Protocol 145-ADS-202

A Phase II Study Evaluating the Safety and Efficacy of MGTA-145 in Combination with Plerixafor for the Mobilization and Transplantation of HLA-Matched Donor Hematopoietic Stem Cells in Recipients with Hematological Malignancies

Resource for Clinical Investigation in Blood and Marrow Transplantation and Magenta Therapeutics, Inc.

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Sponsored by Magenta Therapeutics and the National Marrow Donor Program® (NMDP)

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SPONSOR SIGNATURE PAGE

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

Magenta Therapeutics

_____
John C. Davis Jr., MD, MPH, MS
Chief Medical Officer

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INVESTIGATOR'S AGREEMENT

The signature below constitutes the approval of this protocol and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

_____
Printed Name of Investigator

_____
Signature of Investigator

_____
Date

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the National Marrow Donor Program (NMDP) Institutional Review Board (IRB) for review and approval for sites relying on the NMDP IRB as their IRB of record. Documentation of local IRB submissions will be collected for those sites relying on local IRBs. IRB approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol and consent will require review and approval by the IRB before the changes are implemented to the study with a determination for re-consent for previously enrolled subjects.

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title (Full)	A Phase II Study Evaluating the Safety and Efficacy of MGTA-145 in Combination with Plerixafor for the Mobilization and Transplantation of HLA-Matched Donor Hematopoietic Stem Cells in Recipients with Hematological Malignancies
Protocol Title (Short)	MGTA-145 in Combination with Plerixafor for the Mobilization and Transplantation of HLA-Matched Donor Hematopoietic Stem Cells in Recipients with Hematological Malignancies
Study Objective(s)	**Primary Hypothesis:** Human leukocyte antigen (HLA) matched donors receiving injections of plerixafor at 240 µg/kg combined with MGTA-145 0.015 mg/kg will safely mobilize sufficient CD34+ cells (at least 2.0 x 10^6 CD34+ cells/kg actual recipient weight) following one day of leukapheresis to support hematopoietic stem cell transplantation (HSCT). The hematopoietic cells mobilized by MGTA-145 + plerixafor will be functional and will result in prompt and durable hematopoietic recovery following transplantation into HLA-matched siblings and matched unrelated recipients with hematological malignancies. **Primary Objectives:** To determine the proportion of donors whose cells can be successfully mobilized and collected with a sufficient CD34+ cell dose using same-day, single-dose MGTA-145 + plerixafor as the mobilizing agents. Donor mobilization following MGTA-145 + plerixafor will be considered successful if ≥ 2.0 x 10^6 CD34+ cells/kg actual recipient weight are collected in one leukapheresis collection. All donors receiving MGTA-145 + plerixafor will be included in the analysis of the primary objective. **Secondary Objectives:** *Donor related* 1. To determine the proportion of donors whose cells can be successfully mobilized and collected with a target CD34+ cell dose of at least 4.0 x 10^6 $CD34^+$ cells/kg actual recipient weight in one apheresis collection 2. To ascertain the incidence and severity of acute adverse events (AEs) before and during apheresis experienced by donors receiving MGTA-145 + plerixafor 3. To characterize the adverse effects experienced by donors receiving MGTA-145 + plerixafor

	Recipient Related 1. To determine the incidence of and kinetics of neutrophil and platelet recovery after transplantation of hematopoietic cells mobilized with MGTA-145 + plerixafor 2. To determine the incidence of primary and secondary graft failure after transplantation of hematopoietic cells mobilized with MGTA-145 + plerixafor 3. To determine the incidence and severity of acute and chronic graft versus host disease (GVHD) after transplantation of hematopoietic cells mobilized with MGTA-145 + plerixafor 4. To determine the incidence of treatment-related mortality and disease relapse/progression after transplantation of hematopoietic cells mobilized with MGTA-145 + plerixafor 5. To determine the probability of progression-free and overall survival after transplantation of hematopoietic cells mobilized with MGTA-145 + plerixafor 6. To characterize the adverse effects experienced by recipients receiving grafts mobilized by MGTA-145 + plerixafor
Study Population	The donor population for the study includes those subjects undergoing peripheral blood mobilization and collection of grafts for allogeneic HSCT. The recipient population for the study includes those subjects with acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL) or myelodysplastic syndrome (MDS) receiving a hematopoietic stem cell transplant using the product obtained from a donor who underwent mobilization using MGTA-145 in combination with plerixafor.
Study Design/Phase	This is a Phase II, open-label, multicenter, prospective study of MGTA-145 + plerixafor mobilized HLA-matched sibling and matched unrelated donor allografts for myeloablative HSCT in recipients with hematological malignancies. Donors will undergo 1 or 2 days of mobilization and apheresis. The target collection is at least 4.0×10^6 CD34+ cells/kg actual recipient weight. Donors who achieve this target in one day will not undergo a second day of mobilization and apheresis. Donors who collect $< 4.0 \times 10^6$ CD34+ cells/kg actual recipient weight will undergo a second day of mobilization and apheresis. AEs will be reported using event terms and grading for severity per the Common Terminology Criteria for Adverse Events (CTCAE) version 5. Donors will be contacted at Week 1, Month 1, and Month 6 to assess the donor's medical condition. Donors will have blood work at Month 1. The design utilizes established Center for International Blood and Marrow Transplant Research (CIBMTR) transplant recipient follow up procedures to capture transplant outcome data. NMDP will implement the study within its clinical investigation group and with Resource for Clinical Investigation in

