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

Investigational Product: MGTA-145

Protocol Number: 145-SCD-204

IND Number: 139251

Development Phase: 2

Sponsor:

Magenta Therapeutics, Incorporated

100 Technology Square, 5th Floor

Cambridge, MA 02139

Protocol Amendment 1, Version 3.0: 05 October 2021

SIGNATURE PAGE

STUDY TITLE: 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

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Electronically signed by: Doug Girgenti Reason: I have approved this document Date: Oct 8, 2021 09:28 EDT

08-Oct-2021

Douglas Girgenti, MD
Senior Medical Director
Magenta Therapeutics, Inc.

Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure (IB) for MGTA-145. I have read the 145-SCD-204 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guidelines on Good Clinical Practice (GCP), effective in the United States (US) from 09 May 1997, and applicable US Food and Drug Administration (FDA) regulations set forth in 21 Code of Federal Regulations (CFR) §50, 54, 56, and 312.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Magenta.

_____

Printed Name of Investigator

_____

Signature of Investigator Date
Name/Address of Study Center:

PROCEDURES IN CASE OF EMERGENCY

Please refer to the appropriate study materials for emergency contact information.

Serious Adverse Event Reporting

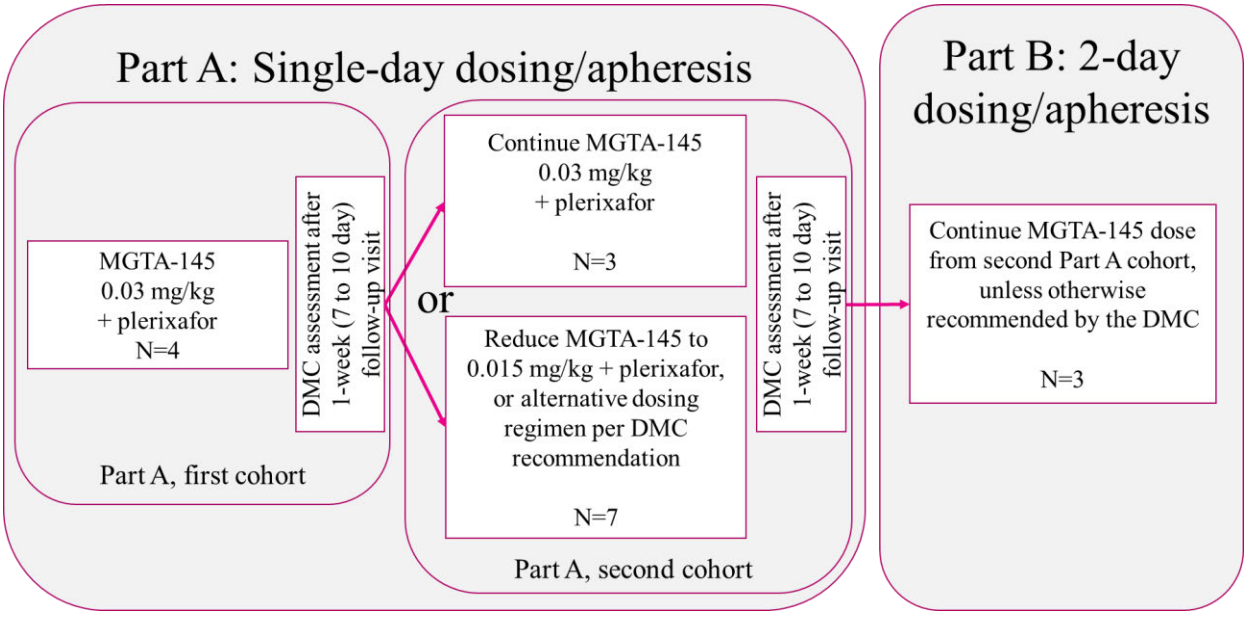
Refer to Section 11.2.3 for definitions and Section 11.5 for complete reporting requirements for serious adverse events (SAEs).

Serious adverse events (initial and follow-up) must be reported to Magenta's safety vendor (Premier) within 24 hours of awareness of the SAE or changes to an existing SAE. This should be done by emailing or faxing a signed copy of the SAE Report Form using the contact details below:

Premier SAE Reporting Contact Details

Email: [redacted]

1. SYNOPSIS

Name of Sponsor/Company: Magenta Therapeutics, Incorporated, Cambridge, MA		
Name of Investigational Product: MGTA-145		
Name of Active Ingredient: MGTA-145 (Gro Beta Truncate [GroβT], a CXC chemokine receptor 2 [CXCR2] agonist)		
Protocol Number: 145-SCD-204	**Phase:** Phase 2	**Country:** United States (US)
Title of Study: 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		
Study Center(s): Approximately 3 US study centers are planned for enrollment of subjects.		
Number of Subjects: Approximately 10 to 14 evaluable subjects are planned to be enrolled in this two-part study. • **Part A** has a planned enrollment of approximately 7 to 11 evaluable subjects. • **Part B** has a planned enrollment of approximately 3 evaluable subjects.		
Study Design: This is a two-part Phase 2, open-label, multicenter study. The study design is illustrated below. 		
Methodology: Approximately 10 to 14 patients with sickle cell disease (SCD) are planned to be enrolled in this 2-part study. Part A evaluates single-day mobilization and apheresis in 2 sequential patient cohorts, then Part B evaluates two-day mobilization and apheresis in a single		

patient cohort, following administration of 2 consecutive-day single doses of MGTA-145 and plerixafor, respectively.

Part A and Data Monitoring Committee (DMC) assessment: Part A has a planned enrollment of approximately 7 to 11 evaluable subjects. The first cohort of 4 subjects is to receive a single 0.24 mg/kg subcutaneous (SC) dose of plerixafor followed 2 hours later by a single 0.03 mg/kg intravenous (IV) dose of MGTA-145. Apheresis is planned to commence within approximately 30 minutes of MGTA-145 dosing. For this initial cohort, only one subject will be dosed and apheresed on a single-day, and each subject will complete the 1-week follow-up visit before a subsequent subject can be dosed.

After the first cohort has completed the 1-week follow-up visit, an independent DMC, comprising of 3 members with medical expertise in stem cell transplantation and treatment of patients with SCD, will evaluate the safety, pharmacokinetics (PK), and mobilization kinetics of MGTA-145 before the second cohort of subjects is allowed to be enrolled. The DMC may recommend enrolling an additional 3 subjects at the 0.03 mg/kg MGTA-145 dose, an additional 7 subjects at a reduced dose of 0.015 mg/kg MGTA-145, or an alternative but lower dosing regimen for this cohort. The MGTA-145 dose will not be escalated during either Parts A or B of the study.

After the second cohort has completed the 1-week follow-up visit, the DMC will likewise evaluate the safety, PK, and mobilization kinetics of MGTA-145 before subjects may be enrolled into Part B. Criteria for the DMC recommendations regarding cohort progression and dosing regimen will be defined in the DMC Charter.

Part B: Part B has a planned enrollment of approximately 3 evaluable subjects. Subjects will receive single doses of MGTA-145 and plerixafor on 2 consecutive days, followed by apheresis on each dosing day. The dose of MGTA-145 will be identical to that of the second Part A cohort, unless otherwise recommended by the DMC.

All subjects in Parts A and B will be observed at the investigational site from Day -1 until at least one day after the last apheresis, attend a 1-week follow-up visit 7 to 10 days after the last MGTA-145 infusion, and attend an end-of-study phone visit approximately 30 days after the last MGTA-145 infusion.

Hematopoietic stem cells obtained by apheresis (HPC-A) will be processed according to standardized clinical cell therapy laboratory procedures. Peripheral blood and HPC-A will be stored for testing (e.g., exploratory pharmacodynamic (PD) evaluation, cell characterization, and process characterization) and approximately $2x10^6$ CD34+ cells/kg are to be cryopreserved at clinical sites for potential future use by study subjects as backup reserve, should subjects decide to proceed with allogeneic hematopoietic cell transplant or autologous gene therapy.

Overall Objectives: The overall objective of Part A is to investigate the efficacy, safety, tolerability, PK, and PD of a single dose of MGTA-145 for HSC mobilization and apheresis collection when given IV, in combination with plerixafor administered SC, to patients with SCD.

The overall objective of Part B is to investigate the efficacy, safety, tolerability, PK, and PD of MGTA-145 for HSC mobilization and apheresis collection when administered IV, in combination with plerixafor administered SC, to patients with SCD on 2 consecutive days, using the optimum MGTA-145 dose as determined during Part A.

Objectives and Endpoints: Study objectives and associated endpoints for Part A are listed below:

Part A Primary Objectives	**Part A Primary Endpoints**
To characterize the efficacy of a single dose of MGTA-145 and plerixafor for HSC mobilization and apheresis collection in patients with SCD	• Determination of the yield of $CD34^+$ cells ($CD34^+$ cells/kg) after 1 dose of MGTA-145 and plerixafor followed by apheresis
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 (e.g., serum chemistry, hematology)
Part A Secondary Objectives	**Part A Secondary Endpoints**
To measure the mobilization effects of single-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
To characterize the immunogenicity of MGTA-145 in patients with SCD	• Presence and titers of anti-drug antibodies

Part A Exploratory Objectives	Part A 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 • Characterization of hematopoietic cell function by mouse engraftment studies and/or colony formation assays
To assess gene-modifying potential of mobilized $CD34^+$ cells in patients with SCD	• Assessment of ability to select and gene-modify $CD34^+$ cells
HSC=hematopoietic stem cells; PD=pharmacodynamic(s); PK=pharmacokinetic(s); SCD=sickle cell disease; TEAE=treatment-emergent adverse event; TESAE=treatment-emergent serious adverse event	

Study objectives and associated endpoints for Part B are listed below:

Part B Primary Objectives	Part B Primary Endpoints
To characterize the efficacy of 2 consecutive days of dosing with MGTA-145 and plerixafor for HSC mobilization and apheresis collection in patients with SCD	• Determination of the yield of $CD34^+$ cells after 2 consecutive days of MGTA-145 and plerixafor mobilization and apheresis collection in patients with SCD
To characterize the safety and tolerability of MGTA-145 in patients with SCD	• Incidence of TEAEs, including drug-related TEAEs, $\geq$Grade 3 TEAEs, TESAEs, and TEAEs leading to study drug discontinuation • Incidence of treatment-emergent $\geq$Grade 3 clinical laboratory abnormalities • Clinically significant changes from baseline in vital signs and laboratory parameters (e.g., serum chemistry, hematology)
Part B Secondary Objectives	**Part B Secondary Endpoints**
To measure the mobilization effects of 2 consecutive days of	• Determination of peak peripheral blood $CD34^+$ counts

dosing with MGTA-145 and plerixafor in the peripheral blood in patients with SCD	
To characterize the PK profile of MGTA-145 in patients with SCD	• Determination of PK exposures
To characterize the immunogenicity of MGTA-145 in patients with SCD	• Presence and titers of anti-drug antibodies
Part B Exploratory Objectives	**Part B Exploratory Endpoints**
To characterize the phenotype and function of cells collected by apheresis in patients with SCD	• Flow cytometric characterization of the cells collected following MGTA-145 and plerixafor mobilization and apheresis • Characterization of hematopoietic cell function by mouse engraftment studies and/or colony formation assays
To assess gene-modifying potential of mobilized HSC in patients with SCD	• Assessment of the ability to select and gene-modify HSC
HSC=hematopoietic stem cell; PD=pharmacodynamic(s); PK=pharmacokinetic(s); TEAE=treatment-emergent adverse event; TESAE=treatment-emergent serious adverse event	

Number of Subjects (planned): Approximately 10 to 14 evaluable subjects are planned in total. Part A has a planned enrollment of approximately 7 to 11, and Part B has a planned enrollment of approximately 3 evaluable subjects.

Sample Size Justification: There are no statistical hypotheses in this trial, therefore there is no sample size calculation. To address the objectives assessing proof of concept of mobilizing $CD34^+$ cells after 1 or 2 days of dosing with MGTA-145 and plerixafor, a minimum sample size of 10 evaluable subjects is considered adequate.

Based on the safety profile including 79 subjects dosed with MGTA-145 in Phase 1 study 145-HV-101, 10 evaluable subjects are deemed a minimal number to assess common drug-related safety events.

The most commonly observed adverse event (AE) in subjects treated with MGTA-145 is transient musculoskeletal pain, most often presenting as back pain occurring within 10 minutes of study treatment administration and generally resolving approximately 10 minutes later. -With 10 evaluable subjects, there is sufficient subject exposure to assess for this AE.

