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.

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INTRODUCTION

- Background: IMDs including mucopolysaccharidosis type IH (MPS1/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 hematopoietic 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 transplant 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
  - Chimerism, 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 Loes 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 with Loes score ≤10, and with neurologic functional score ≤1
- MLD that is asymptomatic late-infantile, or asymptomatic/minimally symptomatic juvenile onset
- Early attenuated GLD (Krabbe disease)

HLA Match Criteria: Eligible CB units were matched at ≥ 6 of 8 HLA loci (A, B, C and DRB1) using allele-based typing with minimum TNC of 1.0 x 10^7/kg

Conditioning Regimen: The reduced toxicity MAC regimen consists of anti-thymocyte globulin (days -9 to -6) followed by fludarabine (40 mg/m^2 days -5 to -2) and busulfan (total exposure 21,000 to 22,000 µM/min/L^{-1} days -5 to -2).

GVHD Immunoprophylaxis Regimen: Cyclosporin and methylprednisolone.

RESULTS

Patient Characteristics

Disease-Patient #	Age (y)	HLA Allele Match	TNC dose x10^7/kg (expanded fraction)	CD34+ dose x10^6/kg (expanded fraction)	TNC Total x10^8/kg (expanded + depleted)
MPS1-1	1.7	7/8	16.4	60	1.99
MPS1-2	1.3	7/8	27.4	109	3.13
MPS1-3	0.3	7/8	27.0	111	3.31
cALD-1	7.1	8/8	13.1	58	1.54
cALD-2	6.7	7/8	25.7	110	2.79

One patient had a protocol deviation at time of conditioning and was *a priori* deemed non-evaluable for analysis. Reported results are for per protocol patients.

Days in Hospital Outcomes

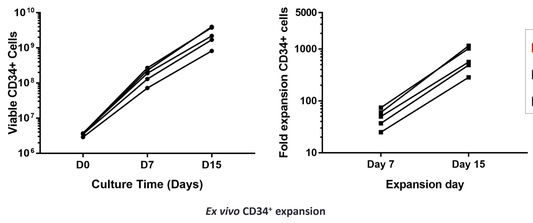
Disease-Patient #	Days in Hospital Post- Transplant
MPS1-1	17
MPS1-2	22
MPS1-3	25
cALD-1	12
cALD-2	19

Median Days in Hospital: 19 Days

Historical Data Days in Hospital: 32 Days

UMN Historical data with unmanipulated CB

MGTA-456 Expansion



Ex vivo CD34+ expansion

Median expansion: 561-fold

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

Median infused TNC dose: 26.4 x10^7/kg

Neutrophil Recovery and Chimerism Outcomes

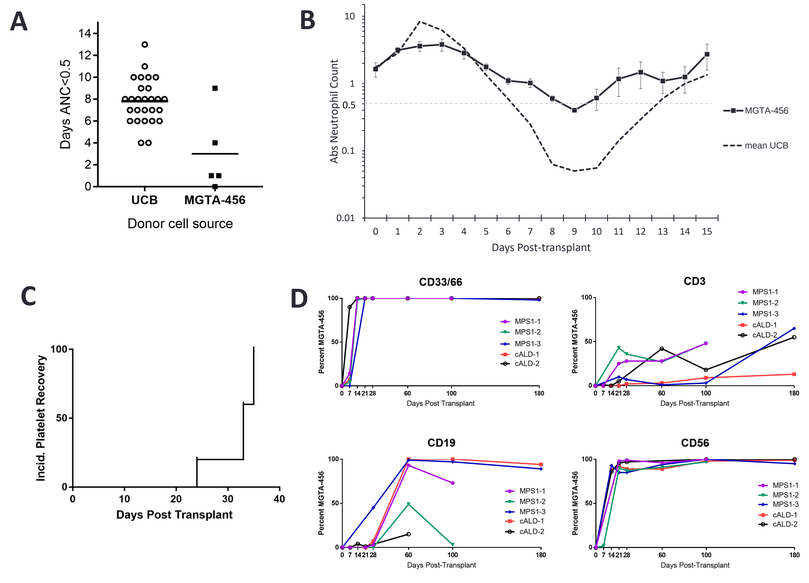
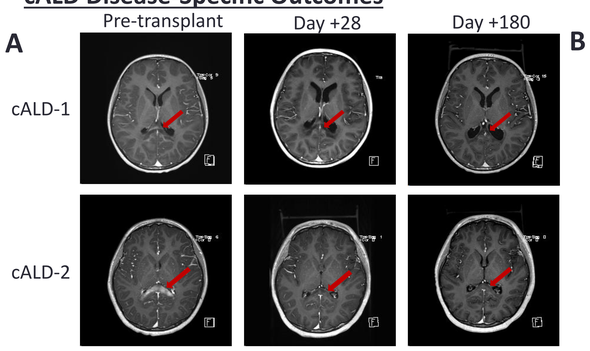