	Blood and Marrow Transplantation (RCI BMT) Data Safety Monitoring Board (DSMB) oversight.
Treatment Description	*Donor:* Eligible donors will receive subcutaneous plerixafor at 240 µg/kg actual donor weight followed by MGTA-145 infusion approximately 2 hours later and commence apheresis as soon as feasible thereafter. Some donors will require a second dose of MGTA-145 + plerixafor and apheresis the day after the first collection to reach the target CD34+ cell collection goal. The target CD34+ cell dose is ≥ 4.0 x 10^6/kg actual recipient weight with a minimum of ≥ 2.0 x 10^6/kg actual recipient weight. *Recipient:* Eligible recipients will undergo conditioning using a myeloablative regimen after an adequate allograft has been collected from the donor. Allograft will be cryopreserved and stored until transplant Day 0. GVHD prophylaxis may include post-transplant cyclophosphamide or a calcineurin phosphatase inhibitor in combination with methotrexate, mycophenolate mofetil, or sirolimus in accordance with local institutional guidelines. Recipients will receive G-CSF 5 µg/kg/day starting day +7 until absolute neutrophil count (ANC) > 1.5 x 10^9/L for two consecutive days.
Planned Number of Subjects	Approximately 28 donors. With a 5% drop out prior to transplant, it is anticipated that this will lead to 28 donors evaluable for mobilization endpoints and 26-27 recipients available for transplant follow up. The study employs a two-stage Simon minimax design in which 13 donors are enrolled in stage 1 and 15 donors are enrolled in stage 2.
Planned Number of Sites	Up to 10
Method of Assigning Patients to Treatment	Single arm, non-randomized
Follow-up Schedule	Donors will be followed from Day 1 (Baseline, MGTA-145 infusion) through 6-months post-mobilization. Donors will also complete survey assessments from prior to mobilization through 1-month post-mobilization. Recipients will be followed from Day 0 (Day of Transplant) through 1-year post-transplant. Recipients will be asked to co-enroll on the CIBMTR Outcomes Database Protocol. This study will require CRF-track data collection for those subjects that consent to CIBMTR Outcomes research.
Study Duration	2.5 years (1.5 years enrollment + up to 1-year follow-up)

Participation Duration	6 months for donors 1 year for recipients
Key Inclusion Criteria	Donor Inclusion Criteria: 1. Donor medical suitability and eligibility will be determined following Institution or NMDP/Be The Match standards 2. Age 18-65 years old at the time of signing informed consent 3. 8/8 (HLA- A, B, C, and DRB1) HLA-matched sibling or volunteer unrelated donor 4. Fulfill Institution or NMDP/Be The Match criteria to serve as a mobilized blood cell donor 5. Serum creatinine < 1.5 x institution upper limit of normal (ULN) or estimated creatinine clearance (CRCL) > 50 mL/min using the Modification of Diet in Renal Disease Study (MDRD) equation or similar method
	Recipient Inclusion Criteria: 1. At least 18 years old at the time of signing informed consent 2. Has an available 8/8 (HLA- A, B, C, and DRB1) HLA-matched sibling or volunteer unrelated donor willing to donate peripheral blood stem cells (PBSC) for transplant 3. Fulfill additional individual Transplant Center Criteria for transplant beyond NMDP/Be The Match criteria 4. One of the following diagnoses: • Acute myelogenous leukemia (AML) in 1st remission or beyond with ≤ 5% marrow blasts and no circulating blasts. Documentation of bone marrow assessment will be accepted within 45 days prior to the date of consent. • Acute lymphoblastic leukemia (ALL) in 1st remission or beyond with ≤ 5% marrow blasts and no circulating blasts. Documentation of bone marrow assessment will be accepted within 45 days prior to the date of consent. • Patients with myelodysplasia (MDS) with no circulating blasts and with less than 10% blasts in the bone marrow (higher blast percentage allowed in MDS due to lack of differences in outcomes with < 5% or 5-10% blasts in MDS). Documentation of bone marrow assessment will be accepted within 45 days prior to the date of consent. 5. Cardiac function: Left ventricular ejection fraction at least 45% based on most recent echocardiogram or MUGA results obtained via standard of care 6. Estimated creatinine clearance acceptable per local institutional guidelines

	7. Pulmonary function: diffusing capacity of the lungs for carbon monoxide (DLCO) corrected for hemoglobin at least 50% and forced expiratory volume in first second (FEV1) predicted at least 50% based on most recent DLCO results obtained via standard of care 8. Liver function acceptable per local institutional guidelines 9. Karnofsky performance status (KPS) of 70% or greater 10. Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) score of 4 or less
Key Exclusion Criteria	<u>Donor Exclusion Criteria:</u> 1. Donor unwilling or unable to give informed consent, or unable to comply with the protocol including required follow-up and testing 2. Donor already enrolled on another investigational agent study 3. Pregnant or breastfeeding females, sexually active female and male donors not willing or able to use adequate contraception, or males who do not agree to refrain from donating sperm, from the time of consent through 3 months after treatment with MGTA-145 + plerixafor
	<u>Recipient Exclusion Criteria:</u> 1. Subject unwilling or unable to give informed consent, or unable to comply with the protocol including required follow-up and testing 2. Subject whose donor does not meet the eligibility criteria and is a screen fail 3. Subjects with a prior allogeneic transplant 4. Subjects with active, uncontrolled infection at the time of the transplant preparative regimen 5. Pregnant or breastfeeding females, sexually active female or male subjects not willing or able to use adequate contraception, or males who do not agree to refrain from donating sperm, from the time of consent through 3 months after PBSC infusion 6. Subjects with clinical evidence of active Central Nervous System (CNS) tumor involvement as evidenced by documented disease on examination of spinal fluid or MRI within 45 days of start of conditioning 7. A condition, which, in the opinion of the clinical investigator, would interfere with the evaluation of primary and secondary endpoints 8. Planned treatment with a new investigational agent from the time of transplant through 30 days post-transplant

