Preliminary Phase 2 Results Demonstrate Engraftment with Minimal Neutropenia with MGTA-456, a CD34+ Expanded Cord Blood (CB) Product in Patients Transplanted for Inherited Metabolic Disorders (IMD)

Paul J Orchard, MD[1], Glen D Raffel, MD PhD[2], Carolyn EH Condon, MPH[2], Catherine A Monaghan[2], Demetra Vernet[2], Suzanne T Sheirr[2], Jennifer A Braun, RN BSN[1], Ryan Shanley, MS[1], Troy C Lund, MD MS PhD[1], Anthony E Boitano, PhD[2], Michael P Cooke, PhD[2], John C Davis Jr, MD MPH[2] and John E Wagner, MD[1]

[1] Division of Pediatric Blood and Marrow Transplantation, University of Minnesota, Minneapolis, MN [2] Magenta Therapeutics, Cambridge, MA

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). 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. In previous phase 1/2 studies, 24 adult and 3 pediatric patients with hematologic malignancies treated with myeloablative conditioning (MAC) and MGTA-456 demonstrated a median 324-fold expansion of CD34+ cells. All patients engrafted with the time to neutrophil recovery significantly reduced by a median of 9 days compared to historical controls (2). Furthermore, it was 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 x10^6/kg (expanded fraction)	CD34+ dose x10^6/kg (expanded fraction)	TNC Total x10^8/kg (expanded + depleted)	Days in Hospital Post-Transplant
MPS1-1	1.7	7/8	164	60	1.99	17
cALD-1	7.1	8/8	131	58	1.54	12
MPS1-2	1.3	7/8	274	109	3.13	22
MPS1-3	0.3	7/8	270	111	3.31	25
cALD-2	6.7	7/8	257	110	2.79	19

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.

MGTA-456 Expansion

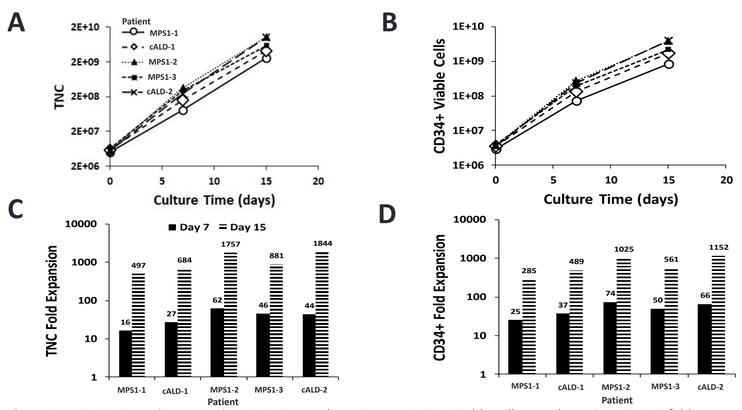


Figure 1. MGTA-456 *ex vivo* expansion. A. TNC vs. culture time. **B.** CD34+ Viable cells vs. culture time. **C**. TNC fold expansion at day 7 and 15. **D.** CD34+ Viable Cell Fold expansion at day 7 and 15. CD34+ viable cell number calculated by multiplying TNC by %viable by %CD34+. n=5 MGTA-456 clinical batches (does not include 1 batch was aborted due to poor UCB unit quality).

