Magenta Therapeutics: Inherited Metabolic Disorders (IMDs) Program Overview

What is MGTA-456 and how does it work in IMDs?

IMDs are fatal, childhood disorders and currently the only approved treatment that can stop or hold back the disease is a stem cell transplant. A stem cell transplant, also known as a hematopoietic stem cell transplant (HSCT), is when healthy cells from another person are given to a patient. The cells find their way into the bone marrow and the brain where they grow and start to make healthy blood and immune system. Research has shown that a higher dose of stem cells for the transplant increases the likelihood of success and is linked to better disease outcomes.

MGTA-456 is a cell therapy available in a clinical trial and designed to rapidly halt disease progression of IMDs. MGTA-456 contains high numbers of stem cells and is expected to increase the likelihood of a successful transplant and reduce the risks of prolonged neutropenia, where a person has too few neutrophils, a type of white blood cells that help fight infections. Donor cells from the bone marrow cross into the brain to correct the disease and the high cell dose of MGTA-456 may help the speed and consistency of the effect.

The U.S. Food and Drug Administration (FDA) has granted Regenerative Medicine Advance Therapy (RMAT) designation for MGTA-456. RMAT designation is a dedicated program designed to expedite the development and review of regenerative medicines intended to treat serious conditions with an unmet medical need

Where is MGTA-456 being studied?

Magenta is currently studying MGTA-456 in patients with IMDs in a Phase 2 clinical trial, **IMD-001** and an associated Long-term Safety study. A Phase 2 clinical trial looks to see if the therapy works, in addition to making sure the therapy is safe. Patients between the ages of 6 months to 16 years with Hurler syndrome (MPS-1), cerebral adrenoleukodystrophy (cALD), metachromatic leukodystrophy (MLD) or globoid cell leukodystrophy (GLD) (also referred to as Krabbe disease) are eligible for these studies.

IMD-002 is a follow-up study to evaluate the long-term safety and efficacy outcomes of patients with inherited metabolic disorders who received MGTA-456 in the IMD-001 study. The study does not involve the use of an investigational product.

Additional detail about IMD-002 study can be found on Clinicaltrials.gov using identifier NCT04008849.

What is the goal of the IMD-001 study?

The primary goal of the IMD-001 study is to assess the number of patients in whom MGTA-456 successfully engraft, as well as the speed and durability of engraftment. Engraftment is when the cells received from the transplant move through the bloodstream into the bone marrow and begin to grow and make new blood and immune cells. New enzymes are also produced that can correct the disease and other potential benefits will also be looked at for each disease. The study will also look at the safety of MGTA-456.

How do I Participate in the IMD-001 Study?

Additional detail about the IMD-001 study can be found in the table below:

IMD-001 Protocol Title	
A Phase 2, Single-arm, Open-label Study to Evaluate the Safety and Efficacy of MGTA-456 in Patients with Inherited Metabolic Disorders (IMD) Undergoing Hematopoietic Stem Cell Transplantation	
Patient Population	**Enrollment Goal**
Patients with Hurler syndrome (MPS-1), cerebral adrenoleukodystrophy (cALD), metachromatic leukodystrophy (MLD) or globoid cell leukodystrophy (GLD, also referred to as Krabbe disease)	12 patients
Primary Objective	**Secondary Objectives**
Incidence of engraftment	Incidence of infusion toxicities
Key Inclusion Criteria	**Key Exclusion Criteria**
• Diagnosed with Hurler syndrome, cALD), MLD), or GLD / Krabbe) • Adequate organ function • Availability of eligible donor material	• Availability of a matched-related donor who is not a carrier of the same genetic defect • Active infection at screening • Prior myeloablative conditioning • History of human immunodeficiency virus infection
Connect with a Study Center	
Children's Healthcare of Atlanta - Emory University Atlanta, Georgia, United States, 30322 Contact: Lakshmanan Krishnamurti, MD Lakshmanan.Krishnamurti@choa.org	**Duke University** Durham, North Carolina, United States, 27710 Contact: Vinod K Prasad, MD vinod.prasad@duke.edu
University of Minnesota Minneapolis, Minnesota, United States, 55455 Contact: Paul J Orchard, MD orcha001@umn.edu	**Cincinnati Children's Hospital Medical Center** Cincinnati, Ohio, United States, 45229 Contact: Pooja Khandelwal, MD Pooja.Khandelwal@cchmc.org
Clinicaltrials.gov Identifier and Link	**Contact Magenta Clinical Trials**
NCT03406962	857-242-0170 clinicaltrials@magentatx.com

What results has MGTA-456 shown in IMDs?

MGTA-456 was well tolerated and all five patients with IMDs treated to date with MGTA-456 had successful neutrophil engraftment and have shown evidence of disease benefit.

Key disease results in patients with cALD:

- Both patients had stable neurological function scores, a measure of patient brain and nerve function, which remained unchanged between baseline and six months after transplant, suggesting progression of the disease has been halted.
- The Loes score, a method for measuring the severity of brain abnormalities found on Magnetic Resonance Imaging (MRI), also remained stable in both patients after six months.
- Both patients showed resolution of gadolinium enhancement on MRI, an indicator of brain inflammation, by one-month post-transplant, and the resolution persisted at six months, which was the longest time after treatment so far. Gadolinium is a chemical element that when injected into the body improves the quality of the MRI images (or pictures).

- Durable resolution of gadolinium enhancement is linked with long-term disease benefit in patients with cALD.

Key disease results in patients with Hurler Syndrome:

- All three patients with Hurler syndrome achieved normal levels of blood enzyme by Day 42 post-transplant. Blood enzyme is deficient in untreated patients with Hurler syndrome. This suggests that transplant with MGTA-456 is affecting the disease process in these patients.
    - Normalization of blood enzyme after transplant has been significantly associated with improvement in disease outcomes.
    - Patients showed a marked decline in urine total glycosaminoglycan (GAG) after transplant. Patients with MPS have high amounts of GAGs in their body tissues and their urine. This is why high amounts of GAGs in a patient's urine are often used to diagnose MPS.

Magenta Therapeutics, Cambridge, MA

At Magenta, we are developing medicines to bring the curative power of stem cell transplant to more patients. Our programs are designed to transform patient preparation, stem cell collection, and stem cell matching and dose; and reduce post-transplant complications such as graft-versus-host disease when the donated stem cells attack the body.