Statistical Methods	
Primary Statistical Analysis Plan	The primary endpoint of this study is the collection of a clinically adequate allograft in one apheresis session. A donor is considered successful for this endpoint if ≥ 2.0 x 10^6 CD34+ cells/kg actual recipient weight are collected in one leukapheresis collection using MGTA-145 + plerixafor. The proportion of donors who mobilize ≥ 2.0 x 10^6 CD34+ cells/kg actual recipient weight in one leukapheresis collection will be estimated along with a 90% confidence interval for consistency with the one-sided type I error rate of 5%. A 95% confidence interval will also be provided. The primary analysis will use the Donor Treated Population, where donors who do not undergo apheresis will be considered a failure for this endpoint.
Sample Size Justification	The sample size for this study is 28 donors receiving at least one dose of the combination regimen of MGTA-145 + plerixafor. It is expected that 90% of donors treated with MGTA-145 + plerixafor will mobilize ≥ 2.0 x 10^6 CD34+ cells/kg within one leukapheresis collection. MGTA-145 + plerixafor is considered an unacceptable mobilizing agent if fewer than 70% of donors achieve this cell-dose threshold within one leukapheresis collection. Using a two-stage Simon minimax design, assuming the true successful collection probability of 90%, 28 donors provide 85% power to reject the probability of successful collection of 70% or lower using a one-sided Type I error α=0.05. This is equivalent to testing the null hypothesis H0: $p \leq 0.70$ against the alternative hypothesis H1: $p > 0.70$ with 85% power to contrast a successful collection probability of 90% vs. 70%.

1.2 Schedule of Activities (SOA)

1.2.1 Assessments of Donors

Study Visit	Screening[1]	Day 1 (Baseline)[2]	Day 1 (Plerixafor Dosing)[2]	Day 1 (MGTA-145 Dosing)[2]	Post-LA, Day 1	Day 3-4[3]	Week 1[4]	Month 1[4]	Month 6[4] End of Study
Study Day	**-30 - 1**	**1**	**1**	**1**	**1**	**3-4**	**7 (±2 days)**	**28 (±7 days)**	**180 (±14 days)**
Informed Consent	X								
Medical History and Medications	X	X							
Physical Exam, Height and Weight	X[5]	X[6]							
Vital Signs[7]	X		X[8]	X[9]	X				
KPS	X								
ECG	X								
CBC with differential and platelet count	X	X[6]			X			X	
Serum Creatinine & PT/PTT	X								
Serum Pregnancy Test[10]	X	X[10]							
Urinalysis	X								
Infectious disease markers[11]	X								
ABO/Rh Typing	X								
Chimerism	X								
Donor Survey Assessments[12]		X[12]			X	X		X	
ADA Sample		X[6]						X	
Flow cytometric analysis for CD34+ cells		X[6]		X[13]	X[14]				
Plerixafor Dosing			X[15]						
PK				X[16]					
MGTA-145 Infusion				X[17]					
Leukapheresis (LA)				X[18]					
Colony Forming Unit					X[14]				
Graft Immunophenotyping					X[14]				
Medical assessment (Virtual visit)							X	X	X
AEs/SAEs[19]	X								

[1] Screening occurs up to 30 days prior to the start of stem cell mobilization; screening and determination of eligibility of unrelated donors is managed by Be The Match Donor Services.
[2] If donor undergoes a second day of mobilization and apheresis, all Day 1 assessments must be repeated and donors will follow the same schedule (i.e., Day 7 will remain Day 7)
[3] Donor survey visit only. CIBMTR SRG will contact donors.
[4] Study site staff will contact donors at Week 1, Month 1, and Month 6 for virtual visits to assess donor medical condition. Donors will have blood work at Month 1.
[5] Height only required at Screening
[6] To be obtained prior to dosing
[7] Vital signs include blood pressure, pulse, respiration rate and temperature
[8] Vital signs and AEs monitored prior to plerixafor dosing; and 30 minutes (±10 minutes) and 60 minutes (±10 minutes)) following injection; and per local institutional guidelines
[9] Vital signs and AEs monitored prior to MGTA-145 dosing; during infusion; and 30 minutes (±10 minutes), 60 minutes (±10 minutes, 120 minutes (±20 minutes), and 240 minutes (±20 minutes) following start of infusion
[10] For females of childbearing potential. Day 1 test can be performed up to 48 hours prior to dosing
[11] Infectious disease markers collected as required by FDA
[12] CIBMTR SRG will contact donors to complete survey assessments. Baseline donor survey assessment to be administered up to 14 days prior to Day 1. See Table 9.7
[13] To be collected after MGTA-145 infusion but prior to apheresis
[14] Sample will come from the apheresis product
[15] Plerixafor will be administered subcutaneously at 240 µg/kg/actual donor weight approximately 2 hours prior to planned leukapheresis
[16] PK samples to be collected prior to MGTA-145 infusion (within 60 minutes of the start of the infusion) and 15-30 minutes after start of infusion
[17] MGTA-145 administered at dose of 0.015 mg/kg via IV infusion over 3 minutes approximately 2 hours after plerixafor; the infusion time may range from 1 to 10 minutes if clinically indicated
[18] As soon as feasible after MGTA-145 infusion (approximately 30 minutes post infusion), begin apheresis to process at least 4 times blood volume, but no more than the institutional limit.
[19] SAEs to be reported from informed consent through 6 months post mobilization. AEs to be collected from informed consent through 72 hours post mobilization. See Table 9.8