Neutrophil Recovery and Chimerism Outcomes

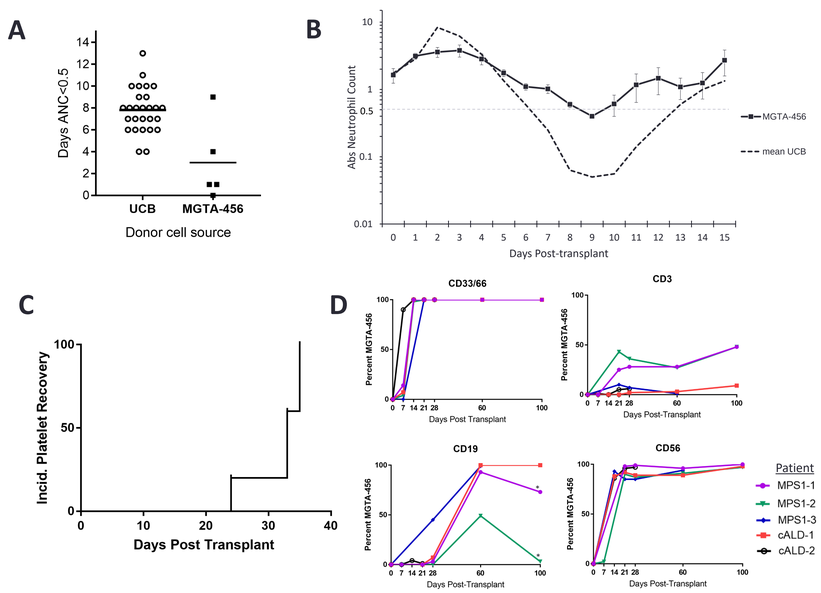
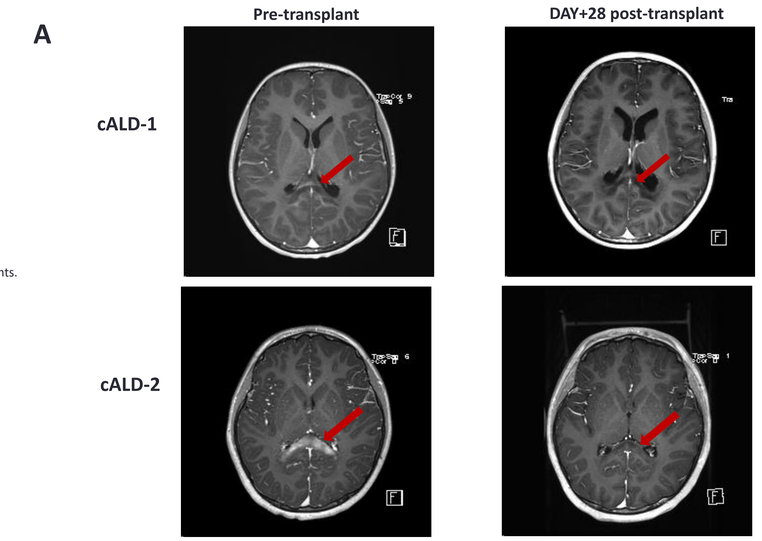


Figure 2. Neutrophil recovery and engraftment. A. Days of neutropenia. Number of days absolute neutrophil count (ANC) <0.5 x 10^9 cells/dL from day of transplant to day of recovery of patients treated per protocol compared to umbilical cord blood historical cohort. **B. ANC recovery.** Daily ANC values +/- 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 100 days post-transplant. * Patients with autoimmune cytopenia.

cALD Disease-Specific Outcomes



MPS1 Disease-Specific Outcomes

Figure 3. Disease-specific outcome measures. A. Contrast enhancement in brain MRI images from cALD patients at screening and at day +28 post-transplant showing resolution. Red arrows indicate areas of inflammation on screening and resolution of contrast-enhancement by day +28. **B.** Urine total glycosaminoglycan (GAG) levels and blood leukocyte IDUA enzyme activity measured at screening and at timepoints post-transplant in MPS1 patients. * Patients with autoimmune cytopenia.

Safety

MGTA-456 was well tolerated with only two infusion-related adverse events of grade 1 vomiting and grade 3 nausea. 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. At the time of the data cutoff, two evaluable MPSI patients developed autoimmune cytopenia (AIC) (not related to MGTA-456) which is a known complication reported in 20-56% of IMD patients undergoing HSCT that resulted in death of one patient 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%) engraftment in all patients with marked reduction in days of neutropenia (median of 1 day, range 0-9) in comparison to a median of 8 days in a historical cohort with identical conditioning. 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 total GAG levels post-transplant and cALD patients had resolution of pathologic brain MRI enhancement as early as day +28 post-transplant. These data, in combination with the previous 27 hematologic malignancy patients treated, suggest that MGTA-456 substantially enhances the engraftment potential of CB. Based on these promising data, MGTA-456 has potential to improve transplant-related outcomes in patients undergoing HSCT and increasing the availability of well-matched CB units that may have been previously excluded due to inadequate CD34+ dose.

REFERENCES

(1)Lum et al 2017 Bone Marrow Transplant 52:846-53; Mallhi et al 2017 BBMT 23:119-25
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(3)Prasad et al 2008 Blood 112:2979-89
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