3±4.9 (170)</td>
<td>-0.8±3.7 (155)</td>
<td>34.8±5.2 (181)</td>
</tr>
</tbody>
</table>

P value represents between group difference in change in variable from baseline to 26-weeks.
Relative Improvement in Exercise Measures

- Change in Peak VO₂ (mL/min): P=0.071
- Change in VO₂ at VAT (mL/min): P=0.012
- Change in Work Rate at VAT (watts): P=0.021
# Secondary Outcomes, Mean ± SD (n)

<table>
<thead>
<tr>
<th></th>
<th>Udenafil</th>
<th>Placebo</th>
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<th>p</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Change</td>
<td>Baseline</td>
<td>Change</td>
</tr>
<tr>
<td>MPI</td>
<td>0.44±0.21 (150)</td>
<td>-0.02±0.11 (122)</td>
<td>0.45±0.16 (155)</td>
<td>-0.01±0.19 (128)</td>
</tr>
<tr>
<td>lnRHI</td>
<td>0.46±0.24 (184)</td>
<td>0.07±0.30 (163)</td>
<td>0.47±0.33 (186)</td>
<td>0.05±0.37 (165)</td>
</tr>
<tr>
<td>Log BNP</td>
<td>2.46±1.00 (200)</td>
<td>0.08±0.90 (187)</td>
<td>2.27±1.14 (199)</td>
<td>0.03±1.13 (191)</td>
</tr>
</tbody>
</table>

*P value represents between group difference in change in variable from baseline to 26-weeks*
<table>
<thead>
<tr>
<th>Safety</th>
<th>Udenafil</th>
<th>Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache / migraine</td>
<td>69 (35%)</td>
<td>50 (25%)</td>
<td>0.049</td>
</tr>
<tr>
<td>Facial flushing</td>
<td>32 (16%)</td>
<td>12 (6%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Increased erection (<em>males only</em>)</td>
<td>13 (12%)</td>
<td>2 (2%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Abdominal pain / discomfort</td>
<td>13 (7%)</td>
<td>13 (7%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>11 (6%)</td>
<td>3 (2%)</td>
<td>0.053</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9 (5%)</td>
<td>15 (8%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Nausea / vomiting</td>
<td>10 (5%)</td>
<td>11 (6%)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

P value represents between group difference in listed adverse event
Limitations

• This study did not include detailed hemodynamics (e.g., cardiac catheterization or cardiac MRI)

• Based on exclusion criteria, these results may not apply to patients with significant co-morbidities or very low peak VO₂

• The duration of the trial precluded long-term assessment of safety, addressed in the FUEL Open-Label Extension Trial
Conclusion

• Treatment with udenafil (87.5 mg bid) was:
  • Not associated with a statistically significant improvement in oxygen consumption at peak exercise
  • Associated with statistically significant improvements in sub-maximal exercise performance measured at the ventilatory anaerobic threshold
  • Not associated with changes in myocardial performance index, reactive hyperemia index, or log BNP
  • Well-tolerated and safe, with adverse events limited to those known to be associated with PDE5 inhibitors
Clinical Implications

• Our study extends recent findings highlighting the importance of sub-maximal exercise in the understanding of Fontan physiology

• Unlike peak VO₂, sub-maximal exercise is not constrained by the physiologic ceiling of central venous pressure inherent in exercise physiology after Fontan palliation

• An improvement in sub-maximal exercise has real implications for the day-to-day activities of adolescents with Fontan physiology

• This is first large clinical trial to show improvements in measures of clinically relevant exercise performance in those with single ventricle heart disease after Fontan palliation
Acknowledgements

• This work could not have been completed without the contributions of the PHN investigators and study coordinators and the support of NIH / NHLBI

• Thank you to Mezzion Pharma and the staff at Healthcare / New England Research Institutes

• Thank you to the advocacy groups that supported this effort

• Thank you to all of the children that agreed to participate in the FUEL Trial and the families that dealt with the logistics