ENDPOINTS FOR GENE THERAPY CLINICAL TRIALS: Pompe Disease

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Endpoints for Pompe disease

Overview

• Liver depot gene therapy for Pompe disease
• Challenges with developing endpoints
• Validated endpoints for Pompe disease
• Applying endpoints in gene therapy
Conflict of Interest

Disclosures

• Dr. Dwight Koeberl and Duke University might benefit financially, if the experimental treatments discussed here prove effective and are successful commercially.

• Dr. Koeberl has served as a consultant for Sangamo Therapeutics and for Genzyme Sanofi, Amicus, and Vertex.

• Dr. Koeberl has received grant support from Viking Therapeutics, Genzyme Sanofi, Roivant Rare Diseases, and Amicus.

• Dr. Koeberl has equity in Actus Therapeutics, which is developing gene therapy for Pompe disease.
Liver Depot Gene Therapy Strategy

- A one-time gene therapy treatment
  Can be used with enzyme replacement therapy to reduce immunogenecity
- Liver targeted delivery and expression.
- Activation of regulatory T cells.
  - Suppress previously formed anti-rhGAA antibodies.
  - Enhanced efficacy.
- Orphan Drug Designation

Gene Therapy with AAV8-LSPhGAA. Treatment with rAAV8 converts the liver depot for continuous secretion of the enzyme therapy (rhGAA) correcting the GAA deficient. Liver expression induces immune tolerance to rhGAA, by reducing antibodies through suppression by regulatory T cells.
## Comparison of ERT and Liver Depot Gene Therapy

<table>
<thead>
<tr>
<th></th>
<th>ERT</th>
<th>AAV8-LSPhGAA*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stability</strong></td>
<td>Short half-life in blood</td>
<td>Continuous GAA in bloodstream</td>
</tr>
<tr>
<td><strong>GAA delivery to muscle</strong></td>
<td>Lack of uptake in skeletal muscle</td>
<td>Increased delivery to muscle</td>
</tr>
<tr>
<td><strong>Immune Responses</strong></td>
<td>High titer antibody response</td>
<td>Immune tolerance induction</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>Some patients fail to respond</td>
<td>Larger patient population</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>Partial</td>
<td>More complete correction</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>Yes</td>
<td>Decreased</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Every 1-2 weeks</td>
<td>Single dose</td>
</tr>
</tbody>
</table>

*Gene therapy data from laboratory studies, not a clinical trial*
Experiment (Gene therapy vs. ERT)

• Comparison of 3 groups
  – AAV8-LSPhGAA (8E+11 vg/kg)
  – ERT
  – No treatment

• Evaluate after one month

• Muscle GAA activity and glycogen content
Direct Comparison of AAV8-LSPhGAA With ERT

- Increased GAA activity and decreased glycogen content

![Graphs showing GAA activity and glycogen levels across different tissues (Liver, Heart, Diaphragm, Quad) with untreated, ERT, and AAV conditions.](image)
Challenges with developing endpoints

AAV8-LSPhGAA in Adults with Pompe Disease
Challenges with developing endpoints

• Standard of care should not be withheld
• Overlapping effects with gene therapy
• Goal is a standalone
Validated endpoints for Pompe disease

Clenbuterol in Adults with Pompe Disease
Phase I/II Clinical Trial of Clenbuterol

- **Baseline**: Assess
- **Week 6**: Start clenbuterol
- **Week 12**: Dose increase
- **Week 18**: Assess
- **Week 52**: Assess
## Characteristics of Study Population

<table>
<thead>
<tr>
<th></th>
<th>Clenbuterol (n=8)</th>
<th>Placebo (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median)</td>
<td>52</td>
<td>32</td>
</tr>
<tr>
<td>Gender</td>
<td>5M:3F</td>
<td>2M:3F</td>
</tr>
<tr>
<td>Duration of ERT, months</td>
<td>75 (38-102)</td>
<td>21 (15-72)</td>
</tr>
<tr>
<td>(median, range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline FVC, % predicted</td>
<td>50</td>
<td>89</td>
</tr>
<tr>
<td>(median)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline 6MWT, meters</td>
<td>350</td>
<td>450</td>
</tr>
<tr>
<td>(median)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline 6MWT, % predicted</td>
<td>51</td>
<td>72</td>
</tr>
<tr>
<td>(median)</td>
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</tr>
</tbody>
</table>
Effect of Clenbuterol on 6MWT