Figure 2. Neutrophil recovery and engraftment. A. Days of neutropenia. Number of days absolute neutrophil count (ANC) <0.5 x 10^9 cells/dL from day of transplant to day of recovery of patients treated per protocol compared to umbilical cord blood historical cohort. **B. ANC recovery.** Daily ANC values +/- SEM after transplant with MGTA-456 (solid line) from day of transplant to day +15 in patients treated per protocol compared with historical UCB cohort treated at the same institution with the identical conditioning regimen (2014-2018) (dotted line). UCB n=27; MGTA-456 n=5. **C. Platelet Recovery.** Incidence of patients achieving >20x10^9 platelets/ul for 7 days without transfusion for 7 days prior. **D. MGTA-456 Chimerism.** Chimerism of peripheral blood of patients in sorted cell populations as indicated over the first 180 days post-transplant.

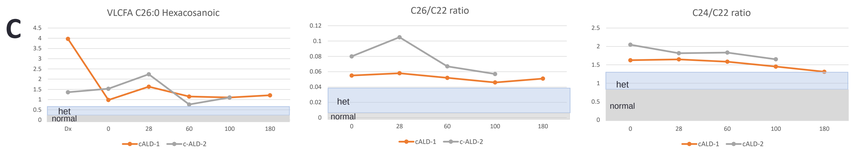
cALD Disease-Specific Outcomes



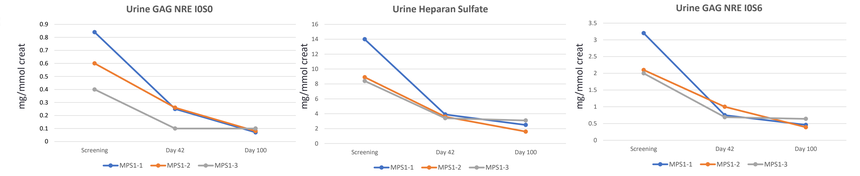
B

Day post-transplant	Screening	+28	+60	+100	+180
Loes Score	3	3	3	3	3
Gadolinium enhancement	Y	N	N	N	N
Neurologic function score	0	-	-	-	0

Day post-transplant	Screening	+28	+60	+100	+180
Loes Score	2	2	2	2	2
Gadolinium enhancement	Y	N	N	N	N
Neurologic function score	0	-	-	-	0



MPS1 Disease-Specific Outcomes



E

Patient	Screening	Day +42	Day +60	Day +100
MPS1-1	Low	Normal	Normal	Normal
MPS1-2	Low	Normal	Normal	Quantity not sufficient
MPS1-3	Low	Normal	Normal	Normal

Figure 3. Disease-specific outcome measures. A. Contrast enhancement in brain MRI images from cALD patients at screening and through Day +180 post-transplant showing consistent resolution. Red arrows indicate areas of inflammation on screening, resolution of contrast-enhancement by Day +28 that remained enhancement negative through Day +180. **B.** Neurologic function scores (NFS) and Loes scores remained stable from baseline to Day +180. NFS **C.** Very long chain fatty acids (VLCFA) plasma ratios in cALD patients trend toward stabilization or possible decrease over time. **D.** Urine total glycosaminoglycan (GAG) levels and **E.** Blood leukocyte IDUA enzyme activity measured at screening and at timepoints post-transplant in MPS1 patients through Day +100.

Safety

MGTA-456 was well tolerated with only two infusion-related adverse events of grade 1 vomiting and grade 3 nausea as of 22-Mar-2019 datacut. All patients achieved primary engraftment. Two patients experienced skin-only aGVHD (Stage 1 and Stage 3) each resolved with steroid treatment. No patients have experienced cGVHD. SAEs of autoimmune cytopenia (AIC) (not related to MGTA-456) developed in two evaluable patients which is a known complication reported in 20-56% of IMD patients and is more frequent in young patients undergoing HSCT. Of the two patients with AIC SAEs, one resulted in death at day +143 and the other required a second transplant.

CONCLUSIONS

These results in IMD patients treated with MGTA-456, containing highly expanded CD34+ cell doses, demonstrated early and robust (5/5; 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 cells/kg and median total nucleated cell dose of 26.4 x 10^7/kg from the expanded portion. MPS1 patients had a reduction in urinary Hurler-specific GAG levels post-transplant and normalization of blood leukocyte IDUA enzyme activity. cALD patients had stabilized or trending decrease of VLCFA levels, resolution of pathologic brain MRI enhancement as early as Day +28 post-transplant that was consistently gadolinium negative through Day +180. Both Loes and NFS 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

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(3) Prasad et al 2008 Blood 112:2979-89
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