1.2.2 Assessments for Recipients

Study Visit	Screening[1]	Day 0	Days 1-21[2]	Day 28 ± 3 days	Day 56 ± 7 days	Day 100 ± 7 days	Day 180 ± 14 days	Day 365 ± 14 days
Informed Consent	X							
Medical History and Medications[3]	X							
Physical Exam and Vital Signs[4]	X	X[5]	X	X	X	X	X	X
Height and Weight	X							
KPS	X						X	X
CBC with differential and platelet count	X	X[5]	X[6]	X[7]	X[8]	X[8]	X	X
Serum creatinine/AST/ALT/LDH/Total bilirubin	X	X[5]	X[9]	X	X	X	X	X
Serum Pregnancy Test	X[10]							
Urinalysis	X							
Infectious disease markers[11]	X[12]							
ABO/Rh Typing	X[12]							
Chimerism	X[12]			X		X	X	X
Disease specific staging and assessment	X							X
Assessment of HCT-CI score	X							
Bone marrow assessment	X[13]							X[14]
Allograft Infusion		X						
GVHD Assessment [15]			X	X	X	X	X	X
Immune Reconstitution				X		X	X	X
AEs/SAEs[16]		X						

[1] Screening occurs up to 45 days prior to the start of the conditioning regimen
[2] Visits to occur Day +1 through neutrophil recovery or Day +21 (whichever is first)
[3] Includes most recent echocardiogram or MUGA and DLCO results obtained via standard of care
[4] Vital signs include blood pressure, pulse, respiration rate, and temperature
[5] To be obtained prior to receiving allograft
[6] CBC with differential and platelet counts to be performed daily until neutrophil recovery occurs; in the event that neutrophil recovery occurs but not platelet recovery, a CBC should continue to be obtained daily until platelet count recovery or Day +21 (whichever is first)
[7] If platelet and/or neutrophil recovery has not occurred at this time, CBC to be performed 3 times per week until recovery
[8] If platelet and/or neutrophil recovery has not occurred at this time, CBC to be performed 2 times per week until recovery
[9] Blood chemistries performed 2 times per week
[10] For females of childbearing potential
[11] Infectious disease markers collected as required by FDA
[12] May be performed earlier than 45 days prior to the start of the conditioning regimen
[13] Documentation of bone marrow assessment will be accepted within 45 days prior to the date of consent
[14] Bone marrow aspirate and biopsy required if leukocyte count is outside of the normal laboratory range at the transplant center and/or platelet count is < 100 x 10^9/L
[15] Recipients will be assessed for or the development of acute GVHD weekly at Days 1-100 and for chronic GVHD at Days 100, 180, and 365 and more frequently as clinically indicated
[16] SAEs to be reported from Day 0 through 1-year post-transplant; Related AEs to be collected from Day 0 through 1-year post-transplant

2 INTRODUCTION

2.1 Study Rationale

Subjects with protocol-specified advanced hematological malignancies who are appropriate candidates for hematopoietic stem cell transplantation (HSCT) and who have an HLA-identical (8/8 HLA antigen matched) sibling donor or 8/8 matched unrelated donor will be eligible for this study. If the subject and donor are eligible and provide informed consent, the donors will be mobilized with plerixafor subcutaneously at a dose of 240 µg/kg actual donor weight, followed approximately 2 hours later by an intravenous infusion of 0.015 mg/kg MGTA-145. The donors will undergo leukapheresis commencing as soon as feasible after MGTA-145 dosing. At the end of the leukapheresis, the collected graft will be analyzed by standard flow cytometry for CD34+ cell content. If the graft contains ≥ 4.0 x 10^6 CD34+ cells/kg actual recipient weight after the first leukapheresis collection, the mobilization will be considered clinically successful and complete. If the graft contains < 4.0 x 10^6 CD34+ cells/kg actual recipient weight after the first leukapheresis collection, the donor will undergo a second day of plerixafor and MGTA-145 infusion mobilization and apheresis.