- Distance walked trended higher at Week 18
- Predicted 6MWD (%) significantly higher at Weeks 18 and 52

No change seen in placebo group
Effect of Clenbuterol on PFTs

Increased respiratory muscle strength based upon significantly improved performance on the MIP test
Effect of Clenbuterol Upon Biochemical Correction

(A) Significantly increased GAA activity (34%)
(B) Significantly decreased glycogen content (50%) in the clenbuterol group.
Effect Of Clenbuterol On Muscle

Clenbuterol

Baseline

Week 52

Placebo

Clenbuterol

Placebo
Applying endpoints in gene therapy

AAV8-LSPhGAA in Adults with Pompe Disease
Phase I Clinical Study

- 6 Adult patients, 3x2 design (Low and Higher Dose)
- Safety (primary endpoint):
  - Incidence of adverse events (AE) and serious AE
  - Clinical laboratory abnormalities
- Efficacy (secondary endpoints):
  - Muscle function (6 minute walk and pulmonary function testing)
  - GAA activity in muscle biopsy and serum
  - Antibody formation
  - Urinary biomarker
Validated Endpoints

- Our data reveal **favorable initial safety and efficacy data** for adjunctive clenbuterol therapy in LOPD patients.

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>Week 52</th>
<th>Change</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWT (m)</td>
<td>373</td>
<td>389</td>
<td>4%</td>
<td>0.08</td>
</tr>
<tr>
<td>6MWT (%)</td>
<td>58</td>
<td>61</td>
<td>5%</td>
<td>0.03</td>
</tr>
<tr>
<td>GSGC (pt)</td>
<td>16</td>
<td>14</td>
<td>-13%</td>
<td>0.004</td>
</tr>
<tr>
<td>QMFT (pt)</td>
<td>40</td>
<td>47</td>
<td>18%</td>
<td>0.007</td>
</tr>
<tr>
<td>FEV1 (%)</td>
<td>58</td>
<td>65</td>
<td>12%</td>
<td>0.06</td>
</tr>
<tr>
<td>FVC (%)</td>
<td>60</td>
<td>64</td>
<td>7%</td>
<td>0.11</td>
</tr>
<tr>
<td>MEP (%)</td>
<td>40</td>
<td>54</td>
<td>35%</td>
<td>0.06</td>
</tr>
<tr>
<td>MIP (%)</td>
<td>51</td>
<td>69</td>
<td>35%</td>
<td>0.004</td>
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<tr>
<td>Issue</td>
<td>Response</td>
<td></td>
<td></td>
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<tr>
<td>-------------------------------</td>
<td>---------------------------------</td>
<td></td>
<td></td>
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<tr>
<td>Ongoing benefits</td>
<td>Stably treated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluctuating GAA</td>
<td>Timing of visits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Need to stop ERT</td>
<td>Criteria for withdrawal</td>
<td></td>
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</table>
Surrogate Endpoint: Muscle Glycogen?

- Pompe disease is a glycogen storage disease; glycogen accumulation is integral to pathogenesis
- Decreased glycogen correlated with bioactivity and/or efficacy
  - Proof of concept experiments
  - Preclinical experiments
  - Clinical trial of clenbuterol
- Initial validation in Phase I/II clinical trial of clenbuterol
Project Team

Clinical Investigators

Edward Smith
Clinical Investigator
Neuromuscular Specialist

Laura Case
Physical therapy
-Muscle testing
-Pompe expertise

Lead Investigators

Dwight Koeberl
-Leads gene therapy program
-Multiple investigator-initiated clinical trials

Priya Kishnani
Co-Investigator
-Internationally recognized expertise

Translational Team

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Regulatory Affairs

Ashley Richardson
Office of Corporate Research Collaborations

Dennis Thomas
Office of Licensing and Ventures

Clinical Laboratories

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Biochemical genetics
-CAP, CLIA laboratory
-Biomarker analysis

Deeksha Bali
Glycogen storage disease
-CAP, CLIA laboratory
-GAA and glycogen testing
Summary

• Phase I study of liver depot gene therapy in Pompe disease
• Secondary endpoints validated in Pompe disease
• ERT interacts with gene therapy
• Address by understanding the dynamics of Pompe disease therapy
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