MGTA-456 Cell Therapy in Inherited Metabolic Diseases (IMD) Yields Rapid and Durable Long-Term Improvement of Disease-Specific Outcomes in a Phase 2 Trial

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TCT Presentation
February 19, 2020
**CROSS-CORRECTION OF DISEASE BY DONOR-DERIVED MYELOID CELLS IN BRAIN POST-TRANSPLANT**

**STRATEGIES TO CROSS-CORRECT**

### Allogeneic HSC Transplant
- > 2,000 transplants performed since 1980 with documented disease-modifying capabilities
- Cord blood is a common source of HSCs
- Cord blood inventory provides rapid access to patients

### Autologous Gene Therapy
- Limited by challenging manufacturing processes
- Unknown effects of transduction efficiency, dose and durability
- Not yet broadly available
MGTA-456 is a High Dose Cell Therapy With Expanded CD34+ Stem Cells

*Differentiation is blocked by proprietary aryl hydrocarbon receptor (AHR) antagonist, driving HSC self-renewal and expansion*

**No AHR Antagonist**

**+AHR Antagonist**
Cord blood unit sourced from public bank

Selection of CD34+ cells

Fraction 1. CD34+ enriched
Stem and progenitor cells; responsible for engraftment

Fraction 2. CD34+ depleted
CD34 depleted cells for engraftment and immune reconstitution

15 Day expansion of CD34+ cells

Cryopreserved

Cryopreserved

MGTA-456 Intravenously dosed as two fractions
MGTA-456 may address unmet needs in IMD HSCT

While umbilical cord blood (UCB) is a preferred unrelated donor source—

<table>
<thead>
<tr>
<th>UCB use has significant drawbacks</th>
<th>Potentially addressed by MGTA-456</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Extended time to engraftment (neutrophil, and to CNS), and subsequent disease impact</td>
<td><img src="chart.png" alt="Graph showing CD34+ Cell Number" /></td>
</tr>
<tr>
<td>• Graft failure remains a risk</td>
<td>50 patients transplanted In Heme Malignancies to date with 100% engraftment</td>
</tr>
<tr>
<td>• Low cell dose limiting available well-matched cords especially in larger patients</td>
<td></td>
</tr>
<tr>
<td>• Extended time in hospital</td>
<td>Phase 1/2 Trial of MGTA-456 in Hematologic Malignancies Wagner et al Cell Stem Cell 2016</td>
</tr>
<tr>
<td></td>
<td>Open Phase 2 IIT in Hematologic Malignancies at UMN; NCT03674411</td>
</tr>
<tr>
<td></td>
<td>Interim results presented at Poster #304 Session 1 Feb 19, 6:30-8:00 pm</td>
</tr>
</tbody>
</table>
IMD-001: Phase 2 Study of MGTA-456 in Inherited Metabolic Diseases (IMDs)

Phase 2 open label, single-arm study across four inherited metabolic disorders: MPS-IH, cALD, MLD or GLD
ClinicalTrials.gov NCT03406962

Cohort 1 (enrollment complete)
Transplantation with fresh MGTA-456 Busulfan/Fludarabine MAC

Cohort 2 (enrolling)
Transplantation with fresh MGTA-456 Busulfan/Cytarabine MAC

Primary Endpoints
• Incidence of neutrophil recovery by day 42
• Time to neutrophil recovery

Secondary Endpoints
• Incidence of infusion-related toxicities
• Incidence of late hematological graft failure
• Incidence of platelet recovery
• Time to platelet recovery
• Incidence of graft vs. host disease
• Mortality within 100 days and 1 year

Sites
• UMN
• Duke
• Emory
• Cincinnati Children’s

Long Term Follow Up Study
ClinicalTrials.gov NCT04008849

Enrolled patients followed up to 4 years post-transplant with MGTA-456

• Approximately 12 pediatric patients
• Followed for 1 year
<table>
<thead>
<tr>
<th>Disease-Patient #</th>
<th>Age (y)</th>
<th>HLA Allele Match</th>
<th>TNC dose $\times 10^7$/kg (expanded fraction)</th>
<th>CD34$^+$ dose $\times 10^6$/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>

**Ex vivo CD34$^+$ Expansion**

- **Median expansion:** 561-fold
- **Median infused CD34$^+$ dose:** $110 \times 10^6$/kg
- **Median infused TNC dose:** $26.4 \times 10^7$/kg
IMD-001: Improved Hematopoietic Recovery Observed Compared to Standard of Care

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 controls

Days in Hospital

- Median 19 days MGTA-456 vs. >30 historical UCB controls
IMD-001: Rapid Donor Derived Myeloid Chimerism with MGTA-456
Immune Reconstitution of MGTA-456 Compared to Cord Blood
IMD-001: Low Rates of GVHD and A Safety Profile in Line with HSCT

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

**Adverse Events**
- No SAE’s reported within 48 hours of dosing
- Most commonly reported events (>1 pt) pyrexia, infection, autoimmune cytopenia
  - Analysis of multi-institutional data on autoimmune cytopenias showed higher risk associated with Busulfan/Fludarabine conditioning prompting change to Busulfan/Cyclophosphamide conditioning for cohort 2.
- No SAE’s have been attributed to MGTA-456
- Safety profile in line with standard of care
Normalization of blood leukocyte IDUA activity after HSCT has been significantly associated with improvement in disease outcomes.

All patients achieved normalization by Day 42.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Screening</th>
<th>Day+42</th>
<th>Day+60</th>
<th>Day+100</th>
<th>Day+180</th>
<th>1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPS1-1</td>
<td>Low</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>MPS1-2</td>
<td>Low</td>
<td>Normal</td>
<td>Normal</td>
<td>Quantity not sufficient</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>MPS1-3</td>
<td>Low</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Low'</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Blood leukocyte enzyme level reported per reference range of laboratory utilized.

* Poor sample quality, concurrent plasma IDUA activity reported as normal.
MPS IH-specific GAGs decline post-transplant
Early resolution is maintained through 1 year post transplant
cALD: Neuroinflammation Stabilized within 28 Days of Transplant

Standard of Care

Gadolinium Resolution Post HSCT

Outcomes Post MGTA-456 Transplant

Gadolinium Resolution

Days Post MGTA-456 Transplant

Screening 28 60 100 180 365

Pt 1 Y N N N N N

Pt 2 Y N N N N N

Stable NFS

Loes Score

NFS Score

0 1 2 3 4

scr 180 365

Stable Loes Scores

0 1 2 3 4 5

scr 28 60 100 180 365

Orchard et al Blood 2019

Raymond et al BBMT 2019
Preliminary neurocognitive testing to 1 year

cALD:

MPS1:
MGTA-456 for the Treatment of IMDs: Summary

- MGTA-456 infusion well-tolerated with minimal reactions
- Immune reconstitution comparable to unmanipulated UCB
- Transplantation with MGTA-456 results in rapid engraftment
- Impact on disease observed early and maintained through 1 year
  - cALD: Early and durable resolution of neuroinflammation
  - Hurler: Normalization of blood leukocyte IDUA
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