Diagnosis and Criteria for Inclusion:

1. Subject must be 18 to 35 years of age, inclusive.
2. Subject must weigh ≥30 kg at screening.
3. Subject must have a documented diagnosis of SCD with documentation of SCD genotype by medical history
4. Subject must present with a feasible manual or automated exchange transfusion plan to achieve Hemoglobin S (HbS) <30% within 1 week of mobilization.
5. Subject taking hydroxyurea must comply with a washout period of at least 30 days prior to mobilization dosing. Subjects must be able to safely discontinue hydroxyurea to participate in the study.
6. Subject must have a local laboratory screening white blood cell (WBC) count >2.0 x 10^9/L, absolute neutrophil count (ANC) >1.0 x 10^9/L, and platelet count >150 x 10^9/L.
7. Subject must have a local laboratory screening estimated glomerular filtration rate (eGFR) of at least 60 mL/min/1.73 m^2 based on the CKD-Epi equation.
8. Subject must have a local laboratory screening alanine aminotransferase (ALT) value <2.5 x upper limit of normal (ULN).
9. Subject's cardiac and pulmonary status must be sufficient to undergo apheresis, as assessed by the Investigator.
10. Subject must sign an Institutional Review Board (IRB)-approved informed consent form (ICF) and be willing to comply with the requirements of the protocol.

Criteria for Exclusion for Parts A and B:

1. Subject with a vaso-occlusive event (VOE) requiring a visit to a healthcare facility within 30 days prior to screening.
2. Subject with onset of clinically apparent cerebrovascular accident (CVA) or retinal infarct within 2 years prior to screening or determined to be at high risk of CVA, based on concomitant disease (e.g., moyamoya), or imaging (e.g., trans-cranial doppler study).
3. Subject with splenomegaly, splenic sequestration, sickle hepatopathy, priapism requiring inpatient treatment, acute chest syndrome requiring supplemental oxygen, or osteomyelitis within 6 months prior to screening. Subjects with a history of splenomegaly or splenic sequestration may be included if they have undergone a splenectomy.
4. Subject having surgery requiring greater than local anesthesia within 3 months of screening, except for placement of a central venous access device.
5. Subject who has received or plans to receive anticoagulation at the time of screening, except for study-related procedures.

6. Subject who, by medical history, requires rare donor registry red blood cell (RBC) units for transfusion, or is unable to receive routine transfusion. Eligible study subjects must have undergone prior work-up for the presence of red cell alloantibodies and confirmation of available compatible blood product support.
7. Subject who has undergone or attempted and failed previous HSC collection.
8. Subject who has had a prior autologous or allogeneic transplantation, inclusive of gene therapy.
9. Subject who has received experimental therapy within 4 weeks prior to providing informed consent or is enrolled in another interventional experimental protocol.
10. Subject with poorly controlled diabetes mellitus, as assessed by the Investigator.
11. Subject who has an uncontrolled cardiovascular condition, including clinically significant cardiac arrhythmia, congestive heart failure, angina, myocardial infarction, or unstable pulmonary arterial hypertension within 6 months prior to screening.
12. Subject with a history of or who has a positive screening laboratory test for human immunodeficiency disease (HIV), hepatitis B, hepatitis C, or human T-cell leukemia virus (HTLV).
13. Subject with active infection or co-morbid condition that places the subject at high risk for treatment complications, as assessed by the Investigator.
14. Subject with a known allergy to or contraindication for MGTA-145 or plerixafor administration, or medications routinely administered during apheresis.
15. Male subject not willing or able to use a highly effective method of contraception for 3 months during and after treatment with MGTA-145 and plerixafor, or female subject who is pregnant or breastfeeding, or sexually active and not willing or able to use a highly effective method of contraception for 3 months during and after treatment with MGTA-145 and plerixafor.

Investigational Product, Dosage, and Mode of Administration:

MGTA-145 injection is provided as a sterile solution for intravenous infusion in 2 mL Type I amber glass vials. MGTA-145 is formulated in [redacted]. Each vial contains 1 mL of a 20 mg/mL solution. Up to two daily 0.03 mg/kg doses of MGTA-145 will be administered as a single 3- to 10-minute IV infusion approximately 2 hours after 0.24 mg/kg SC administration of plerixafor.

Plerixafor (injection) is provided as a sterile, preservative-free, clear, colorless to pale yellow, isotonic solution for SC injection. Each mL of the sterile solution contains 20 mg of plerixafor. Each single-use vial is filled to deliver 1.2 mL of the sterile solution that contains 24 mg of plerixafor and 5.9 mg of sodium chloride in Water for Injection adjusted to a pH of 6.0 to 7.5 with hydrochloric acid and with sodium hydroxide, if required.

Duration of Treatment Part A:

Screening Period: up to 30 days

Dosing and Follow-up Period: approximately 30 days

Duration of Treatment Part B:

Screening Period: up to 30 days

Dosing and Follow-up Period: approximately 30 days

Reference Therapy, Dosage, and Mode of Administration:

Not applicable

Criteria for Evaluation:

Safety: Subject safety will be assessed based on monitoring of AEs, vital signs, physical examinations, clinical laboratory evaluations, and development of anti-drug antibodies. Adverse events will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Pharmacokinetics: PK samples will be collected for all subjects enrolled in Parts A and B at the timepoints outlined in the Schedules of Assessments.

Pharmacodynamics: During Parts A and B, peripheral blood will be collected at the timepoints specified in the Schedule of Assessments to measure changes in $CD34^+$ and $CD34^+CD90^+CDRA^-$ cell counts, as well as T-cell subtypes, B cells, monocytes, granulocytes, and natural killer (NK) cells. Cell counts will be analyzed using fluorescent flow cytometry.

Changes in cell functionality will be assessed in terms of colony-forming units (CFUs) using an automated colony-counting device or manually with an inverted microscope.

Statistical Methods:

A formal statistical analysis plan (SAP) will be developed and finalized prior to database lock. This document will provide further details regarding the definition of analyses, any data handling conventions, and analyses methodology to address all study objectives.

Statistical summaries will be descriptive in nature. All continuous variables will be summarized by dose cohort and visit (as applicable) using descriptive statistics (number of observations [n], mean, median, standard deviation [SD], minimum, and maximum). All categorical variables will be summarized by dose cohort and visit using frequency counts and percentages. Subjects who receive MGTA-145 will be included in the analyses. Data will be presented in aggregate and by cohort, if applicable. Subject baseline characteristics, including demographics and important disease characteristics, will be described using descriptive statistics.

Primary Endpoint; Part A:

- The $CD34^+$ cells/kg apheresis yield with 1 apheresis session after MGTA-145 + plerixafor dosing will be presented at each dose of MGTA-145 evaluated. A mean yield and 95% confidence interval (CI) will be presented.
- The number and percentage of subjects with administration-related toxicities and TEAEs will be summarized.

Primary Endpoint; Part B:

- The total $CD34^+$ cells/kg apheresis yield after 2 consecutive days of MGTA-145 + plerixafor mobilization and apheresis collection will be presented. A mean yield and 95% CI will be presented.
- The number and percentage of subjects with administration-related toxicities and TEAEs will be summarized.

Secondary Endpoints; Parts A & B:

Peak peripheral blood $CD34^+$ counts will be summarized by time point relative to MGTA-145 dosing. Apheresis collection yields after 2 consecutive days of mobilization will be summarized for Part B.

Plasma concentrations of MGTA-145 will be listed, and a summary by time point for each dose cohort will be presented. Graphs of the individual subject concentration versus time profiles, as well as the arithmetic mean (±SD) concentration versus nominal time profiles, will be presented on a linear and log (concentration)/linear (time) scale.

All exploratory endpoints will be analyzed using descriptive statistics as well as graphical methods, when appropriate.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCQ-Me®	Adult Sickle Cell Quality of Life Measurement Information System
β-hCG	Beta-human chorionic gonadotropin
CBC	Complete blood count
CD-ROM	Compact disc read-only memory
CFR	Code of Federal Regulations
CFU	Colony-forming unit
CFU-GM	Granulocyte-macrophage colony-forming unit
CFU-GEMM	Granulocyte-erythrocyte-macrophage-megakaryocyte colony-forming unit
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
CVA	Cerebrovascular accident
CXCL2	CXC chemokine ligand 2
CXCR2	CXC chemokine receptor 2
CXCR4	CXC chemokine receptor 4
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECLIA	Electrochemiluminescent immunoassay
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of study
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
GCP	Good Clinical Practice

Abbreviation or Specialist Term	Explanation
G-CSF	Granulocyte-colony stimulating factor
GroβT	Gro Beta Truncate
HbS	Hemoglobin S
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
HPC-A	Hematopoietic stem cells obtained by apheresis
HSC	Hematopoietic stem cells
HSCT	Hematopoietic stem cell transplantation
HTLV	Human T-cell leukemia virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MMP-9	Matrix metallopeptidase 9
NCI	National Cancer Institute
NK	Natural killer (cells)
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PROMIS®	Patient-Reported Outcomes Measurement Information System
PT	Preferred term
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous

Abbreviation or Specialist Term	Explanation
SCD	Sickle Cell Disease
SD	Standard deviation
SDF-1α	Stromal-derived factor-1α
SEM	Standard error of the mean
SOC	System organ class
SUSAR	Suspected unexpected serious adverse event
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
ULN	Upper limit of normal
US	United States
USB	Universal serial bus
VOE	Vaso-occlusive event
WBC	White blood cell

4. INTRODUCTION

With prevalence estimated to be at least 20 million globally and 100,000 in the United States (US),[1] sickle cell disease (SCD) is the most common inherited blood disorder in much of the world.[2] Sickle cell disease is caused by an autosomal recessive point mutation in the β-globin gene *HBB*, resulting in abnormal β-globin protein (hemoglobin SS disease), or by compound heterozygosity of hemoglobin S with another β-globin chain abnormality, e.g., hemoglobin C or β-thalassemia. Owing to the relative protection against malaria conferred by the heterozygotic state, SCD is largely distributed in populations originating from sub-Saharan Africa, Middle East, and the Indian subcontinent, in areas where malaria prevalence is high. In the US, approximately one in 400 to 700 African Americans is born with SCD.[1,3]

The formation of abnormal hemoglobin tetramers, which polymerize into filaments under low oxygen tension, results in deformable, sickle-shaped erythrocytes with abnormal rheology, leading to vaso-occlusion, ischemic tissue damage, and hemolysis-associated endothelial dysfunction.[4] Patients with SCD are vulnerable to bacterial infections, largely due to splenic dysfunction, and frequently suffer lifelong pain and fatigue.[5] Pain is the leading cause of US hospitalizations for patients with SCD, with an estimated burden of $1.1 billion, and is associated with poor health-related quality of life and early mortality.[6,7] Patients with SCD demonstrate higher rates of healthcare utilization, as manifest by emergency department utilization, hospitalization, and readmission rates, each correlating with age and SCD-related complications.[8]

Neonatal screening for SCD, performed routinely prior to hospital discharge, permits early medical intervention (e.g., penicillin prophylaxis for patients <5 years old), thereby reducing early morbidity and mortality of SCD. Other treatments, including hydroxyurea, blood transfusions, and pain medications including opioids, are largely palliative and unfortunately, many patients generally still have a poor quality of life due to recurring painful vaso-occlusive events (VOEs) and subsequent end-organ damage. While newer medications (e.g., L-glutamine, voxelotor, crizanlizumab) may improve mortality as well as morbidity of the disease, it is nonetheless estimated that most patients with SCD will not live beyond their fifth or sixth decade.[9]

Since first performed in 1984,[10] allogeneic hematopoietic cell transplantation has demonstrated the potential for cure or long-term amelioration of SCD, with long-term overall and event-free survival rates of more than 90%.[11] However, considering the potential for serious and potentially life-threatening side effects, use of hematopoietic stem cell transplantation (HSCT) is limited to patients with severe SCD in whom potential benefits outweigh the risk of the procedure (e.g., patients with a history of stroke, acute chest syndrome, recurrent pain crisis requiring exchange transfusions, nephropathy, retinopathy, osteonecrosis of multiple joints, priapism). Allogeneic transplant incurs notable risks of graft-versus-host disease and graft rejection,[12] and requires a matching bone marrow or stem cell donor, which has further limited utilization in this population.[13,14]

Early results of autologous HSCT, using addition of a non-sickling gene or gene editing to increase fetal hemoglobin, suggest that this approach may provide a favorable option for patients with SCD. However, while peripheral blood collection is preferable to bone marrow harvest of HSCs, mobilization of HSCs with granulocyte-colony stimulating factor (G-CSF) has been

associated with severe sickle cell crises and death in patients with SCD or trait.[15,16] Licensed in the US since 2008, plerixafor (Mozobil®, Genzyme) is a small molecule, reversible antagonist of chemokine receptor 4 (CXCR4), currently indicated to be used in combination with G-CSF to mobilize HSCs to the peripheral blood for collection and subsequent autologous transplantation in patients with multiple myeloma and non-Hodgkin's lymphoma.[17] Plerixafor acts by disrupting binding to the receptor's cognate ligand, stromal-derived factor-1α (SDF-1α) chemokine ligand 12 (CXCL12), thereby resulting in mobilization of $CD34^+$ HSCs into the peripheral blood. More recently, plerixafor alone has demonstrated efficacy in the mobilization of sufficient HSC for collection in patient populations, including SCD.[18,19,20] However, as many as 75% of patients with SCD require 2 or more cycles of multi-day plerixafor administration and apheresis in order to collect sufficient HSCs for genetic modification and infusion, and vaso-occlusive crisis remains a risk with each mobilization and apheresis procedure,[21] with approximately 30% of plerixafor-mobilized patients reported to have experienced VOEs of at least Grade 3 severity during and after harvesting, and approximately 20% of patients reported to have experienced serious vaso-occlusive pain within 2 days post-procedure. Hypomagnesemia, hypokalemia, and hypocalcemia have also been reported commonly among patients with SCD mobilized with plerixafor, although most events were Grade 1 or 2 in severity. Approximately half of patients with SCD require opioid medications within a week prior or subsequent to mobilization and apheresis.[22] Nonetheless, mobilization with plerixafor seems to result in an apheresis product superior to bone marrow harvest, based on the concentration of high-quality $CD34^+$ HSCs most suitable for *ex vivo* manipulation and autologous transplantation.[22]

Magenta Therapeutics, Inc. (Magenta) is developing MGTA-145 for the mobilization of $CD34^+$ cells when used in combination with plerixafor. MGTA-145 (aka 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). MGTA-145 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 HSCs 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. The addition of plerixafor helps enhance the release of MMP-9, leading to increased mobilization of hematopoietic cells.