If the sum of the grafts collected after two days is ≥ 2.0 x 10^6/kg of actual recipient weight, the mobilization will have achieved the minimum dose and will be considered completed and clinically successful. Allografts will be cryopreserved prior to infusion. If the donor fails to mobilize a graft containing at least 2.0 x 10^6/kg CD34+ cells/kg of actual recipient weight after two leukapheresis procedures, mobilization will be considered unsuccessful. The center will be allowed to use that graft (regardless of the total CD34+ cell dose) at their discretion, and the recipient will be followed. Alternatively, the treating center may choose to remobilize the donor with granulocyte colony stimulating factor (G-CSF) or collect bone marrow for transplantation as a supplement or replacement for the MGTA-145 + plerixafor mobilized graft.

For recipients for whom $\underline{\geq}$ 2.0 x 10^6 CD34+ cells/kg were collected from the donor following MGTA-145 + plerixafor, the collected allograft will be used as the primary allograft for transplantation. Recipients will be followed until one-year post-transplant and donors will be followed until six-months post-mobilization for important secondary endpoints.

2.2 Background

2.2.1 Defining the optimal allograft source: bone marrow versus peripheral blood

G-CSF-based mobilization is a relatively safe and effective alternative to bone marrow harvesting for collection of hematopoietic stem cells (HSC) prior to allografting.[1-3] Several randomized trials performed in recipients of HLA-matched sibling allografts have been reported comparing G-CSF mobilized peripheral blood (MPB) to bone marrow (BM).[4-9] These trials demonstrate that G-CSF MPB is associated with more rapid hematopoietic recovery, similar rates of acute graft versus host disease (GVHD), and higher rates of chronic GVHD compared to BM.[10,11] Early regimen-related mortality appears to be lower with MPB, particularly in recipients with advanced hematological malignancies. Overall survival appears to be improved in recipients with advanced stage disease transplanted using MPB versus BM. Thus, in virtually all US transplant centers, G-CSF MPB has largely supplanted harvested BM in recipients receiving HLA-identical sibling transplantation. Similarly, the majority of volunteer unrelated donor allografts collected for adults with hematological malignancies are from MPB in preference to BM. A randomized trial of MPB vs. BM showed similar 2-year survival between groups with a higher chronic GVHD incidence with MPB grafts (53% vs 41%) but lower graft failure with MPB (3% vs 9%).[12]

Despite the increasing utilization of MPB, the dose of CD34+ cells required to optimize transplant outcomes is presently unknown. While it appears that grafts containing CD34+ cell doses > 2.0 x 10^6/kg recipient weight promote prompt and durable recovery, some studies suggest that CD34+ cell doses > 8.0 x 10^6/kg may result in a higher risk of both acute and chronic GVHD.[13,14] The mechanisms underlying this relationship are uncertain, and not all studies are in agreement.[8,15,16] Nevertheless, the optimal

cellular composition of a G-CSF MPB allograft necessary to promote reliable recovery without increasing the risk of GVHD or other complications remains to be determined.

2.2.2 Experience of Donors Mobilized with G-CSF

In addition to improving hematopoietic recovery, it was theorized that G-CSF based stem cell mobilization would reduce the morbidity associated with donor stem cell harvesting, primarily by replacing a painful surgical procedure with a simple outpatient apheresis. Early reports suggested G-CSF based mobilization was relatively safe and well tolerated by the majority of donors.[1-3,17] More recent data suggest that while virtually all donors complete the stem cell mobilization and collection procedure, many G-CSF mobilized donors experience significant albeit transient morbidity following G-CSF stimulation.[18-21] In a retrospective study performed using data from the International Bone Marrow Transplant Registry (IBMTR) and European Bone Marrow Transplant (EBMT) Group, 1321 donors undergoing Peripheral Blood (PB) mobilization and leukapheresis (LA) were analyzed.[19] In order to achieve a target CD34+ cell dose set by the transplant programs, over 60% of donors required more than one LA procedure, and 15% greater than two. Surprisingly, approximately 20% of donors required placement of central venous catheter (CVC). The overall rate of serious complications associated with G-CSF MPB donation was 1.1%, higher in comparison to the 0.5% rate observed following bone marrow donation. Two recent prospective studies performed concurrently with the randomized trials found similar overall rates of complications comparing BM to G-CSF MPB donation.[20,21] Pain, fatigue, and anxiety were the most frequently reported adverse events (AEs). Rowley et al. noted that pain experienced by G-CSF stimulated donors worsened with each day of treatment and peaked at the time of Leukapheresis (LA).[20] In contrast to the crescendo nature of the pain experienced by the G-CSF mobilized donors, pain and discomfort experienced by BM donors was clearly related to anesthesia and multiple needle punctures on the day of donation. The symptom burden reported with both methods of stem cell procurement was similar, with pain a prominent symptom in both groups. Equivalent mean levels of maximal pain, average pain, and pain duration throughout the day were observed in both groups. These findings were essentially corroborated by a similar study performed as part of a French randomized trial.[21] Pulsipher performed a similar analysis of volunteer unrelated donors receiving five to six days of G-CSF for stem cell mobilization and found that 57% of donors experience moderate (48%) or severe (9%) bone pain and overall 38% experience grade 2 or 3 toxicity.[22] Unfortunately, there are few data available regarding the impact of inconvenience, loss of work days, and economic cost incurred during the 4-6 day process of G-CSF based mobilization.

