INTRODUCTION

- Background: IMDs including mucopolysaccharidosis type I (MPS/Hurler Syndrome), cerebral onset adrenoleukodystrophy (CALD), metachromatic leukodystrophy (MLD), and globoid cell leukodystrophy (GLD) are progressive, fatal diseases affecting the central nervous system which are treatable through allogeneic hematopoetic stem cell transplantation (HSCT). Cord blood (CB), in the absence of a matched donor, is the preferred source of stem cells as it is rapidly available and allows greater flexibility in allele matching. However, as a result of low cell doses, CB transplants are associated with prolonged periods of neutropenia and increased risk of graft failure up to ~20% in IMD patients (1). MGTA-456 is a first-in-class individualized cell therapy produced from a single CB unit using an aryl hydrocarbon receptor antagonist in a 15-day expansion culture of CD34+ cells. MGTA-456 had a median 324-fold expansion of CD34+ cells in previous phase I/II studies with 24 adult and 3 pediatric patients undergoing myeloablative transplants for hematologic malignancies. All patients engrafted with the time to neutrophil recovery significantly reduced by a median of 9 days compared to historical controls (2). Furthermore, it has been previously shown that higher CD34+ dose correlates with improved engraftment and outcomes in IMD transplant patients (3), leading us to postulate that an increased CD34+ dose provided by MGTA-456 would reduce the length of neutropenia and risk of graft failure in IMD patients as well as improve disease specific outcome measures.

STUDY OBJECTIVES

Primary Objective:
- Evaluate the effect of MGTA-456 on the rate of neutrophil recovery

Key Secondary Objectives:
- Evaluation of the safety of MGTA-456 in patients with IMD
- Characterization of engraftment
- Chimereism, incidence of neutrophil and platelet recovery
- Assessment of incidence of acute and chronic GvHD and transplant-related mortality (TRM)
- Assessment of disease-specific indicators
  - MPS1: Leukocyte IDUA enzyme activity, Urine GAG levels
  - CALD: Brain MRI enhancement and Loe scores
  - Neurodevelopment and resource utilization

STUDY DESIGN

Study Design: A phase 2, open-label trial (NCT03406962)

Patient Population: Enrollment ~12 IMD patients, age <16 yo who lack a non-carrier HLA-matched related donor. Eligible diagnoses are:
- MPS1 (Hurler Syndrome)
- CALD: Blood MRI enhancement and Loe scores
- Neurodevelopment and resource utilization

Study Aims:
- To determine the safety and feasibility of MGTA-456
- To determine the impact of MGTA-456 on neutrophil recovery, platelet recovery, and disease specific outcomes

Endpoints:
- Days in neutropenia (ANC < 0.5 x 10^9/L)
- Normalised TNC dose x10^9/kg
- CD34+ dose x10^6/kg
- TNC dose x10^6/kg

RESULTS

Patient Characteristics

<table>
<thead>
<tr>
<th>Disease</th>
<th>Patient #</th>
<th>Age (y)</th>
<th>HLA Match</th>
<th>TNC dose x10^9/kg (expanded fraction)</th>
<th>CD34+ dose x10^6/kg (expanded fraction)</th>
<th>TNC Total x10^6/kg (expanded fraction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPS1-1</td>
<td>1.7</td>
<td>7/8</td>
<td></td>
<td>16.4</td>
<td>60</td>
<td>1.59</td>
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<tr>
<td>MPS1-2</td>
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<td>7/8</td>
<td></td>
<td>27.4</td>
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<tr>
<td>MPS1-3</td>
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<td>27.0</td>
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<td>3.31</td>
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<td></td>
<td>13.1</td>
<td>58</td>
<td>1.54</td>
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<tr>
<td>CALD-2</td>
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<td>7/8</td>
<td></td>
<td>26.7</td>
<td>110</td>
<td>2.79</td>
</tr>
</tbody>
</table>

Mean TNC count in MGTA-456 recipients was 3.5 x10^4/L to rapid, sustained improvement in early disease course.

Neutrophil Recovery and Chimerism Outcomes

- Median infused CD34+ dose: 110 x10^6/kg
- Median infused TNC dose: 26.4 x10^6/kg

Days in Hospital Outcomes

<table>
<thead>
<tr>
<th>Disease-Patient</th>
<th>Days in Hospital Post-Transplant</th>
<th>Median Days in Hospital: 19 Days</th>
<th>Historical Data Days in Hospital: 32 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient #1</td>
<td>17</td>
<td>(3.5-7.5)</td>
<td>(3.5-10)</td>
</tr>
<tr>
<td>Patient #2</td>
<td>17</td>
<td>(3.5-7.5)</td>
<td>(3.5-10)</td>
</tr>
<tr>
<td>Patient #3</td>
<td>17</td>
<td>(3.5-7.5)</td>
<td>(3.5-10)</td>
</tr>
</tbody>
</table>

Neutrophil recovery in patients treated with MGTA-456 showed a reduction in neutrophil count compared to unmanipulated CB.

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

Paul J Orchard, MD1, Glen D Raffel, MD PhD2, Carolyn EH Condon, MPH2, Catherine A Monaghan2, Jennifer A Braun, RN BSN3, Ryan Shanley, MS1, Troy C Lund, MD MS4, Ashish Gupta MD1, Anthony E Boitano, PhD2, Michael P Cooke, PhD3, John C Davis Jr, MD MPH2 and John E Wagner, MD1

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CONCLUSIONS

These results in IMD patients treated with MGTA-456, containing highly expanded CD34+ cell doses, demonstrated early and robust (5%, 100%) primary engraftment in all patients with marked reduction in days of neutropenia (median of 1 day). Platelet recovery occurred in a median of 33 days. Time to discharge after transplant was a median of 19 days. MGTA-456 contained a median 561-fold expansion of CD34+ cells after culture with a median infused CD34+ cell dose of 110 x 10^6/kg and median total nucleated cell dose of 26.4 x 10^6/kg from the expanded portion. MGTA-456 patients had a reduction in urinary Hurler-specific GAG levels post-transplant and normalisation of blood leukocyte IDUA enzyme activity. CalD patients had stabilized or trending decrease of VLFCA levels, resolution of pathologic brain MRI enhancement as early as Day +28 post-transplant that was consistently pathologically normal through Day +180. Both Loe and NIS scores, which measure MRI progression of brain disease and functional outcomes respectively, remained stable through Day +180. These data show MGTA-456 has a more rapid engraftment than unmanipulated CB. Furthermore, transplantation with MGTA-456 leads to rapid, sustained improvement in early disease specific outcome measures that strongly correlate with long-term disease outcomes.

REFERENCES

(3) Pardoe et al 2008 Blood 112:2979-84