Preclinical studies in mice, rats, and non-human primates demonstrated that MGTA-145, when administered simultaneously with plerixafor, leads to rapid and robust mobilization of $CD34^+$ cells, including $CD34^+CD90^+CD45RA^-$ cells within minutes to hours.

Phase I study 145-HV-101 evaluated MGTA-145 administered with or without plerixafor to 79 healthy volunteers, to determine the safety and dose of MGTA-145. The study had 4 parts. In Part A, subjects received a single dose of MGTA-145 alone (0.0075 to 0.3 mg/kg). In Part B, subjects received a single dose of MGTA-145 (0.015 to 0.15 mg/kg) with plerixafor. In Part C, subjects received 2 daily doses of MGTA-145 (0.03 and 0.07 mg/kg) and plerixafor. In Part D, subjects received a single dose of MGTA-145 (0.015 or 0.03 mg/kg) and plerixafor, followed by same-day apheresis. MGTA-145 was found to have acceptable safety and tolerability, with the most common side effect being transient back pain, lasting less than 20 minutes in most patients. In Part A, back pain was seen in 79% (19/24) of volunteers receiving single agent MGTA-145 vs. 0% (0/12) of volunteers receiving plerixafor. There were no other treatment-emergent

adverse effects (TEAE) observed among subjects in Part A receiving MGTA-145 (0.0075 to 0.3 mg/kg). When MGTA-145 (0.015 to 0.15 mg/kg) was combined with plerixafor in Part B, TEAE were observed in 81% of subjects, compared to 57% of patients receiving plerixafor alone. TEAE in the MGTA-145 and plerixafor arm included back pain/musculoskeletal pain in 63%, nausea in 18%, diarrhea and dizziness in 16% each, abdominal pain in 13%, headache in 11%, vomiting in 8%, and paresthesia in 5% of subjects. This data is shown in Table 2 below.

Table 2: Adverse Events Observed with MGTA-145 and Plerixafor in Phase 1 Study 145-HV-101

	Part A		Part B		Part C		Part D
	MGTA-145 (0.0075 - 0.3 mg/kg)	Placebo	MGTA-145 + plerixafor (0.015 - 0.15 mg/kg)	Plerixafor	MGTA-145 + plerixafor (0.03 - 0.07 mg/kg)	Plerixafor	MGTA-145 + plerixafor (0.015 - 0.03 mg/kg)
	n=24 n (%)	n=12 n (%)	n=38 n (%)	n=14 n (%)	n=8 n (%)	n=2 n (%)	n=8* n (%)
Subjects with any drug related TEAE	**19 (79.2)**	**-**	**31 (81.6)**	**8 (57.1)**	**6 (75.0)**	**-**	**8 (88.9)**
Diarrhea	-	-	6 (15.8)	5 (35.7)	1 (12.5)	-	1 (11.1)
Nausea	-	-	7 (18.4)	2 (14.3)	1 (12.5)	-	4 (44.4)
Abdominal discomfort/pain	-	-	5 (13.2)	4 (28.6)	-	-	3 (33.3)
Vomiting	-	-	3 (7.9)	1 (7.1)	-	-	1 (11.1)
Back pain / Musculoskeletal pain[2]	19 (79.2)	-	24 (63.2)	2 (14.3)	4 (50.0)	-	3 (33.3)
Dizziness / Lightheadedness	-	-	5 (15.6)	1 (7.1)	-	-	4 (44.4)
Headache	-	-	4 (10.5)	1 (7.1)	2 (25.0)	-	2 (22.2)
Dysgeusia	-	-	-	2 (14.3)	-	-	-
Paraesthesia	-	-	2 (5.3)	-	1 (12.5)	-	1 (11.1)

There was no dose response in AEs, so data are aggregated.
[1] All AEs are grade 1 except for grade 2 abdominal pain (1), nausea (1), and back pain (1) in the plerixafor + MGTA-145 0.075 mg/kg 2h stagger cohort (Part B) and grade 2 headache (1) in the plerixafor + MGTA-145 0.015 mg/kg cohort (Part D).
[2] Back pain was associated with MGTA-145 infusion, lasted <20 minutes in most cases and did not require medical therapy.
* A 9th subject enrolled in Part D but did not undergo leukapheresis.

At the 0.03 mg/kg dose, the peak median $CD34^+$ cell count in peripheral blood following MGTA-145 and plerixafor administration was 40 cells/µL (range 18 to 63), which was higher than that observed with plerixafor alone (median 24, range: 13 to 78). The dose of 0.03 mg/kg was determined to be safe and effective, with predictable, dose-linear pharmacokinetics (PK) that are not affected by the coadministration of plerixafor. Administration of plerixafor followed by MGTA-145 after a 2-hour interval was associated with better stem cell mobilization outcomes than administration of plerixafor followed by MGTA-145 after a 10-minute interval, as determined by peripheral blood $CD34^+$ cell counts, and will therefore be the regimen used in this trial.

The median peak $CD34^+$ cell counts observed after administration of various doses of MGTA-145 with plerixafor is provided in Table 3.

Importantly for patients with SCD, for whom substantial apheresis yields of up to $15x10^6$ $CD34^+$ cells/kg or more may be required for successful genetic modification and subsequent aHSCT, the 0.03 mg/kg dose of MGTA-145 resulted in the highest median peripheral $CD34^+$ cell count (40 cells/µL (range 18 to 63), as shown in Table 3.

Likewise important for patients with SCD, Phase 1 evaluation demonstrated limited neutrophil activation following MGTA-145 administration, based on changes in L-selectin, CD11b, CD18,

and CD66 from baseline. In the 145-HV-101 study, the 0.03 mg/kg dose of MGTA-145 demonstrated the least change from baseline for these markers of neutrophil activation. Thus, MGTA-145 0.03 mg/kg, in combination with plerixafor 0.24 mg/kg, represents the optimal dosing regimen in patients with SCD, both with regard to subject safety and anticipated mobilization response. Evaluation of the optimal MGTA-145 dose in patients with SCD will provide the greatest opportunity to minimize the number of apheresis sessions required to reliably collect sufficient HSCs, and likely minimize inter-subject variability in mobilization responses, where patients who mobilize poorly may gain incremental benefit from the 0.03 mg/kg dose. Based on similar rationale, investigator-initiated Phase 2 PoC study BMT-362 (conducted under IND 151874) evaluated and has demonstrated that administration of 0.03 mg/kg MGTA-145 in combination with plerixafor safely and successfully mobilizes HSCs for collection in patients with multiple myeloma undergoing aHSCT.[23]

Table 3: Median peak $CD34^+$ Counts Observed After Administration of Various Doses of MGTA-145 with Plerixafor–Data from Phase I Study 145-HV-101

Mobilization Regimen	MGTA-145 Dose (mg/kg)	Peak $CD34^+$ Count/µL Median (Range)
MGTA-145 + Plerixafor	0.07	26 (11 to 42)
	0.03	40 (18 to 63)
	0.015	36 (18 to 86)
Placebo + Plerixafor	0	26 (13 to 78)

A regimen of MGTA-145 in combination with plerixafor may provide the potential for greater yield of HSCs, requiring a shorter duration/number of mobilization and apheresis cycles, with improved safety and tolerability in patients with SCD as well as other inherited disorders for which future genetic modification and autologous transplantation may prove curative. Therefore, this Phase 2 PoC study evaluates the efficacy and safety of MGTA-145, administered concomitantly with plerixafor, to patients with SCD for the purpose of HSC mobilization and collection via apheresis.

While patients may benefit from participation in the study (apheresis product will be stored by the investigational sites for potential future transplantation), there is no immediate individual clinical benefit to patients who agree to participate in this study. The study is anticipated to yield important generalizable knowledge about mobilization and apheresis using MGTA-145 in the SCD patient population. The study population is therefore planned to include patients 18 to 35 years of age.

5. TRIAL OBJECTIVES AND PURPOSE

The overall objective of Part A is to investigate the efficacy, safety, tolerability, PK, and pharmacodynamics (PD) of a single dose of MGTA-145 for HSC mobilization and apheresis collection when given intravenously (IV) in combination with plerixafor administered SC to patients with SCD.

The overall objective of Part B is to investigate the efficacy, safety, tolerability, PK, and PD of MGTA-145 for HSC mobilization and apheresis collection when given IV in combination with plerixafor administered SC to patients with SCD on 2 consecutive days, using the optimum MGTA-145 dose as determined during Part A.

5.1. Part A Objectives and Endpoints

Study objectives and associated endpoints for Part A are listed in Table 4:

Table 4: Part A Objectives and Endpoints

Part A Primary Objectives	**Part A Primary Endpoints**
To characterize the efficacy of a single dose of MGTA-145 and plerixafor for HSC mobilization and apheresis collection in patients with SCD	• Determination of the yield of $CD34^+$ cells ($CD34^+$ cells/kg) after 1 dose of MGTA-145 and plerixafor followed by apheresis
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 (e.g., serum chemistry, hematology)
Part A Secondary Objectives	**Part A Secondary Endpoints**
To measure the mobilization effects of single-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
To characterize the immunogenicity of MGTA-145 in patients with SCD	• Presence and titers of anti-drug antibodies
Part A Exploratory Objectives	**Part A 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 • Characterization of hematopoietic cell function by mouse engraftment studies and/or colony formation assays
To assess gene-modifying potential of mobilized $CD34^+$ cells in patients with SCD	• Assessment of ability to select and gene-modify $CD34^+$ cells
HSC=hematopoietic stem cells; PD=pharmacodynamic(s); PK=pharmacokinetic(s); SCD=sickle cell disease; TEAE=treatment-emergent adverse event; TESAE=treatment-emergent serious adverse event	

5.2. Part B Objectives and Endpoints

Study objectives and associated endpoints for Part B are listed in Table 5:

Table 5: Part B Objectives and Endpoints

Part B Primary Objectives	Part B Primary Endpoints
To characterize the efficacy of 2 consecutive days of dosing with MGTA-145 and plerixafor for HSC mobilization and apheresis collection in patients with SCD	• Determination of the yield of $CD34^+$ cells after 2 consecutive days of MGTA-145 and plerixafor mobilization and apheresis collection in patients with SCD
To characterize the safety and tolerability of	• Incidence of TEAEs, including drug-related TEAEs, $\geq$Grade 3 TEAEs, TESAEs, and TEAEs leading to study drug discontinuation

MGTA-145 in patients with SCD	• Incidence of treatment-emergent ≥Grade 3 clinical laboratory abnormalities • Clinically significant changes from baseline in vital signs and laboratory parameters (e.g., serum chemistry, hematology)
Part B Secondary Objectives	**Part B Secondary Endpoints**
To measure the mobilization effects of 2 consecutive days of 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
To characterize the immunogenicity of MGTA-145 in patients with SCD	• Presence and titers of anti-drug antibodies
Part B Exploratory Objectives	**Part B Exploratory Endpoints**
To characterize the phenotype and function of cells collected by apheresis in patients with SCD	• Flow cytometric characterization of the cells collected following MGTA-145 and plerixafor mobilization and apheresis • Characterization of hematopoietic cell function by mouse engraftment studies and/or colony formation assays
To assess gene-modifying potential of mobilized HSC in patients with SCD	• Assessment of the ability to select and gene-modify $CD34^+$ cells
HSC=hematopoietic stem cell; PD=pharmacodynamic(s); PK=pharmacokinetic(s); TEAE=treatment emergent adverse event; TESAE=treatment-emergent serious adverse event	

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This Phase 2, multicenter, open-label study will be conducted in 2 parts (Parts A and B). Part A is intended to characterize the efficacy, safety, PK, and PD of a single dose of MGTA-145 and plerixafor for HSC mobilization and apheresis collection in patients with SCD. Part B is intended to characterize the efficacy of 2 consecutive days of dosing with MGTA-145 and plerixafor for HSC mobilization and apheresis collection in patients with SCD.