In summary, G-CSF MPB donation is relatively safe but is associated with significant morbidity, similar in overall intensity in comparison to BM donation but with a different distribution of peak intensity. The leukapheresis procedure itself has not been associated with significant morbidity in most studies unless a CVC is required. Morbidity increases with each day of G-CSF administration. While the available data suggest that G-CSF MPB donation is associated with lower risk of serious adverse events (SAEs) relative to BM, it remains associated with significant morbidity and inconvenience. Accordingly, a less toxic, more rapid, yet efficient method for the collection of MPB from related and volunteer donors is desirable and would represent a clear advance.

2.2.3 Mechanism of G-CSF Induced Stem Cell Mobilization: Critical Role of CXCR4 and SDF-1 Interaction

Many groups have had a longstanding interest in elucidating the mechanistic basis for G-CSF induced HSC mobilization. Most studies suggest that G-CSF induces HSC mobilization indirectly through its effects on proteases elaborated by marrow neutrophils, resulting in cleavage of adhesive interactions (e.g., VLA-4/VCAM-1) and remodeling of matrix proteins within the bone marrow microenvironment.[23-26] Recent data suggest the interaction between the CXC chemokine receptor CXCR4 and its ligand stromal derived factor-1 (SDF-1) plays a key role in stem cell mobilization.[23-26] CXCR4 is a member of the large family of seven transmembrane domain receptors coupled to heterotrimeric G1 proteins. Binding with its only known ligand SDF-1 (also known as CXCL12) results in activation of multiple signal transduction pathways ultimately triggering chemotaxis. Targeted disruption of either molecule is lethal in mice,

resulting in failure of HSC migration from liver to bone marrow, defects in B- lymphopoiesis, and cerebellar dysgenesis.[27-29] Interactions between SDF-1 and CXCR4 critically regulate the homing and migration of human SCID repopulating cells from BM, umbilical cord blood (UCB), and G-CSF MPB transplanted into NOD/SCID recipients.[23,30] Efficient mobilization of murine stem and progenitor cells is observed following injection of adenovirus expressing SDF-1 or after injection of methionine-SDF-1, both resulting in a gradient of SDF-1 from BM to PB.[31]Treatment of mice and primates with sulfated polysaccharides (e.g. fucoidan) results in a rapid increase in circulating SDF-1 and subsequent stem cell mobilization.[32] Lapidot and colleagues have suggested a model wherein G-CSF stimulation induces proteases, notably neutrophil elastase and perhaps other matrix metalloproteinases, that markedly reduce local bone marrow levels of SDF-1, resulting in the egress of hematopoietic stem and progenitor cells from the BM into the PB.[26,33] Taken together, mounting evidence supports a primary role for the CXCR4/SDF-1 axis in both murine and human stem and progenitor cell mobilization and suggests this interaction provides a novel target to induce the migration of HSC and progenitors from BM into PB.

2.2.4 Plerixafor is a Potent and Selective Antagonist of the CXCR4/SDF1 Interaction

The bicyclam derivative plerixafor was first described for its potent and selective inhibition of human immunodeficiency virus (HIV) type 1 and 2 replication through binding to the chemokine receptor CXCR4, used by T- tropic HIV for entry into the cell.[34-39] Plerixafor also potently, specifically, and reversibly blocks the binding of CXCR4 with its only known natural ligand, SDF-1; it has no effect on other cell surface chemokine receptors.[34,40-42] Initial clinical trials of plerixafor evaluated its safety and efficacy in the treatment of patients with HIV-1 infection.[43] In these studies, transient increases in white blood cell counts were observed immediately following injection of plerixafor. Similar findings were also noted in healthy volunteers.[44] These observations prompted studies to evaluate the effects of plerixafor on mobilization of hematopoietic stem and progenitor cells.

2.2.5 Plerixafor Chemistry

Plerixafor is a bicyclam of the following chemical composition 1,1'-[1,4- phenylenebis(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane. Its structure is shown in Figure 1.

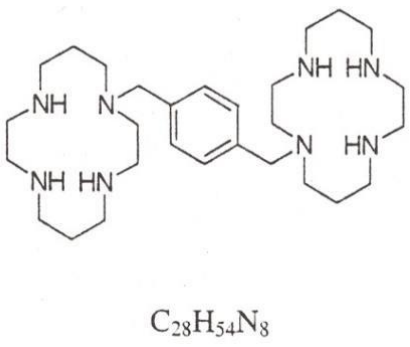


Figure 1. PLERIXAFOR chemical structure

2.2.6 MGTA-145 Background and Chemistry

Magenta Therapeutics is developing MGTA-145 as a potential alternative to G-CSF for the mobilization of CD34+ cells when used in combination with plerixafor. MGTA-145 (aka Gro-Beta Truncate or GroβT) is a CXCR2 agonist. 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, CD34+CD90+CD45RA cells, and hematopoietic progenitor cells. When GroβT (SB-251353; also known as Garnocestim manufactured by Glaxo SmithKline Beecham) was clinically tested in healthy volunteers as a monotherapy, a statistically significant increase in mobilization of HSCs was observed.[45] In addition, preclinical studies in mice, rats, and non-human primates demonstrated that MGTA-145 administered

with plerixafor leads to rapid and robust mobilization of CD34+, CD34+CD90+CD45RA- cells, and hematopoietic progenitor cells within minutes to hours.

Company or Laboratory Codes

MGTA-145, GROβT acetate salt, GROβT. Its structure is shown in Figure 2.

