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A Phase 2, Open-label Study to Evaluate the Efficacy and Safety of MGTA-145 in Combination With Plerixafor for the Mobilization of Hematopoietic Stem Cells in Patients With Sickle Cell Disease

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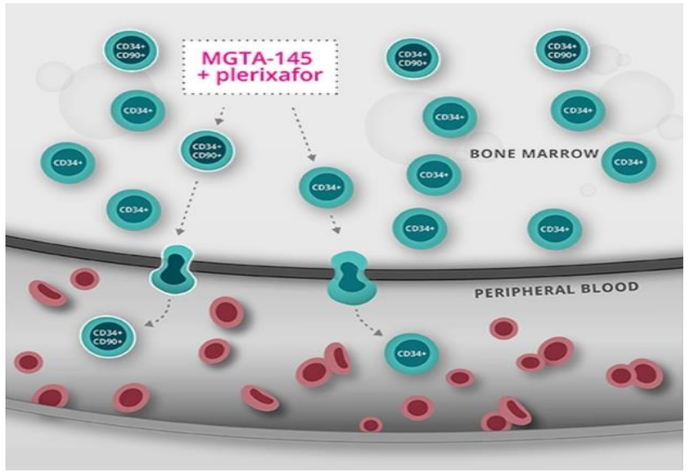
BACKGROUND

- Despite significant, potentially life-threatening risks, allogeneic hematopoietic cell transplant (HCT) is the only cure for sickle cell disease (SCD)[1]
- Ongoing gene therapy clinical trials using autologous hematopoietic stem and progenitor cells (HSPCs) are promising and may be an option for those who lack a suitable donor[2]
- Obtaining high numbers of HSPCs is challenging in patients with SCD, as granulocyte colony-stimulating factor can lead to the development of severe and sometimes fatal sickle cell crises[3]
- Peripheral blood mobilization with plerixafor (Mozobil®, Genzyme) is safe and effective in SCD; however, some patients require ≥2 cycles of mobilization and apheresis to collect sufficient HSPCs for genetic manipulation, and the risk of vaso-occlusive crisis remains with each mobilization and apheresis procedure[4-6]
- Agents are needed that augment mobilized HSPC yields, reduce apheresis time, and number of mobilization and apheresis cycles

Figure 1. MGTA-145 in Combination With Plerixafor Harnesses the Natural Mechanism of Stem Cell Mobilization



- MGTA-145 (called Gro Beta Truncate or GroβT) is a 4 amino acid-truncated protein variant of CXC chemokine ligand 2 (CXCL2), an agonist of cell-surface chemokine receptor CXC chemokine receptor 2 (CXCR2; **Figure 1**)
- MGTA-145-induced mobilization is mediated by matrix metallopeptidase-9 (MMP-9)
- After MGTA-145 binds to CXCR2, MMP-9 is released from neutrophils, resulting in the cleavage of adhesive molecules that tether HSPCs to the bone marrow niche
- The addition of plerixafor, an antagonist of CXCR4, inhibits cross-communication between CXCR4 and CXCR2 receptors which normally function to diminish the CXCR2 response
- When MGTA-145 is given with plerixafor, the release of MMP-9 is enhanced, leading to increased mobilization of HSPCs (**Figure 1**)

Figure 2. Current Standard-of-Care Mobilization vs Potential Benefits of MGTA-145

Current Limitations With Standard-Of-Care	MGTA-145 Potential: Safe, Reliable, Predictable, and Rapid Mobilization and Collection
Gene therapy requires a high number of functional stem cells to engraft	Boosts mobilization of functional stem cells compared to plerixafor alone
Multiple mobilization and apheresis cycles are required to collect a sufficient number of stem cells	Streamlined process: fewer apheresis sessions = faster time to transplant and streamlined manufacturing
Multiple cycles impact patient safety: linked to life-threatening SAEs including vaso-occlusive events	Fewer apheresis sessions = more favorable safety profile
G-CSF is contraindicated in SCD mobilization	Potential to be a proof-of-concept study in SCD and demonstrate that MGTA-145 could be used for multiple HSPC gene therapies

G-CSF, granulocyte colony-stimulating factor; HSPC, hematopoietic stem and progenitor cell; SAE, serious adverse event; SCD, sickle cell disease.

- Results from the phase 1 study (145-HV-101), which was conducted in healthy volunteers, supported a starting dose of 0.03 mg/kg: following MGTA-145 and plerixafor administration, peak CD34+ cell count in peripheral blood was higher than that observed with plerixafor alone (**Table 1**)

Table 1. Data in Healthy Volunteers (145-HV-101)[7]

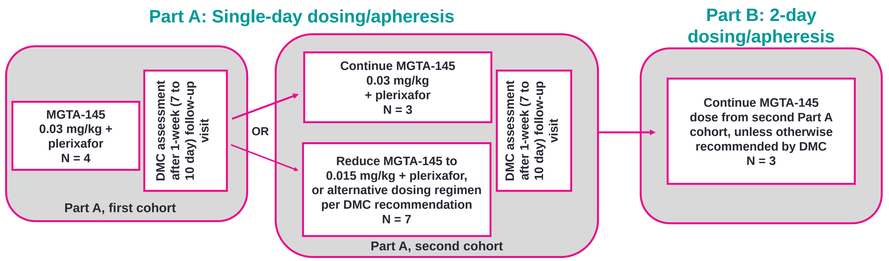
Mobilization Regimen	MGTA-145 Dose (mg/kg)	Peak CD34⁺(#/μL) Median (range)
MGTA-145 + plerixafor	0.015	36 (18-86)
	0.03	40 (18-63)
	0.07	26 (11-42)
Plerixafor	0	26 (13-78)