The study design and subject procedural flow schematic for Parts A and B are illustrated in Figure 1. The Schedule of Assessments for Part A is provided in

Table 6, and the Schedule of Assessments for Part B is provided in Table 7. The Schedule of Assessments for blood and immune cell composition for Parts A and B is provided in Table 8.

Figure 1: Part A (Single Dose) and Part B (Single Dose on 2 Consecutive Days)

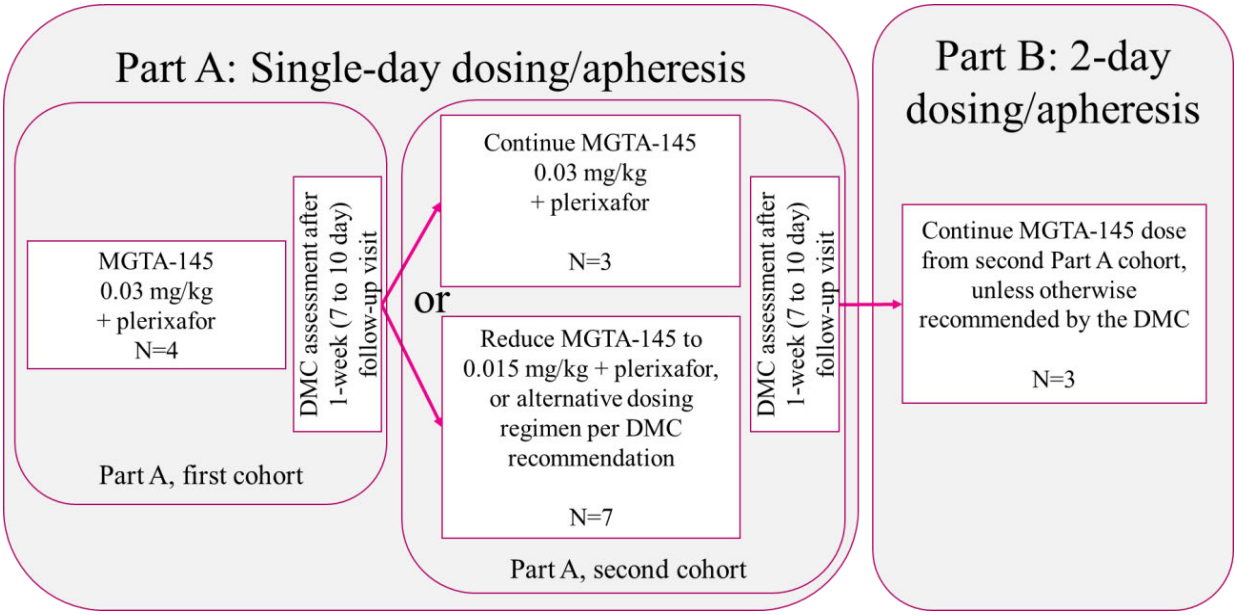

Table 6: Schedule of Assessments: Part A (Single Dose)

Study Period Procedures	Screening	Baseline	Mobilization /Apheresis	1-week follow-up (Day 7 to 10)[b]	End of Study (Day 30)[b]
	Day -30 to -2	Day -1	Day 1		
Informed consent	X				
Medical history	X	X			
Inclusion/exclusion criteria review	X				
Height		X			
Weight		X		X	
Physical examination	X	X		X	
Symptom-directed physical examination			X		
Vital signs [a]	X	X	X	X	
Serology [c]	X				
Serum or urine β-hCG (females)	X	X			
12-lead ECG	X				
Urinalysis		X	X	X	
Chemistry [d]	X	X	X	X	
Hematology [e]	X	X	X	X	
Anti-drug antibodies		X		X	
Plerixafor administration			X		
MGTA-145 administration [f]			X		
Apheresis procedure			X		
Apheresis yield [g]			X		
PROMIS and ASCQ-Me questionnaires [h]			X	X	
Non-serious AEs and SAEs [i]	X	X	X	X	X[j]
Concomitant medications	X	X	X	X	X[j]

AE=adverse event; ASCQ-Me=Adult Sickle Cell Quality of Life Measurement Information; BPI=Brief Pain Inventory; β-hCG=beta-human chorionic gonadotropin; CFU= colony-forming unit; ECG=electrocardiogram; PK=pharmacokinetics; NRS=Numeric Rating Scale; SAE=serious adverse event

[a] Vital sign measurements will be taken in the sitting position after the subject has been resting for 5 minutes. Vital signs should be taken before any blood samples are drawn.

[b] If a subject does not complete dosing, there will not be follow-up visits. If a subject received MGTA-145 but did not complete apheresis, then follow-up visits are required.

[c] All subjects enrolled in Parts A will be screened for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), human T-cell leukemia virus (HTLV), and hepatitis C virus (HCV) at the screening visit. Subjects who are HCV antibody positive must have a HCV ribonucleic acid (RNA) polymerase chain reaction (PCR) test.

[d] Clinical chemistry consists of sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, albumin, total and indirect bilirubin. Clinical chemistry sample collection should be done prior to dosing on Day 1. All other clinical chemistry sample collections will be done on the morning of the assessment day.

[e] Hematology is complete blood count (CBC) with platelets and leukocyte differential. Hematology sample collection should be done prior to dosing on Day 1 and Day 2. All other hematology sample collections will be done on the morning of the assessment day.

[f] MGTA-145 is to be administered via a 3 to 10-minute IV infusion, approximately 2 hours after plerixafor SC injection. Instructions regarding administration are provided in the Study Pharmacy Manual.

[g] Total nucleated cell count and $CD34^+$ cell count in absolute numbers and per kg.

[h] ASCQ-Me® and PROMIS® questionnaires will be completed prior to dosing on Day 1.

[i] Collection of non-serious AEs and SAEs will begin once the Informed Consent Form (ICF) has been signed. Any SAE occurring after the reporting period must be promptly reported if a causal relationship to study drugs is suspected.
[j] End-of-study visit phone call will occur 30 days (±3 days) after the last dose of MGTA-145 was received, to assess adverse events and concomitant medications.

Table 7: Schedule of Assessments: Part B (Single Dose on 2 Consecutive Days)

Study Period Procedures	Screening	Baseline	Mobilization/Apheresis [b]		1-week follow-up (Day 8 to 11)[c]	End of Study (Day 30)[c]
	Day -30 to -2	Day -1	Day 1 Part B	Day 2 Part B only		
Informed consent	X					
Medical history	X	X				
Inclusion/exclusion criteria review	X					
Height		X				
Weight		X			X	
Physical examination	X	X			X	
Symptom-directed physical examination			X	X		
Vital signs [a]	X	X	X	X	X	
Serology [d]	X					
Serum or urine β-hCG (females)	X	X				
12-lead ECG	X					
Urinalysis		X	X	X	X	
Chemistry [e]	X	X	X	X	X	
Hematology [f]	X	X	X	X	X	
Anti-drug antibodies		X			X	
Plerixafor administration			X	X		
MGTA-145 administration [g]			X	X		
Apheresis procedure			X	X		
Apheresis yield [h]			X	X		
PROMIS and ASCQ-questionnaires [i]			X		X	
Non-serious AEs and SAEs [j]	X	X	X	X	X	X[k]
Concomitant medications	X	X	X	X	X	X[k]

AE=adverse event; ASCQ-Me=Adult Sickle Cell Quality of Life Measurement Information; BPI=Brief Pain Inventory; β-hCG=beta-human chorionic gonadotropin; CFU= colony-forming unit; ECG=electrocardiogram; PK=pharmacokinetics; NRS=Numeric Rating Scale; SAE=serious adverse event

[a] Vital sign measurements will be taken in the sitting position after the subject has been resting for 5 minutes. Vital signs should be taken before any blood samples are drawn.

[b] For Part B, mobilization/collection will occur on 2 consecutive days.

[c] If a subject does not complete dosing, there will not be follow-up visits. If a subject received MGTA-145 but did not complete apheresis, then follow-up visits are required.

[d] All subjects enrolled in Part B will be screened for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), human T-cell leukemia virus (HTLV), and hepatitis C virus (HCV) at the screening visit. Subjects who are HCV antibody positive must have a HCV ribonucleic acid (RNA) polymerase chain reaction (PCR) test.

[e] Clinical chemistry consists of sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, albumin, total and indirect bilirubin. Clinical chemistry sample collection should be done prior to dosing on Day 1 and Day2. All other clinical chemistry sample collections will be done on the morning of the assessment day.

[f] Hematology is complete blood count (CBC) with platelets and leukocyte differential. Hematology assessments will be done on the morning of the assessment day.

[g] MGTA-145 is to be administered via a 3 to 10-minute IV infusion, approximately 2 hours after plerixafor SC injection. Instructions regarding administration are provided in the Study Pharmacy Manual.
[h] Total nucleated cell count and $CD34^+$ cell count in absolute numbers and per kg.
[i] ASCQ-Me® and PROMIS® questionnaires will be completed prior to dosing on Day 1.
[j] Collection of non-serious AEs and SAEs will begin once the Informed Consent Form (ICF) has been signed. Any SAE occurring after the reporting period must be promptly reported if a causal relationship to study drugs is suspected.
[k] End-of-study visit phone call will occur 30 days (±3 days) after the last dose of MGTA-145 was received, to assess adverse events and concomitant medications.

Table 8: Schedule of Assessments (Parts A and B) – Blood and Immune Cell Composition

Assessments	Day 1 (Parts A and B) and Repeated on Day 2 (Part B Only)						
	Within 1 Hour Prior to Plerixafor Dosing	1 Hour After Plerixafor Dosing	Within 15 Min Prior to MGTA Dosing	Post MGTA-145 Dosing			Apheresis Product [a]
				30 Min Prior to Apheresis	15 Min Prior to Apheresis	5 Min Prior to Apheresis	
Peripheral Blood $CD34^+$ analysis	X	X	X			X	
Graft Immunophenotyping							X [a]
PK blood samples [b]			X	X	X	X [b]	
CFU analysis							X [a]

[a] Samples will be aliquoted from final HPA-C
[b] PK time points are within 15 minutes prior to MGTA-145 dosing and at 2 time points, spaced at least 15 minutes apart, prior to the initiation of apheresis. If apheresis is not initiated within 45 minutes of MGTA-145 dosing, a third PK sample is to be drawn within 5 minutes prior initiation of apheresis.

6.2. Study Duration

6.2.1. Duration of Treatment Part A:

Screening Period: up to 30 days

Dosing and Follow-up Period: approximately 30 days

6.2.2. Duration of Treatment Part B:

Screening Period: up to 30 days

Dosing and Follow-up Period: approximately 30 days

6.3. Methodology

Approximately 10 to 14 patients with SCD are planned to be enrolled in this 2-part study. Part A evaluates single-day mobilization and apheresis in 2 sequential patient cohorts, then Part B evaluates two-day mobilization and apheresis in a single patient cohort, following administration of single and 2 consecutive-day doses of MGTA-145 and plerixafor, respectively.

Part A and Cohort Review Committee assessment: Part A has a planned enrollment of approximately 7 to 11 evaluable subjects. The first cohort of 4 subjects is to receive a single

0.24 mg/kg SC dose of plerixafor followed 2 hours later by a single 0.03 mg/kg IV dose of MGTA-145. Apheresis is planned to commence within approximately 30 to 45 minutes of dosing. For this initial cohort, only one subject will be dosed and apheresed on a single-day, and each subject will complete the 1-week follow-up visit before a subsequent subject can be dosed.

After the first cohort has completed the 1-week follow-up visit, an independent Data Monitoring Committee (DMC), comprising 3 members with medical expertise in the conduct of stem cell transplantation in patients with SCD as well as the conduct of clinical trials in general, will evaluate the safety, PK, and mobilization kinetics of MGTA-145 before the second cohort may be enrolled. The DMC may recommend enrolling an additional 3 subjects at the 0.03 mg/kg MGTA-145 dose or an additional 7 subjects at a reduced dose of 0.015 mg/kg MGTA-145 or an alternative but lower dosing regimen for this cohort. The MGTA-145 dose will not be escalated during either Parts A or B.

After the second cohort has completed the 1-week follow-up visit, the DMC will likewise evaluate the safety, PK, and mobilization kinetics of MGTA-145 before subjects may be enrolled into Part B. Criteria for the DMC recommendations regarding cohort progression and dosing regimen will be defined in the DMC Charter.

Part B: Part B has a planned enrollment of approximately 3 evaluable subjects. Subjects will receive single doses of MGTA-145 and plerixafor on 2 consecutive days, followed by apheresis on each dosing day. The plerixafor and MGTA-145 doses on each of the 2 consecutive days will be identical to that of the second Part A cohort, unless otherwise recommended by the DMC.