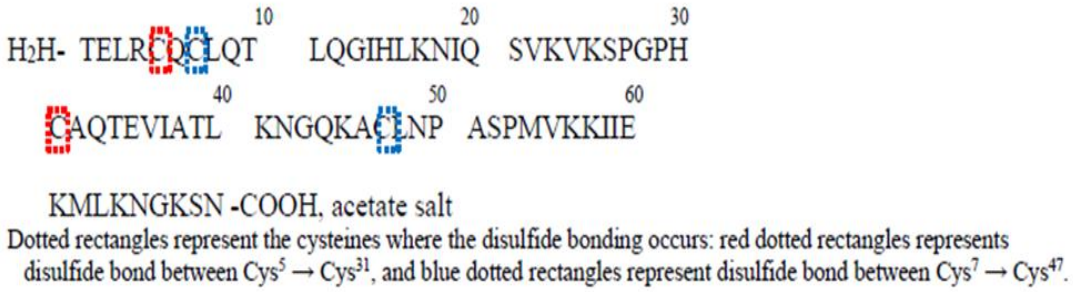


Figure 2: MGTA-145 Amino Acid Sequence

2.2.7 Pharmacokinetics of Plerixafor

The pharmacokinetic behavior of plerixafor following intravenous administration is characterized by elimination from the plasma in a bi-exponential manner with a terminal elimination half-life of approximately 3 hours following a single dose. Plerixafor absorption following subcutaneous administration is rapid and essentially complete, with peak plasma levels occurring within 0.5–1 hour of dosing. Plerixafor is extensively protein bound to both human serum albumin and 1-acid glycoprotein; however, protein binding does not appear to have a major influence on toxicity. Saturation of protein binding sites may occur at plasma plerixafor concentrations in excess of those likely to be achieved in any ongoing or planned clinical studies. Findings from animal studies performed using 14C-labelled-plerixafor suggest that the parent molecule is the major circulating form of the drug in plasma, with a number of potential metabolites noted in urine.

2.2.8 Pharmacokinetics of MGTA-145

The pharmacokinetics of MGTA-145 following administration in combination with plerixafor was evaluated in the Phase I 145-HV-101 study and are summarized in Figure 3. The C_{max} and Area Under the Curve (AUC) of MGTA-145 increased along with dose linearly in the dosing range of 0.0075 mg/kg – 0.3 mg/kg. The mean C_{max} of MGTA-145 ranged from 34.5 µg/L to 1469.3 µg/L, and the mean area under the concentration-time curve from time zero to time of last measurable concentration (AUC_{last}) of MGTA-145 ranged from 17.6 h*µg/L to 2290.7 h*µg/L. Co-administration of plerixafor did not change the pharmacokinetics (PK) of MGTA-145. Accumulation was not observed following the second of two daily doses of MGTA-145.

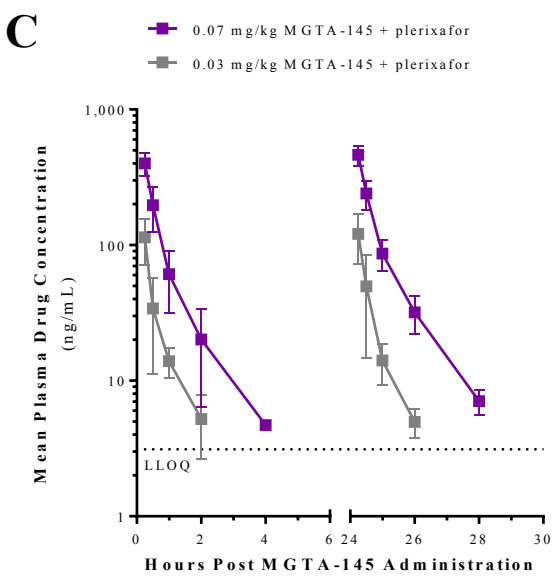


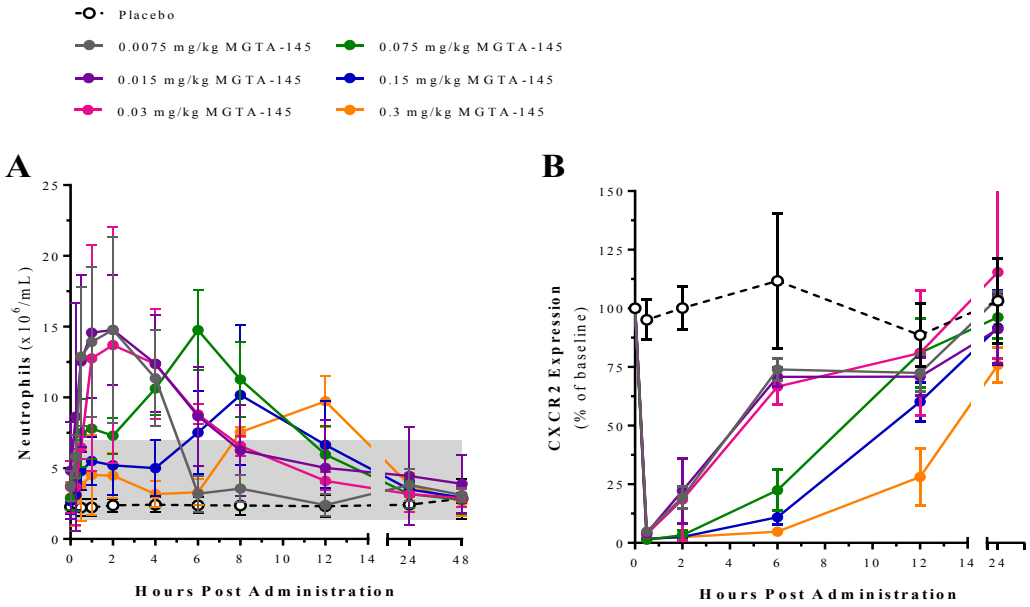
Figure 3. Pharmacokinetics of two daily doses of MGTA-145 administered in combination with plerixafor. All data expressed as mean ± standard deviation.