- MGTA-145 given at a dose of 0.03 mg/kg demonstrated predictable, dose-linear pharmacokinetics (PK), which was not affected by the coadministration of plerixafor
- Plerixafor followed by MGTA-145 after a 2-hour interval was associated with better stem cell mobilization outcomes, as determined by peripheral blood CD34⁺ cell counts
- MGTA-145 was found to have acceptable safety and tolerability with the most common side effect being transient musculoskeletal pain, primarily reported as back pain which generally resolved within approximately 10 minutes following the infusion
  - Other side effects included mostly mild to moderate nausea, diarrhea, dizziness, abdominal pain, headache, vomiting, and paresthesia

STUDY DESIGN AND METHODS

- This phase 2, open-label, 2-part study (NCT05445128) will enroll approximately 10-14 adults ages 18-35 years with SCD, at 3 sites in the United States (**Table 2**)
- In Part A the first cohort will receive a single 0.24 mg/kg subcutaneous dose of plerixafor followed by a single 0.03 mg/kg intravenous dose of MGTA-145, with apheresis occurring within approximately 30-45 minutes of MGTA-145 dosing (**Figure 3**)
- After a 1-week follow-up visit and an independent data monitoring committee (DMC) review, the second cohort with additional participants may be enrolled and given plerixafor and a 0.03 or 0.015 mg/kg or lower dose of MGTA-145
- Following a 1-week follow-up visit and a second DMC review, participants will be enrolled in Part B and will receive, on 2 consecutive days, plerixafor and the same dose of MGTA-145 as the second Part A cohort, followed by apheresis on each dosing day

Figure 3. MGTA-145 Phase 2 Clinical Trial Design



DMC, data monitoring committee.

Table 2. Key Eligibility

Key Inclusion Criteria	Key Exclusion Criteria
• Age 18-35 years of age	• Vaso-occlusive event requiring a visit to a healthcare facility within 30 days prior to screening
• Documented diagnosis of SCD with documentation of SCD genotype by medical history	• Onset of clinically apparent CVA or retinal infarct within 2 years prior to screening or determined to be at high risk of CVA
• Must have a feasible manual or automated exchange transfusion plan to achieve sickled hemoglobin <30% within 1 week prior to mobilization	• Splenomegaly or splenic sequestration, sickle hepatopathy, priapism requiring inpatient treatment, acute chest syndrome requiring supplemental oxygen, or osteomyelitis within 6 months prior to screening
• A washout period of at least 30 days prior to mobilization dosing for patients taking hydroxyurea	• Surgery requiring greater than local anesthesia within 3 months of screening (except for placement of a central venous access device)
• Adequate WBC counts (WBC count >2.0 ×10^9/L , ANC >1.0 ×10^9/L, and platelet count >150 ×10^9/L), and hepatic, cardiac, and pulmonary function	• Prior history of autologous or allogeneic transplant, inclusive of gene therapy

ANC, absolute neutrophil count; CVA, cerebrovascular accident; WBC, white blood cell.

STUDY OBJECTIVES

- To evaluate the safety, tolerability, PK, and pharmacodynamics of single-day and 2-consecutive-day dosing with MGTA-145 and plerixafor for the HSPC mobilization and apheresis collection in individuals with SCD (**Table 3**)

Table 3. Summary of Efficacy, Safety, and Exploratory Endpoints

Primary Objectives	Primary Endpoints
Efficacy • To characterize the efficacy of a single dose and 2 consecutive days of dosing of MGTA-145 and plerixafor for HSPC mobilization and apheresis collection in patients with SCD	• Determination of the yield of CD34⁺ cells (CD34⁺ cells/kg) after 1 dose and 2 consecutive days of MGTA-145 and plerixafor followed by apheresis
Safety • To characterize the safety and tolerability of MGTA-145 in patients with SCD	• Incidence of TEAEs, including drug-related TEAEs, grade ≥3 TEAEs, TESAEs, and TEAEs leading to study drug discontinuation • Incidence of treatment-emergent grade ≥3 clinical laboratory abnormalities • Clinically significant changes from baseline in vital signs and laboratory parameters (eg, serum chemistry, hematology)
Secondary Objectives	**Secondary Endpoints**
Efficacy • To measure the mobilization effects of single-day and 2-consecutive-day dosing with MGTA-145 and plerixafor in the peripheral blood in patients with SCD	• Determination of peak peripheral blood CD34⁺ counts
• To characterize the PK profile of MGTA-145 in patients with SCD	• Determination of PK exposures
Safety • To characterize the immunogenicity of MGTA-145 in patients with SCD	• Presence and titers of antidrug antibodies
Exploratory Objectives	**Exploratory Endpoints**
• To characterize the phenotype and function of cells collected by apheresis in patients with SCD	• Flow cytometric characterization of cells collected following MGTA-145 and plerixafor mobilization and apheresis
• To assess gene-modifying potential of mobilized CD34⁺ cells in patients with SCD	• Assessment of ability to select and gene-modify CD34⁺ cells

HSPC, hematopoietic stem and progenitor cell; PD, pharmacodynamics; PK, pharmacokinetics; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

STUDY STATUS

- This study is open for recruitment with up to 14 patients across 3 sites in the United States planned
- The results of this trial will provide data to evaluate if MGTA-145 in combination with plerixafor will rapidly and safely mobilize robust numbers of CD34⁺ HSPCs in patients with SCD

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