All subjects in Parts A and B will be observed at the investigational site from Day -1 until at least one day after the last apheresis and attend a 1-week (7 to 10 days) follow-up visit after the last MGTA-145 infusion. All subjects will attend an EOS phone visit 30 days after the last MGTA-145 infusion.

For both Parts A and B, peripheral $CD34^+$ cell counts will be performed pre- and post-dosing with plerixafor and post-dosing with MGTA-145, up to 5 minutes prior to apheresis (Table 8).

Hematopoietic stem cells obtained by apheresis (HPC-A) will be processed according to standardized clinical cell therapy laboratory procedures. Peripheral blood and HPC-A will be stored for testing (e.g., exploratory PD evaluation, cell characterization, and process characterization) and by the investigational sites for potential future transplantation.

6.4. Number of Subjects

Approximately 10 to 14 evaluable subjects with SCD are planned to be enrolled in this two-part study.

- **Part A** has a planned enrollment of approximately 7 to 11 evaluable subjects.
- **Part B** has a planned enrollment of approximately 3 evaluable subjects.

6.5. Treatment Assignment

This is an open-label study, in which all subjects will receive MGTA-145 and plerixafor as study drug.

All study subjects who are consented (including screen failures) will be assigned a subject identification number. The unique subject identification number will consist of 6 digits (xxxyyy).

The first 3 digits of the number will represent the study site and the second 3 digits will represent the subject at that study site. Any subject identification number that is assigned will not be reused even if a subject does not receive study drug.

6.6. Stopping Rules

6.6.1. Scheduled Stopping Rule Assessments

For the purposes of this study, a vaso-occlusive event (VOE, aka: vaso-occlusive crisis, sickle cell pain crisis) is defined as pain and/or injury as a result of ischemia due to vascular obstruction by sickled RBCs. Clinical manifestations of VOEs may include episodes of acute pain and/or evidence of organ involvement presenting as priapism, acute chest syndrome, splenic sequestration, hepatic sequestration, cerebrovascular ischemic event, or dactylitis.

Patients with SCD are known to commonly experience VOEs during and immediately following mobilization and apheresis, with approximately 30% of plerixafor-mobilized patients reported to have experienced a ≥Grade 3 VOE during and after apheresis, and approximately 20% of patients reported to have experienced serious vaso-occlusive pain within 2 days post-procedure.[20,22] The stopping rules described below have therefore been designed to be triggered if the frequency of Grade 3 VOEs occurring within approximately one week (1-week follow-up visit, occurring 7 to 10 days) after MGTA-145 dosing exceeds that which would be expected using plerixafor alone, to be evaluated at each scheduled DMC assessment. Pain occurring during the infusion or immediately after infusion and resolving within 1 hour of infusion will not be considered a VOE and will not count toward the stopping rule. Furthermore, as described below in Section 6.6.1.3. (Unscheduled Stopping Rule Assessment), the occurrence of a ≥Grade 4 VOE in any subject occurring within approximately one week (1-week follow-up visit, occurring 7 to 10 days) after MGTA-145 dosing will be considered a stopping rule.

6.6.1.1. Scheduled Part A, First Cohort DMC Stopping Rule Assessment

Using the probability data presented in Table 9 below, the likelihood of a Grade 3 VOE occurring in more than 2 of 4 subjects comprising the first Part A cohort within approximately one week would be 8.37%, assuming that the true incidence using plerixafor alone is 30%. Therefore, if more than 2 of the 4 subjects in the first Part A cohort report a Grade 3 VOE within approximately one week (up until the 1-week follow-up visit), no further dosing will take place unless the DMC determines that it is safe to do so.

Table 9: Probabilities of Grade 3 VOEs Occurring in Given Numbers of Study Subjects Undergoing Apheresis in the First Patient Cohort of Part A Within Approximately One Week, if Mobilized with Plerixafor Alone

Greater Than Grade 3 VOE	Probability if True=20%	Probability if True=30%	Probability if True=40%
≥1/4	59.04%	**75.99%**	87.04%
≥2/4	18.08%	**34.83%**	52.48%
≥3/4	2.72%	**8.37%**	17.92%
4	0.16%	**0.81%**	2.56%

6.6.1.2. Scheduled Part A, Second Cohort DMC Stopping Rule Assessment:

Based on the probability data presented in Table 10 below, the likelihood of a Grade 3 VOE occurring in more than 3 of 7 subjects completing Part A within approximately one week would be 12.60%, assuming that the true incidence using plerixafor alone is 30%. Therefore, if more than 3 of 7 patients completing Part A at a specific dosing regimen report a Grade 3 VOE within approximately one week (up until the 1-week follow-up visit), the study will not progress to Part B dosing unless the DMC determines that it is safe to do so.

Table 10: Probabilities of Grade 3 VOEs Occurring in Given Numbers of Study Subjects Undergoing Apheresis in the Second Patient Cohort of Part A Within Approximately One Week, if Mobilized with Plerixafor Alone

Probability of ≥ Grade 3 VOE	Probability if True=20%	Probability if True=30%	Probability if True=40%
≥1/7	79.03%	**91.76%**	97.20%
≥2/7	42.33%	**67.06%**	84.14%
≥3/7	14.80%	**35.29%**	58.01%
≥4/7	3.33%	**12.60%**	28.98%
>5/7	0.47%	**2.88%**	9.63%
>6/7	0.04%	**0.38%**	1.88%
7	0.01%	**0.02%**	0.16%

Furthermore, the DMC may determine that the study should not proceed to the subsequent cohort at the current dosing regimen, based on the entirety of data available, regardless of whether a cohort stopping rule has been met.

6.6.1.3. Unscheduled Stopping Rule Assessment

In addition to the cohort stopping rules outlined above, if within approximately one week (up until the 1-week follow-up visit) after MGTA-145 dosing, any subject develops a Grade ≥4 VOE, or a Grade ≥3 drug-related TEAE (based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0) other than VOE, dosing of the current cohort will not be continued until the DMC assesses whether dosing may continue and whether dosing modifications are needed. In addition to VOEs, Grade 3 AEs known to be associated with plerixafor (i.e., nausea, vomiting, diarrhea, headache [as per plerixafor label]) or MGTA-145 (i.e., musculoskeletal pain that is less than 1 hour in duration from the time pain is first reported) will not count toward this stopping rule.

6.7. Criteria for Study Stopping/Termination

The Sponsor (Magenta) may stop/terminate the study due to the following reasons:

- Emergence of unacceptable safety risk to subjects.
- Failure of the Investigator or site to adhere to the protocol or regulatory requirements.

If the Sponsor decides to stop/terminate the study, the Sponsor will promptly notify the Principal Investigator and the relevant regulatory authority. The Principal Investigator will be responsible for notification of the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Criteria for Inclusion for Parts A and B

1. Subject must be 18 to 35 years of age, inclusive.
2. Subject must weigh ≥30 kg at screening.
3. Subject must have a documented diagnosis of SCD, with documentation of SCD genotype by medical history.
4. Subject must present with a feasible manual or automated exchange transfusion plan to achieve Hemoglobin S (HbS) <30% within 1 week of mobilization.
5. Subject taking hydroxyurea must comply with a washout period of at least 30 days prior to mobilization dosing. Subjects must be able to safely discontinue hydroxyurea to participate in the study.
6. Subject must have a local laboratory screening white blood cell (WBC) count >2.0 x 10^9/L, absolute neutrophil count (ANC) >1.0 x 10^9/L, and platelet count >150 x 10^9/L
7. Subject must have a local laboratory screening estimated glomerular filtration rate (eGFR) of at least 60 mL/min/1.73 m^2 based on the CKD-Epi equation.
8. Subject must have a local laboratory screening alanine aminotransferase (ALT) value <2.5 x upper limit of normal (ULN).
9. Subject's cardiac and pulmonary status must be sufficient to undergo apheresis, as assessed by the Investigator.
10. Subject must sign an IRB-approved informed consent form (ICF) and be willing to comply with the requirements of the protocol.

7.2. Criteria for Exclusion for Parts A and B

1. Subject with a VOE requiring a visit to a healthcare facility within 30 days of screening.
2. Subject with onset of clinically apparent cerebrovascular accident (CVA) or retinal infarct in the 2 years prior to screening or determined to be at high risk of CVA, based on concomitant disease (e.g., moyamoya), or imaging (e.g., trans-cranial doppler study).
3. Subject with splenomegaly, splenic sequestration, sickle hepatopathy, priapism requiring inpatient treatment, acute chest syndrome requiring supplemental oxygen, or osteomyelitis within 6 months of screening. Subjects with a history of splenomegaly or splenic sequestration may be included if they have undergone a splenectomy.
4. Subject having surgery requiring greater than local anesthesia within 3 months of screening, except for placement of a central venous access device.
5. Subject who has received or plans to receive anticoagulation at the time of screening, except for study-related procedures.

6. Subject who, by medical history, requires rare donor registry red blood cell (RBC) units for transfusion, or is unable to receive routine transfusion. Eligible study subjects must have undergone prior work-up for the presence of red cell alloantibodies and confirmation of available compatible blood product support.
7. Subject who has undergone or attempted and failed previous HSC collection.
8. Subject who has had a prior autologous or allogeneic transplantation, inclusive of gene therapy.
9. Subject who has received experimental therapy within 4 weeks of providing informed consent or is enrolled in another interventional experimental protocol.
10. Subject with poorly controlled diabetes mellitus, as assessed by the Investigator.
11. Subject who has an uncontrolled cardiovascular condition, including clinically significant cardiac arrhythmia, congestive heart failure, angina, myocardial infarction, or unstable pulmonary arterial hypertension within 6 months of screening.
12. Subject with a history of or who has a positive screening laboratory test for human immunodeficiency disease (HIV), hepatitis B, hepatitis C, or human T-cell leukemia virus (HTLV).
13. Subject with active infection or co-morbid condition that places the subject at high risk for treatment complications, as assessed by the Investigator.
14. Subject with a known allergy to or contraindication for MGTA-145, plerixafor administration, or medications routinely administered during apheresis.
15. Male subject not willing or able to use a highly effective method of contraception for 3 months during and after treatment with MGTA-145 and plerixafor, or female subject who is pregnant or breastfeeding, or sexually active and not willing or able to use a highly effective method of contraception for 3 months during and after treatment with MGTA-145 and plerixafor.

7.3. Subject Withdrawal Criteria

A subject may be discontinued from the study procedures at the discretion of the Investigator. In such a case, the decision to discontinue the subject will be made by the Investigator in consultation with the study Medical Monitor. Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs when a subject:

- Does not want to continue participation in the study
- Does not want any further study visits or assessments
- Does not want any further study-related contacts

Subjects who discontinue study procedures should not be considered withdrawn from the study unless they withdraw their consent. If a subject withdraws consent, the Investigator must make every effort (e.g., telephone, email, letter) to determine the primary reason for this decision and record this information in the electronic case report form (eCRF). If the subject is willing to

perform end-of-study assessments, these should be conducted. Otherwise, no further assessments should be conducted. All biological material that has not been analyzed at the time of withdrawal must not be used unless written consent is obtained. Further attempts to contact the subject are not allowed unless safety findings require communication or follow-up.

8. TREATMENT OF SUBJECTS

8.1. Description of Study Drug

MGTA-145 is a 4 amino acid-truncated protein variant of the CXCR2 agonist CXCL2.

8.1.1. Dose Cohort(s) Planned for Part A

The initial Part A subject cohort will enroll and complete treatment and 1-week follow-up of 4 evaluable subjects with SCD, aged 18 to 35 years, who will receive an MGTA-145 dose of 0.03 mg/kg approximately 2 hours after receiving a plerixafor dose of 0.24 mg/kg. This will be followed by a DMC review of the safety, PK, PD, and mobilization kinetics data for the 4 subjects who have completed their 1-week follow-up visit.

For the second Part A subject cohort, the DMC may recommend enrolling an additional 3 subjects at the 0.03 mg/kg MGTA-145 dose or an additional 7 subjects at a reduced dose of 0.015 mg/kg MGTA-145 or an alternative dosing regimen, as recommended by the DMC.

8.1.2. Dose Cohort Planned for Part B

Part B has a planned enrollment of approximately 3 evaluable subjects. Subjects with SCD, aged 18 to 35 years, will receive single doses of MGTA-145 and plerixafor on 2 consecutive days, followed by apheresis on each dosing day. The dose of MGTA-145 will be identical to that of the second Part A cohort, unless otherwise recommended by the DMC.

8.2. Concomitant Medications and Supportive Care

Supportive care measures for SCD and its associated complications will be provided in accordance with local institutional guidelines.

Pre-medications will be administered at the discretion of the Principal Investigator according to institutional or center standard for apheresis collection.

A widespread US vaccination campaign against COVID-19 infection is ongoing during the conduct of this study. Vaccination against COVID-19 is essential to protect at-risk patient populations, including adults with SCD. Consistent with the NMDP/Be The Match recommendations, study subjects should receive vaccine when available to them. To distinguish possible side effects of vaccine from study participation, subjects should receive vaccine more than 72 hours before dosing of study drug and mobilization, if possible.

