Robust Engraftment with MGTA-456, a CD34+ Expanded Cell Therapy Product in Patients with Inherited Metabolic Disorders (IMD): Preliminary Phase 2 Trial Results

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TCT Presentation
February 21, 2019
Role of Microglia in Transplant for Inherited Metabolic Diseases

- Derived from CD34$^+$ hematopoietic stem cells
- Following transplant, can locate to the CNS
- Can provide enzyme to the brain through cross-correction, while ERT does not
- Higher doses of CD34$^+$ cells hypothesized to improve microglia engraftment
MGTA-456 utilizes an aryl-hydrocarbon receptor antagonist to expand hematopoietic stem cells ex vivo

No +AHR Antagonist

Hematopoietic Stem Cell

Self-Renewal

Differentiation

Self-Renewal

Self-Renewal

+AHR Antagonist

Hematopoietic Stem Cell

Self-Renewal

Self-Renewal

Differentiation

Self-Renewal

Self-Renewal

Aryl Hydrocarbon Receptor antagonist blocks differentiation and drives HSC self-renewal
MGTA-456: Aryl Hydrocarbon Receptor (AHR) Antagonism for HSC Expansion

Phase I/II Trial of StemRegenin-1 Expanded Umbilical Cord Blood Hematopoietic Stem Cells Supports Testing as a Stand-Alone Graft

John E. Wagner, Claudio G. Brunstein, Anthony E. Boitano, Todd E. Defor, David McKenna, Darin Sumstad, Bruce R. Blazar, Jakub Tolar, Chap Le, Julie Jones, Michael P. Cooke, Conrad C. Bleul
MGTA-456: Product & Process

- First-in-class proprietary allogeneic stem cell therapy
- Increases number of stem cells in a single cord blood unit to yield a higher stem cell dose
- 36 patients treated with MGTA-456 in Phase 1/2 trial in Heme Malignancies showed rapid engraftment.
## Study design

<table>
<thead>
<tr>
<th>Study design</th>
<th>Study in patients with Hurler, cALD, MLD and GLD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong># patients</strong></td>
<td>12</td>
</tr>
<tr>
<td><strong>Sites</strong></td>
<td>• University of Minnesota, Duke, Emory, Cincinnati Children’s</td>
</tr>
<tr>
<td><strong>Primary Endpoints</strong></td>
<td>• Incidence of neutrophil recovery by day 42</td>
</tr>
<tr>
<td></td>
<td>• Time to neutrophil recovery</td>
</tr>
<tr>
<td><strong>Secondary Endpoints</strong></td>
<td>• Incidence of infusion-related toxicities</td>
</tr>
<tr>
<td></td>
<td>• Incidence of late hematological graft failure</td>
</tr>
<tr>
<td></td>
<td>• Incidence of platelet recovery</td>
</tr>
<tr>
<td></td>
<td>• Time to platelet recovery</td>
</tr>
<tr>
<td></td>
<td>• Incidence of graft vs. host disease</td>
</tr>
<tr>
<td></td>
<td>• Mortality within first 100 days and 1 year post infusion</td>
</tr>
<tr>
<td><strong>Exploratory endpoints</strong></td>
<td>• Disease-specific enzyme activity/protein level</td>
</tr>
<tr>
<td></td>
<td>• Immune reconstitution</td>
</tr>
<tr>
<td></td>
<td>• Neurodevelopment outcomes</td>
</tr>
</tbody>
</table>

### New Trial Using MGTA-456 in Patients with Inherited Metabolic Diseases
IMD-001: Single-Arm, open-label Phase 2 Study of MGTA-456 in Inherited Metabolic Diseases

Eligibility
Age <16 years

Diseases
- Hurler syndrome
- Metachromatic leukodystrophy
- Globoid Cell Leukodystrophy
- Cerebral Adrenoleukodystrophy

Cohort 1:
- Fresh Product
- 5 patients treated per protocol
- 1 patient excluded from analysis for protocol deviation

Cohort 2:
- Cryopreserved Product
Patients per protocol; MGTA-456 cell doses administered