Prohibited medications:

Subjects cannot receive treatment with hydroxyurea during this study. Subjects taking hydroxyurea must comply with washout of at least 30 days prior to dosing of study drug. Subjects must be able to safely discontinue hydroxyurea to participate in the study, based on the clinical judgment of the Investigator.

Concomitant treatment with investigational agents is not allowed during the study.

8.3. Treatment Compliance

Administration of MGTA-145 and plerixafor will be performed under the supervision of the Investigator (or designee). Drug accountability procedures will be used to assess treatment

compliance. Compliance with study drug is defined as the subject receiving 100% of the planned dosage. Drug administration will be recorded and any discrepancies with the dosing regimen must be explained in the eCRF.

8.4. Randomization and Blinding

This study is an open-label study; therefore, study personnel and study subjects will not be blinded to the treatment administered/received.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

MGTA-145 is formulated in [redacted].

MGTA-145 injection is provided as a sterile solution for intravenous infusion in 2 mL Type I amber glass vials. Each vial contains 1 mL of a 20 mg/mL solution. Up to two daily 0.03 mg/kg doses of MGTA-145 will be administered as a single 3- to 10-minute IV infusion approximately 2 hours after 0.24 mg/kg SC administration of plerixafor.

Plerixafor (injection) is provided as a sterile, preservative-free, clear, colorless to pale yellow, isotonic solution for SC injection. Each mL of the sterile solution contains 20 mg of plerixafor. Each single-use vial is filled to deliver 1.2 mL of the sterile solution that contains 24 mg of plerixafor and 5.9 mg of sodium chloride in Water for Injection adjusted to a pH of 6.0 to 7.5 with hydrochloric acid and with sodium hydroxide, if required.

Study drug characteristics are summarized in Table 11 below.

Table 11: Study Drug

Product Name:	**MGTA-145**	**Plerixafor**
Dosage Form:	Injection	Injection
Unit Dose:	Single dose 2 mL Type I amber glass vial	Single dose vial
Route of Administration:	IV	SC
Physical Description:	Clear, colorless solution, essentially free of visible particles	Clear, colorless to pale yellow, isotonic solution

9.2. Study Drug Packaging and Labeling

MGTA-145 is supplied in a single dose 2 mL Type I amber glass vials and packaged in cartons. Each vial and carton will be labeled in accordance with regulatory/study requirements.

Commercially available plerixafor will be supplied by the study site in the commercially approved packaging and labeling.

9.3. Study Drug Storage and Stability

MGTA-145 vials should be stored at -20°C ±5°C in the carton to protect from light.

Plerixafor should be stored according to the manufacturer's instructions.

9.4. Study Drug Preparation

A vial of MGTA-145 should be thawed according to the Study Pharmacy Manual prior to use; MGTA-145 vials are stable at 2°C to 8°C for up to 30 days. Once thawed, MGTA-145 should not be refrozen.

Plerixafor is supplied as a ready-to-use formulation.

9.5. MGTA-145 and Plerixafor Administration

MGTA-145 should be diluted in 0.9% saline in accordance with the Study Pharmacy Manual. Dosing solutions of MGTA-145 prepared in 0.9% saline may be stored for no more than 8 hours at room temperature prior to administration. MGTA-145 is to be administered via a 3- to 10-minute IV infusion, approximately 2 hours after plerixafor SC injection. Instructions regarding administration are provided in the Study Pharmacy Manual.

Plerixafor is to be administered SC per the manufacturer's instructions.

9.6. Study Drug Accountability

The Investigator will ensure that the study drug is used only in accordance with this protocol. The Investigator or designee is responsible for recording the details of the IV administration of MGTA-145 on the subject's eCRF.

9.7. Study Drug Handling and Disposal

Periodically, and/or after completion of the study, all used study drug containers (including empty containers) of MGTA-145 must be reconciled and destroyed at the site per the Study Pharmacy Manual. If the site does not have appropriate procedures in place for destroying used study drug, used study drug should be returned to Magenta (or designee) for destruction. Study drug cannot be used for any other purpose than that described in this protocol.

10. PHARMACOKINETIC, PHARMACODYNAMIC, AND IMMUNOLOGIC ASSESSMENTS

10.1. Pharmacokinetic Assessments

Samples for MGTA-145 PK determinations will be collected for all subjects enrolled in Parts A and B at the timepoints outlined in the section below and the Schedule of Assessments.

As specified in Table 8, a plasma sample will be collected within 15 minutes prior to MGTA-145 dosing and at 2 time points, spaced at least 15 minutes apart, prior to the initiation of apheresis. If apheresis is not initiated within 45 minutes of MGTA-145 dosing, a third PK sample will be drawn within 5 minutes prior initiation of apheresis.

Details regarding blood sample collection are provided in the Laboratory Manual.

10.2. Pharmacodynamic Assessments

Changes in cell functionality will be assessed in terms of colony-forming units (CFUs) using an automated colony-counting device (StemVision™ from Stemcell Technologies) or manually with an inverted microscope.

10.2.1. Colony-Forming Unit Analysis

For all subjects enrolled in Parts A and B, whole blood will be collected as outlined in the Schedules of Event (Table 6 for Part A and Table 7 for Part B) to analyze changes in granulocyte-macrophage colony-forming units (CFU-GMs), granulocyte-erythrocyte-macrophage-megakaryocyte colony-forming units (CFU-GEMMs), and erythroid burst-forming units (BFU-Es). Briefly, blood samples will be plated in specially formulated methylcellulose media and cultured for 7 to 10 days at 37˚C with 5% CO_2. The number of CFUs in each sample will be assessed with an automated colony-counting device (StemVision™ from Stemcell Technologies) or manually with an inverted microscope.

Details regarding this collection will be provided in the Laboratory Manual.

10.2.2. Apheresis Yield

Apheresis cell collection as outlined in the Schedule of Events (Table 6 for Part A and Table 7 for Part B) from all subjects enrolled in Parts A and B will proceed according to standardized procedures and start within an hour after MGTA-145 infusion. All subjects will undergo apheresis collection according to institutional practice, not to exceed a total of 8 hours. Apheresis yield will be measured as the total nucleated cell count and $CD34^+$ cell count in absolute numbers and per kilogram. These determinations will be performed using fluorescent flow cytometry.

10.2.2.1. Peripheral Blood $CD34^+$ Counts

For all subjects enrolled in Parts A and B, whole blood samples for determination of peripheral $CD34^+$ cell counts will be collected at the timepoints specified in Table 8. Details regarding peripheral $CD34^+$ cell blood sample collection during Parts A and B are provided in the Laboratory Manual. Determination of changes in $CD34^+$ and $CD34^+CD90^+CDRA^-$ cell counts, as

well as T-cell subtypes, B cells, monocytes, granulocytes, and natural killer (NK) cells will be performed using fluorescent flow cytometry.

Changes in cell functionality will be assessed in terms of CFUs using an automated colony-counting device (StemVision™ from Stemcell Technologies) or manually with an inverted microscope.

10.2.2.2. Exploratory Graft Characterization

For all subjects enrolled in Parts A and B, HPC-A will be collected as outlined in Table 8 to assess graft immunophenotype, function, and ability to select and gene-modify $CD34^+$ cells. Details regarding this collection will be provided in the Laboratory Manual.

10.3. Immunologic Assessments

Plasma samples for measurement of anti-drug antibodies will be collected as outlined in Table 8. Screening for anti-drug antibodies in plasma will be conducted using a bridging immunogenicity assay (electrochemiluminescent immunoassay [ECLIA]). In the initial screen, test samples will be evaluated based on an assay cut point determined by 10+ individual lots of naïve plasma per plate. Samples that test positive will then be re-tested in a confirmatory competitive binding assay where free drug is spiked into the reaction at a 50:1 excess.

Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the Laboratory Manual.

11. ASSESSMENT OF SAFETY

Subject safety will be assessed based on monitoring of AEs, vital signs, physical examinations, clinical laboratory evaluations, and development of anti-drug antibodies. Adverse events will be graded using the NCI CTCAE version 5.0.

Vaso-occlusive events are known to be associated with plerixafor use in patients with SCD undergoing mobilization and apheresis, reaching Grade 3 or higher severity in approximately 30% of patients.[20,22] During each planned post-cohort assessment, the DMC is to evaluate and recommend whether to proceed to the subsequent cohort at the current dosing regimen based on evaluation of safety, PK, and mobilization kinetics. At each assessment, the number and proportion of patients reporting VOEs within approximately one week (1-week follow-up visit, occurring 7 to 10 days) after MGTA-145 dosing will be determined, and the DMC will determine whether a stopping rule has been met (Section 6.6), in which case no further dosing at that dosing regimen will take place unless the DMC determines that it is safe to do so. Pain occurring during the infusion or immediately after infusion and resolving within 1 hour of infusion will not be considered VOE and will not count toward the stopping rule.

In Part B, if a subject has a VOE following the first MGTA-145 infusion, proceeding to the second infusion will be at the Investigator's discretion.

As described below in Section 6.6, the occurrence of a Grade ≥4 VOE in any subject within approximately one week (1-week follow-up visit, occurring 7 to 10 days) after MGTA-145 dosing will be considered a stopping rule.

Excluding VOE, if any subject develops a Grade 3 or higher drug-related TEAE, based on the NCI CTCAE version 5.0, dosing of the current cohort will not be continued until the DMC assesses whether dosing may continue and whether dosing modifications are needed. In addition to VOEs, Grade 3 AEs known to be associated with plerixafor (i.e., nausea, vomiting, diarrhea, headache [as per plerixafor label]) or MGTA-145 (i.e., bone pain that is less than 1 hour in duration from the time the bone pain is first reported) will not count toward this stopping rule.

Pre-medications will be at the discretion of the Principal Investigator according to institutional or center standard for apheresis collection. All subjects will have adequate hydration before and during the apheresis procedure.

Subjects will undergo a transfusion regimen (exchange or simple, as available or needed) targeting hemoglobin (Hb) 10 g/dL (not to exceed 12 g/dL) prior to mobilization and HbS proportion in the blood of <30%; the last exchange transfusion must occur within 7 days of start of mobilization.

11.1. Safety Parameters

11.1.1. Demographic Information

Subject demographic and baseline characteristic data to be collected on all subjects at the screening visit include date of birth, age, sex, race, and predominant ethnicity.

11.1.2. Medical History

Relevant medical history, including SCD genotype, and current medical conditions will be recorded for all subjects at the screening and baseline visits, and will include all prior therapies for the treatment of SCD.

11.1.3. Vital Signs

Vital sign measurements will be obtained at the time points specified in the Schedule of Assessments (Table 6 for Part A and Table 7 for Part B) and include body temperature, systolic and diastolic blood pressure, pulse rate, respiratory rate, and pulse oximetry. All vital sign measurements will be taken in the sitting position after the subject has been resting for 5 minutes. Vital signs should be taken before any blood samples are drawn.

11.1.4. Weight and Height

For all subjects enrolled in Parts A and B, weight (kg) will be documented at the baseline (Day -1) and the 1-week follow-up visit (Day 7 to 10). Subject height (cm) will be measured at the baseline visit.

11.1.5. Physical Examination (Complete and Symptom-directed)

A complete physical examination will be performed for all subjects at screening, baseline (Day -1), and 1-week follow-up visit (Day 7 to 10), for all subjects enrolled in Parts A and B. Complete physical examinations will include general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and nervous system, and will be conducted at the screening visit. Information for each physical examination must be included in the source documentation at the study site and will be recorded on the eCRF.

A pretreatment directed physical examination will be performed on treatment Day 1 of Part A and on treatment Days 1 and 2 of Part B. All directed physical examinations will be symptom-based.

Any physical examination abnormality deemed clinically significant by the Investigator during screening will be reported as medical history. Any physical examination abnormality that emerges or has worsened after signing the ICF assessed as clinically significant by the Investigator will be reported as an AE.

11.1.6. Electrocardiogram

A single recording baseline 12-lead electrocardiogram (ECG) will be obtained for all subjects at screening. Subjects having any clinically significant ECG abnormality, as assessed by the Investigator, will not be allowed to continue in the study.

11.1.7. Clinical Laboratory Assessments

When a laboratory assessment that is listed in the inclusion/exclusion criteria is outside of a protocol-specified range at screening, the assessment may be repeated once prior to study number assignment. If the repeat value remains outside of protocol-specified ranges, the subject will be excluded from the study.

Clinically relevant deviations from the normal range for laboratory test results should be evaluated for criteria defining an AE and reported as such.

Sample collection and handling information for all laboratory evaluations are provided in the Laboratory Reference Manual.

11.1.7.1. Hematology

Hematology assessments will include complete blood count (CBC), including platelet count and leukocyte differential, which will be performed as outlined in the Schedule of Assessments (Table 6 for Part A and Table 7 for Part B).

11.1.7.2. Clinical Chemistry

Clinical chemistry evaluations will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, AST, ALT, alkaline phosphatase, albumin, total and indirect bilirubin, and will be measured per the Schedule of Assessments (Table 6 for Part A and Table 7 for Part B). Clinical chemistry assessments will be done on the morning of the assessment day.

11.1.7.3. Urinalysis

Per the Schedule of Assessments (Table 6 for Part A and Table 7 for Part B), urinalysis, conducted by dipstick, will assess pH, protein, glucose, ketone, urobilinogen, bilirubin, blood, specific gravity, nitrite, and leukocytes.

11.1.7.4. Virus Serology

All study subjects enrolled in Parts A and B will be screened for HIV, hepatitis B surface antigen (HbsAg), HTLV, and HCV at the screening visit. Subjects who are HCV-antibody positive must have a negative HCV ribonucleic acid (RNA) polymerase chain reaction (PCR) test in order to be considered eligible for study participation.

11.1.7.5. Pregnancy Screen

All females of childbearing potential enrolled in Parts A and B will have a serum or urine beta-human chorionic gonadotropin (β-hCG) pregnancy test performed at the screening visit and at baseline (Day -1).

11.1.8. Patient Surveys

Patient Survey forms used in the study as outlined in the Schedule of Assessments (Table 6 for Part A and Table 7 for Part B) are provided in Appendix Section 18.2.

11.1.8.1. ASCQ-ME®

The Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me®) is a patient-reported outcome measurement system that evaluates the physical, mental, and social well-being of adults with SCD across 5 domains, including emotional impact, social functioning, pain, stiffness, and sleep functioning.

For all subjects enrolled in Parts A and B, the ASCQ-Me® will be performed prior to dosing on Day 1 and at the 1-week follow-up visit (Day 7-10).

11.1.8.2. PROMIS®

The Patient-Reported Outcomes Measurement Information System (PROMIS®) evaluates the physical, mental, and social well-being of adults and children living with chronic conditions.

Among the 7 primary PROMIS domains (physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, and pain interference), only the pain intensity and pain interference domains are to be performed in this study, prior to dosing on Day 1 and at the 1-week follow-up visit (Day 7 to 10).

11.1.9. EOS Phone Visit

End-of-study phone visit will occur 30 days (±3 days) after the last dose of MGTA-145 was received, to assess adverse events and concomitant medications.

11.2. Adverse Events and Serious Adverse Events

11.2.1. Adverse Events

Collection of non-serious AEs and serious adverse events (SAEs) will begin once the ICF is signed and continue until the EOS visit. Non-serious AEs and SAE reporting will end at the EOS visit. Any SAE occurring after the reporting period must be promptly reported if a causal relationship to study drugs is suspected.

11.2.2. Adverse Event Definition

An AE is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom, or disease) in a subject or clinical investigation subject administered a medicinal product. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The occurrence of AEs should be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are suspected by the subject or subject's family during or between visits or through physical examination, laboratory test, or other assessments.

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- Induce clinical signs or symptoms
- Are considered clinically significant
- Require therapy or medical intervention

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline values or the previous visit, or values which are considered to be non-typical in subjects with underlying disease. Investigators have the responsibility for managing the safety of individual subjects and identifying and documenting AEs.

From the signing of informed consent, non-serious AEs and SAEs must be recorded on the AE eCRF for subjects who enroll in the study. The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE rather than as the individual signs/symptoms. The AEs should be accompanied by the following information:

1. The CTCAE Grade (version 5.0)

If CTCAE grading does not exist for an AE (and this is rare), use:

Grade 1=mild

Grade 2=moderate

Grade 3=severe

Grade 4=life-threatening

Grade 5- death

2. Relationship to the study treatments (definitely related, probably related, possibly related, unlikely related, not related).
3. Duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
4. Whether it constitutes an SAE (see Section 11.2.4 for the definition of SAE).
5. Action taken regarding study treatments.
6. Outcome (not recovered/not resolved; recovered/resolved; recovered/resolved with sequelae; fatal; or unknown). Death is an outcome of an event. The event that resulted in death must be recorded on the appropriate eCRF and reported as an SAE.

Treatment related AEs and all SAEs should be followed until resolution, stabilization, or until it is judged to be permanent, and an assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. Information regarding common side effects of plerixafor can be found in the product's package insert. This information will be included in the subject's informed consent and should be discussed with the subject during the study as needed.

11.2.3. Adverse Event of Interest

Musculoskeletal pain occurring up to 24 hours post administration of MGTA-145, regardless of severity or relationship to study drug, will be captured as an AE of interest. The severity (based on CTCAE version 5.0), time of onset, duration of back pain, relationship to study drug, outcome, action taken regarding study drug, and any treatment administered will be captured in the electronic data capture (EDC) system.

11.2.4. Serious Adverse Event

A SAE is defined as any appearance of or worsening of any pre-existing undesirable sign(s), symptom(s), or medical conditions(s), which meets any one of the following criteria:

- Is fatal
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, except:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above and not resulting in hospital admission
  - Social reasons and respite care in the absence of any deterioration in the subject's general condition
- Is medically significant (i.e., defined as an event that jeopardizes the subject or may require medical or surgical intervention)

Life-threatening in the context of an SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Any suspected transmission of an infectious agent via a medicinal product is also considered an SAE.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization.

Serious adverse events are to be monitored continuously and have special reporting requirements (see Section 11.5). All SAEs will be followed until resolution, stabilization, or until it is judged to be permanent.

11.3. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE/SAE (related or unrelated). The Investigator should decide

whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE/SAE should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE/SAE, then the AE/SAE should be considered "related."

For the purpose of regulatory reporting requirements, causal relationships of definite, probable, and possible will be considered treatment related, while unlikely and not related will be considered not treatment related.

11.4. Recording Adverse Events

In the event that a subject experiences an AE or SAE, an assessment of the event will be performed at the study site at the time of the incident and recorded on the AE eCRF page. If the subject is not evaluated at the study site at the time of the AE/ SAE, every effort will be made to obtain safety assessment data from the subject's local treating physician. If a subject is prematurely discontinued from study procedures, only safety data considered relevant for the assessment of the MGTA-145 safety profile will be collected in the clinical database.

11.5. Reporting Serious Adverse Events

To ensure subject safety, every SAE occurring after the subject has provided informed consent, through the end of the study, regardless of causality, must be reported to Premier within 24 hours of learning of its occurrence. Drug-related SAEs reported to the study site after the EOS visit should also be reported to Premier.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the Investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

In addition, SAEs (initial and follow-up) must be reported to Premier **within 24 hours of awareness** of the SAE or changes to an existing SAE. This should be done by emailing or faxing a signed copy of the **SAE Report Form** using the contact details below.

Premier SAE Reporting Contact Details

Email: [redacted]

Fax: [redacted]

Follow-up information provided should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation.

If the SAE is not previously documented in the IB and is thought to be related to the investigational treatment, Magenta may urgently require further information from the Investigator for regulatory authority reporting. Magenta may need to issue an Investigator Notification to inform all Investigators involved in any study with the same investigational

treatment that this SAE has been reported. Each site is responsible for notifying their IRB/IEC of these SAEs in accordance with local regulations. Suspected unexpected serious adverse reactions (SUSARs) will be collected and reported to the regulatory authorities and relevant IRBs in accordance with local laws and regulations. It is the responsibility of the Investigator to notify the IRB of SAEs that occur at his or her site per IRB reporting requirements.

11.6. Overdose

For this study, overdose is defined as a dose of study medication higher than the prescribed dose. In the case of overdose, the Investigator should be notified immediately, and supportive care given as indicated. Overdose will not be considered an SAE unless the overdose meets serious criteria as defined in Section 11.2.4. In the event of an overdose, the Magenta Medical Monitor should be notified within 24 hours. The subject should be carefully monitored for potential adverse reactions and symptomatic treatment instituted as per standard of care.

11.7. Reporting Pregnancy

Every pregnancy occurring up to 3 months after the last dose of study drug in subjects or partners of male subjects after the subject was administered MGTA-145, must be reported to Premier within 24 hours of learning of its occurrence. The pregnancy should be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. A pregnancy occurring after signing the ICF and before the subject is enrolled will preclude study participation.

Pregnancy should be recorded on a Premier Pregnancy Data Collection Report Form and be reported by the Investigator to Premier using the contact information provided in Section 11.5.

Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drugs of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

If the father received study drug, consent to report information regarding pregnancy outcome needs to be obtained from the mother.

12. STATISTICS

A formal statistical analysis plan (SAP) will be developed that includes a detailed description of all planned analyses, pre specified exploratory analyses, and any data handling conventions.

12.1. Analysis Sets

Evaluable Analysis Sets: The evaluable analysis set for Part A will include all subjects that have received MGTA-145 and plerixafor and undergone successful apheresis collection. The evaluable analysis set for Part B will include all subjects that have received 2 consecutive doses of MGTA-145 and plerixafor, and successfully completed at least 1 of the 2 apheresis sessions.

The Safety Analysis Set: The safety analysis set will consist of all subjects who are enrolled and received a dose of MGTA-145. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety summaries.

Pharmacokinetics Analysis Set: The PK analysis set will include all subjects with available MGTA-145 PK data and no major protocol deviations with relevant impact on PK data.

Pharmacodynamics Analysis Set: The PD analysis set will include all subjects with available PD data and no major protocol deviations with relevant impact on PD data.

In general, data will be presented for Parts A and B of the study separately.

12.2. Subject Demographic and Other Baseline Characteristics

All data for baseline and demographic variables will be listed by subject. Descriptive summary statistics will be provided.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests, and any other relevant information will be listed by subject.

12.3. Exposure and Concomitant Medications

MGTA-145 and plerixafor administrations (time of infusion, duration of infusion, and dose) will be summarized.

Concomitant treatments will be listed and summarized.

12.4. Analysis of the Primary, Secondary, and Exploratory Endpoints

The endpoints for this study are provided in Section 5.1 and Section 5.2.

12.4.1. Statistical Methods and Analyses

Statistical summaries will be descriptive in nature. All continuous variables will be summarized by dose and visit (as applicable) using descriptive statistics (number of observations [n], mean, median, standard deviation [SD], minimum, and maximum). All categorical variables will be summarized by dose and visit using frequency counts and percentages. Estimated median, 25^{th} and 75^{th} percentiles and standard error of the mean (SEM) from Kaplan-Meier summaries will be presented for all time-to-event variables. Subjects will be grouped by dose in all analyses and results will be presented by Study Part where applicable. Any subject who receives MGTA-145 will be included in the analyses. No formal hypothesis testing will be performed.

12.4.2. Safety

Safety analyses will include summaries of AEs and SAEs. The number and percentage of subjects reporting any TEAEs will be summarized. Adverse events will be tabulated by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) and relationship to treatment. AEs leading to study drug discontinuation and SAEs will be listed. Data listing will be provided for all AEs, TEAEs and SAEs.

Changes in vital signs and clinical laboratory parameters will be assessed from baseline.

12.4.3. Pharmacokinetics

Plasma concentrations of MGTA-145 will be listed and a summary by time point for each dose cohort will be presented using descriptive statistics (n, mean, SD, median, and range).

12.4.4. Pharmacodynamics

Peripheral blood will be collected at the timepoints specified in the Schedule of Assessments to measure changes in $CD34^+$ and $CD34^+CD90^+CDRA^-$ cell counts, as well as various T-cell subtypes, B cells, monocytes, granulocytes, and NK cells. Cell counts will be analyzed using fluorescent flow cytometry.

Changes in cell functionality will be assessed in terms of CFUs using an automated colony-counting device (StemVision™ from Stemcell Technologies) or manually with an inverted microscope.

12.5. Sample Size Calculation

There are no statistical hypotheses in this trial, therefore there is no sample size calculation. To address the objectives assessing proof of concept of mobilizing CD34+ cells after 1 or 2 days of dosing with MGTA-145 and plerixafor, a minimum sample size of 10 evaluable subjects is considered adequate.

Based on the safety profile including 79 subjects dosed with MGTA-145 in Phase 1 study 145-HV-101, 10 evaluable subjects are deemed a minimal number to assess common drug-related safety events.

The AE that is clearly related to MGTA-145 infusion is transient, Grade 1 back pain, which was observed in a majority of volunteers in the Phase 1 study 145-HV-101. With 10 evaluable subjects, there is sufficient subject exposure to assess for this AE.

Subjects enrolled in the study who are discontinued prior to receiving study drug may be replaced.

Additional subject(s) may be enrolled, if necessary, to ensure minimum numbers of evaluable subjects (i.e., subjects without any major protocol deviations affecting the primary endpoint). For the primary endpoint in Part A, 7 evaluable subjects are required; the first and second DMC assessments require 4 and 7 evaluable subjects, respectively. For the primary endpoint in Part B, 3 evaluable subjects are required.