<table>
<thead>
<tr>
<th>Disease-Patient #</th>
<th>Age (y)</th>
<th>HLA Allele Match</th>
<th>TNC dose x10^7/kg (expanded fraction)</th>
<th>CD34^+ dose x10^6/kg (expanded fraction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPS1-1</td>
<td>1.7</td>
<td>7/8</td>
<td>16.4</td>
<td>60</td>
</tr>
<tr>
<td>MPS1-2</td>
<td>1.3</td>
<td>7/8</td>
<td>27.4</td>
<td>109</td>
</tr>
<tr>
<td>MPS1-3</td>
<td>0.3</td>
<td>7/8</td>
<td>27.0</td>
<td>111</td>
</tr>
<tr>
<td>cALD-1</td>
<td>7.1</td>
<td>8/8</td>
<td>13.1</td>
<td>58</td>
</tr>
<tr>
<td>cALD-2</td>
<td>6.7</td>
<td>7/8</td>
<td>25.7</td>
<td>110</td>
</tr>
</tbody>
</table>

Median expansion: 561-fold
Median infused CD34^+ dose: 110 x10^6/kg
Median infused TNC dose: 26.4 x10^7/kg

Ex vivo CD34^+ expansion
Rapid hematopoietic recovery observed with MGTA-456 compared to unmanipulated cord blood

**Neutrophil recovery**
Median days of neutropenia:
- 1 day MGTA-456 (n=5)
- 8 days UCB (n=27) institutional historical control

**Platelet recovery:**
Median 33 days
- MGTA-456 (n=5) vs.
- 35 days historical UCB control
MGTA-456 achieves rapid donor derived myeloid chimerism
## Hospital days until discharge post-transplant

<table>
<thead>
<tr>
<th>Disease-Patient #</th>
<th>Age (y)</th>
<th>Days in Hospital Post-Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPS1-1</td>
<td>1.7</td>
<td>17</td>
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<tr>
<td>MPS1-2</td>
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<tr>
<td>MPS1-3</td>
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<tr>
<td>cALD-1</td>
<td>7.1</td>
<td>12</td>
</tr>
<tr>
<td>cALD-2</td>
<td>6.7</td>
<td>19</td>
</tr>
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</table>

Median 19 days
GVHD and serious adverse events of patients treated per protocol

GVHD
One patient experienced skin-only aGVHD (Stage 2)
  • resolved with steroids
No patients have experienced cGVHD

Autoimmune Cytopenia (AIC): Expected & frequent event in IMD patients post transplant (20-56% incidence; especially in younger pts)
Two young MPS1 patients with AIC SAE:
  • 1 patient died at day +143
  • 1 patient required a 2\textsuperscript{nd} transplant

Both cases deemed not related to MGTA-456
Normalization of blood leukocyte IDUA activity in MPS1 patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Screening</th>
<th>Day +42</th>
<th>Day +60</th>
<th>Day +100</th>
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<tbody>
<tr>
<td>MPS1-1</td>
<td>Low</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>MPS1-2</td>
<td>Low</td>
<td>Normal</td>
<td>Normal</td>
<td>QNS</td>
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<tr>
<td>MPS1-3</td>
<td>Low</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Blood leukocyte enzyme level reported per reference range of laboratory utilized. QNS, quantity not sufficient.

Normalization of blood leukocyte IDUA activity after HSCT has been significantly associated with improvement in: Height, kyphosis, cervical instability, cord compression hip dysplasia, mitral valve insufficiency, overnight hypoxia, hearing loss and corneal clouding in MPS1 patients (n=217)

Urine glycosaminoglycans (GAGs) post-transplant in MPS1 (Hurler) patients

**Urine Heparan Sulfate**

**Urine GAG NRE I0S0**

**Urine GAG NRE I0S6**
Reduction of neuro-inflammation in cALD patients by day 28 post-transplant

<table>
<thead>
<tr>
<th>Day post-transplant</th>
<th>Screening</th>
<th>+28</th>
<th>+60</th>
<th>+100</th>
<th>+180</th>
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<tbody>
<tr>
<td>Loes Score</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Gadolinium enhancement</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
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</table>

Data corrected from Dec 2019
Summary

• 5 patients treated per protocol to date
• Median 561-fold *ex vivo* expansion of CD34\(^+\) cells and median infused CD34\(^+\) cell dose of 110 x 10\(^6\)/kg and TNC dose of 26.4 x 10\(^7\)/kg
• MGTA-456 infusion well-tolerated with minimal reactions
• Transplantation with MGTA-456 results in rapid engraftment: Median 1 day (range 0-9) of neutropenia ≥98% myeloid chimerism by day +14 in evaluable patients
• Disease specific outcomes (enzyme and MRI) demonstrated evidence of early response that is associated with long-term benefits
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