13. DATA REVIEW AND DATABASE MANAGEMENT

13.1. Study Site Monitoring

Before an investigational site can enter a subject into the study, a representative of Magenta will:

- Determine the adequacy of the facilities.
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Magenta or its representatives. This will be documented in a Clinical Study Agreement between Magenta and the Investigator.

During the study, a monitor from Magenta or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the subject's medical records, and other records relevant to the study. This will require access to all original records for each subject (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to Magenta.
- Confirm that AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Magenta and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff need information or advice.

13.2. Data Collection

Designated Investigator staff will enter the data required by the protocol into the eCRFs using fully validated software that conforms to 21 Code of Federal Regulations (CFR) Part 11 requirements. Designated Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs will check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to Magenta. The Investigator must certify that the data entered into the eCRFs are complete and accurate. After database lock, the Investigator will receive any of the following: a compact disc read-only memory (CD-ROM), paper copies, or a password protected universal serial bus (USB) drive of the subject data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the Data Management Reference Manual and Assessment Schedule and can be recorded directly on the eCRFs. All other data captured for this study will have an external originating source (either written or electronic) with the eCRF not being considered as source.

13.3. Database Management and Quality Control

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

Magenta or designee will review the data entered into the eCRFs by investigational staff for completeness and accuracy and will instruct the site personnel to make any required corrections or additions. Queries will be sent to the investigational site using an electronic data query. Designated investigational site staff will be required to respond to each query and confirm or correct the data.

Concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using MedDRA terminology.

The occurrence of any protocol deviations will be determined.

After these actions have been completed and the database has been declared to be complete and accurate, it will be locked, and the treatment codes will be made available for data analysis.

13.4. Audits and Inspections

Authorized representatives of Magenta, a regulatory authority, an IEC, or an IRB may perform on-site or remote audits or inspections, including source data verification. The purpose of a Magenta audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP) guidelines of the International Council for Harmonisation (ICH), and any applicable regulatory requirements. The Investigator should contact Magenta immediately if contacted by a regulatory agency about an inspection.

13.5. Monitoring Committees

A DMC, comprising 3 physicians with medical expertise in stem cell transplantation for patients with SCD, will evaluate the safety, PK, and mobilization kinetics of MGTA-145 after each of the 2 patient cohorts completes Part A of the study, and in the event that a stopping rule has been met, to assess whether dosing may continue and whether dosing modifications are needed.

14. ETHICS

14.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved, or given a favorable opinion in writing by an IRB or IEC as appropriate.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Magenta will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

14.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements, and Magenta's policy on Bioethics.

14.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, and possible risks and benefits of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

Patients will be asked to sign an IRB/IEC-approved ICF prior to any study-specific assessments in this study. Patient consent/assent is required to give Magenta access to patient data; therefore, the patient must sign and date the ICF/assent before an assessment may be collected in the Magenta clinical database under this protocol.

15. DATA HANDLING AND RECORD KEEPING

15.1. Inspection of Records

Magenta will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

15.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Magenta or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

16. PUBLICATION POLICY

Magenta assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report, the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

17. LIST OF REFERENCES

1. Saraf SL, Molokie RE, Nouraie M, et. al. Differences in the clinical and genotypic presentation of sickle cell disease around the world. Paediatr Respir Rev 2014; 15(10): 4-12.
2. Hassell KL. Population estimates of sickle cell disease in the U.S. Am J Prev Med. 2010;38:S512-21.
3. Lorey FW, Arnopp J, Cunningham GC. Distribution of hemoglobinopathy variants by ethnicity in a multiethnic state. Genet Epidemiol 1996; 13: 501-12.
4. Lagresle-Peyrou C, Lefrere F, Magrin E, et al. Plerixafor enables safe, rapid, efficient mobilization of hematopoietic stem cells in sickle cell disease patients after exchange transfusion. Haematologica. 2018;103(5):778-86.
5. Krishnamurti L. Hematopoietic Cell Transplantation for Sickle Cell Disease. Front Pediatr 2021; 8(551170): 1-11.
6. Darbari DS, Brandow AM. Pain-measurement tools in sickle cell disease: where are we now? Hematology 2017; 534-41.
7. Kauf TL, Coates TD, Huazhi L, et al. The cose of health care for children and adults with sickle cell disease. Am J Hematol. 2009;84(6):323-7.
8. Lee S, Vania DK, Bhor M, et al. Patient-Reported Outcomes and Economic Burden of Adults with Sickle Cell Disease in the United States: A Systematic Review. Int J Gen Med. 2020;13:361-77.
9. Quinn CT. Clinical severity in sickle cell disease: the challenges of definition and prognostication. Experimental biology and medicine 2016; 241: 679-88.
10. Johnson FL, Look AT, Gockerman J, et al. Bone -marrow transplantation in a patient with sickle-cell anemia. N Engl J Med 1984; 311: 780-3.
11. Rotz SJ, O'Riordan MA, Kim C, et al. Traffic Light: prognosis-based eligibility for clinical trials of hematopoietic SCT in adults with sickle cell anemia. Bone Marrow Transplantation. 2015; 50: 918-23.
12. Shenoy S. Hematopoietic stem-cell transplantation for sickle cell disease: current evidence and opinions. Ther Adv Hematol. 2013;4(5):335-44.
13. Krishnamurti L. Hematopoietic Cell Trasplantation for Sickle Cell Disease. Front Pediatr. 2021;8(551170:1-11
14. Weber L, Poletti V, Magrin E, et al. An Optimized Lentiviral Vector Efficiently Corrects the Human Sickle Cell Disease Phenotype. Molecule Therapy: Methods & Clinical Developpment 2018; 10:268-80.
15. Prescribing information for Neuopogen (filgrastim) injection. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/103353s5184lbl.pdf
16. Fitzhugh CD, Hseih MM, Bolan CD, et cl. Granulocyte colony-stimulating factor (G-CSF) administration in individuals with sickle cell disease: time for a moratorium? Cytotherapy. 2009;11(4):464-71.

17. Prescribing information for Mozobil (Plerixafor). https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022311s001lbl.pdf
18. Esrick EB, Manis JP, Daley H, et. al. Successful hematopoietic stem cell mobilization and apheresis collection using plerixafor alone in sickle cell patients. Blood Adv. 2018 Oct 9;2(19):2505-2512.
19. Boulad F, Shore T, vanBesien, et. al. Safety and efficacy of plerixafor dose escalation for the mobilization of CD34+ hematopoietic progenitor cells in patients with sickle cell disease: interim results. Haematologica. 2018;103(5):770-7.
20. Uchida N, Leonard A, Stroncek D, et. al. Safe and efficient peripheral blood stem cell collection in patients with sickle cell disease using plerixafor. Haematologica. 2020; 105:e497-501.
21. Hseih MM, Tisdale JF. Hematopoietic stem cell mobilization with plerixafor in sickle cell disease. Haematologica. 2018;103(5):749-50.
22. Tisdale JF, Pierciey FJ, Bonner M, et. al. Safety and feasibility of hematopoietic progenitor stem cell collection by mobilization with plerixafor followed by apheresis vs. bone marrow harvest in patients with sickle cell disease in the multi-center HGB-206 trial. Am J Hematol. 2020;95(9): E239-42.
23. Sidana S, Bankova A, Hosoya H, et al. Phase 2 study of MGTA-145 + plerixafor for rapid and reliable hematopoietic stem cell (HSC) mobilization for autologous transplant in multiple myeloma. J Clin Oncol. 2021;39(15S): Abstract 8023.

18. APPENDICES

18.1. CKD-EPI Equation

The CKD-EPI equation, expressed as a single equation, is:

GFR = 141 × min(Scr/κ, 1)α × max(Scr/κ, 1)-1.209 × 0.993Age × 1.018 [if female] _ 1.159 [if black]

Where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κor 1, and max indicates the maximum of Scr/κ or 1.

18.2. Patient Surveys

18.2.1. Adult Sickle Cell Quality of Life Measurement Information®; v2.0

18.2.1.1. Emotional Impact Domain

ASCQ-Me Emotional Impact Survey Instructions: Answer all the questions by checking the box to the left of your answer.

1. In the past 7 days, how often did you feel completely hopeless because of your health?
   □ Never
   □ Rarely
   □ Sometimes
   □ Often
   □ Always
2. In the past 7 days, how lonely did you feel because of your health problems?
   □ Not at all
   □ A little
   □ Somewhat
   □ Quite
   □ Very
3. In the past 7 days, how depressed were you about your health problems?
   □ Not at all
   □ A little
   □ Somewhat
   □ Quite
   □ Very
4. In the past 7 days, how much did you worry about getting sick?
   □ Not at all
   □ A little bit

□ Somewhat
□ Quite a bit
□ Very much

5. In the past 7 days, how often were you very worried about needing to go to the hospital?
□ Never
□ Rarely
□ Sometimes
□ Often
□ Always

18.2.1.2. Pain Impact Domain

ASCQ-Me Pain Impact Survey Instructions: Answer all the questions by checking the box to the left of your answer.

1. **In the past 7 days, how often did you have pain so bad that you could not do anything for a whole day?**
□ Never
□ Rarely
□ Sometimes
□ Often
□ Always
2. **In the past 7 days, how often did you have pain so bad that you could not get out of bed**?
□ Never
□ Rarely
□ Sometimes
□ Often
□ Always
3. **In the past 7 days, how often did you have very severe pain?**
□ Never
□ Rarely
□ Sometimes
□ Often
□ Always
4. **In the past 7 days, how often did you have pain so bad that you had to stop what you** were doing?
□ Never
□ Rarely
□ Sometimes

□ Often
□ Always

5. **In the past 7 days, how often did you have pain so bad that it was hard to finish what you were doing?**
□ Never
□ Rarely
□ Sometimes
□ Often
□ Always

18.2.1.3. Sleep Impact Domain

ASCQ-Me Sleep Impact Survey Instructions: Answer all the questions by checking the box to the left of your answer.

1. **In the past 7 days, how often did you stay up most of the night because you could not fall asleep?**
□ Never
□ Rarely
□ Sometimes
□ Often
□ Always
2. **In the past 7 days, how often was it very easy for you to fall asleep?**
□ Never
□ Rarely
□ Sometimes
□ Often
□ Always
3. **In the past 7 days, how often did you have a lot of trouble falling asleep?**
□ Never
□ Rarely
□ Sometimes
□ Often
□ Always
4. **In the past 7 days, how often did you stay up all night because you could not fall asleep?**
□ Never
□ Rarely
□ Sometimes
□ Often
□ Always

5. **In the past 7 days, how often did you stay up half of the night because you could not fall asleep?**
   □ Never
   □ Rarely
   □ Sometimes
   □ Often
   □ Always

18.2.1.4. Social Functioning Domain

ASCQ-Me Social Functioning Impact Survey Instructions: Answer all the questions by checking the box to the left of your answer.

1. **In the past 30 days, how much did you rely on others to take care of you because of your health?**
   □ Not at all
   □ A little bit
   □ Somewhat
   □ Quite a bit
   □ Very much
2. **In the past 30 days, how often did your health slow you down?**
   □ Never
   □ Rarely
   □ Sometimes
   □ Often
   □ Always
3. **In the past 30 days, how often did your health make it hard for you to do things?**
   □ Never
   □ Rarely
   □ Sometimes
   □ Often
   □ Always
4. **In the past 30 days, how often did your health keep you from going out?**
   □ Never
   □ Rarely
   □ Sometimes

□ Often

□ Always

5. **In the past 30 days, how much did your health make it hard for you to do things with your friends?**

□ Not at all

□ A little bit

□ Somewhat

□ Quite a bit

□ Very much

18.2.1.5. Stiffness Impact Domain

ASCQ-Me Stiffness Impact Survey Instructions: Answer all the questions by checking the box to the left of your answer.

1. **In the past 7 days, how often were your joints very stiff when you woke up?**

□ Never

□ Rarely

□ Sometimes

□ Often

□ Always

2. **In the past 7 days, how often were your joints very stiff during the day?**

□ Never

□ Rarely

□ Sometimes

□ Often

□ Always

3. **In the past 7 days, how often were your joints so stiff during the day that you could not move?**

□ Never

□ Rarely

□ Sometimes

□ Often

□ Always

4. **In the past 7 days, how often did you wake up so stiff that you could not move?**

□ Never

□ Rarely

□ Sometimes

□ Often

□ Always

5. **In the past 7 days, how often did it take you a very long time to get out of bed because of stiffness?**

□ Never

□ Rarely

□ Sometimes

□ Often

□ Always

18.2.2. PROMIS®-57 Profile v2.1 (Pain Interference and Pain Intensity Domains)

Pain Interference

In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
How much did pain interfere with your day to day activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How much did pain interfere with your ability to participate in social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How much did pain interfere with your household chores?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How much did pain interfere with the things you usually do for fun?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How much did pain interfere with your enjoyment of social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How much did pain interfere with your enjoyment of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
How much did pain interfere with your family life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Pain Intensity

In the past 7 days…

How would you rate your pain on average?	☐ 0 **No pain**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 **Worst pain imaginable**