2.2.9 Pharmacodynamics of MGTA-145

MGTA-145 is a protein that is chemotactic for neutrophils, which express its cognate chemokine receptor, CXCR2. It was expected that administration of MGTA-145 as monotherapy would lead to mobilization of neutrophils with a corresponding increase in white blood cell (WBC) counts. Plerixafor is also known to mobilize WBCs including neutrophils, lymphocytes, monocytes, basophils and eosinophils. Based on this, it was anticipated that MGTA-145 in combination with plerixafor would result in a cumulative increase in the same cell types.

MGTA-145 monotherapy induced immediate and significant mobilization of neutrophils at the lowest dose tested, 0.0075 mg/kg (Figure 4A). Suppression of neutrophil mobilization was observed at MGTA-145 doses greater than 0.03 mg/kg. The mechanism of neutrophil suppression is thought in part to be due to saturation of plasma MGTA-145 levels with increasing doses, resulting in loss of the chemotactic gradient necessary for neutrophil mobilization. MGTA-145 induced rapid downregulation of CXCR2 expression on neutrophils at all dose levels tested demonstrating direct target interaction (Figure 4B). Re-expression of the receptor was dose-dependent with the higher doses of MGTA-145 resulting in a prolonged period of downregulation. Re-expression of the receptor at 0.075 – 0.3 mg/kg (along with continued pharmacokinetic exposure) correlates with the rebound of neutrophil mobilization observed at the higher doses of MGTA-145.

Figure 4. Effect of MGTA-145 Monotherapy on Neutrophil Mobilization and CXCR2 Expression



A. Neutrophil mobilization following a single dose of MGTA-145 monotherapy or placebo. The shaded region represents the normal reference range. **B.** Relative CXCR2 expression in peripheral blood neutrophils following a single dose of MGTA-145 monotherapy or placebo. All data expressed as mean ± standard deviation.

Administration of MGTA-145 two hours after plerixafor led to a median peak WBC count of 36,500 WBC/µL and 33,550 WBC/µL when MGTA-145 was dosed at 0.015 mg/kg or 0.03 mg/kg, respectively. By comparison, the median peak WBC count observed in subjects dosed with placebo + plerixafor in Part B was 23,400 WBC per microliter. This increase was transient, returned to normal range by 24 hours post dosing, and was significantly lower than the threshold for leukocytosis (≥ 100,000 WBC/µL) noted in the NEUPOGEN® (filgrastim, G-CSF) package insert as precautionary for a patient to undergo dose modification (NEUPOGEN Package Insert[46]). The increased WBC counts observed in subjects dosed with MGTA-145 + plerixafor compared to plerixafor alone were predominantly the result of increased neutrophil and monocyte mobilization, with a minimal increase in lymphocyte, basophil, and eosinophil counts. Similar to what was observed in response to MGTA-145 monotherapy, increasing MGTA-145 dose above 0.03 mg/kg suppressed neutrophil mobilization when administered in combination with plerixafor.

2.2.10 Clinical studies evaluating safety of plerixafor

A phase I study [PLERIXAFOR 98-01] established the initial safety and pharmacokinetic profiles for plerixafor.[44] Intravenous doses of 10 to 80 µg/kg and subcutaneous doses of 40 and 80 µg/kg were administered to healthy volunteers and were generally safe and well tolerated. Maximal increases in WBC (approximately three times baseline) were observed at the 40 and 80 µg/kg dose levels in both intravenous and subcutaneous populations.

2.2.10.1 Use of Plerixafor in patients with lymphoma and multiple myeloma

A phase II trial showed significant enhancement of HSC mobilization when plerixafor was combined with G-CSF in patients with non-Hodgkin lymphoma (NHL) and multiple myeloma.[47] Two phase III studies comparing Hematopoietic Stem and Progenitor Cells (HSPC) mobilization with G-CSF alone to G-CSF combined with plerixafor demonstrated a highly significant benefit for the combined arm.[48,49] Importantly, short-term administration of plerixafor has been shown to be well tolerated. Long-term follow up shows no concerns with graft durability or disease progression.[50] Plerixafor is U.S. Food and Drug Administration (FDA) approved for use in combination with G-CSF in patients with NHL and multiple myeloma undergoing stem/progenitor cell mobilization in anticipation of high dose chemotherapy and autologous transplantation.

2.2.10.2 Use of Plerixafor in related stem cell donors

Plerixafor is a safe and more rapid stem cell mobilizing agent for healthy volunteer sibling donors. A study performed at Washington University demonstrated the safety and efficacy of this concept in healthy sibling donors.[51] Twenty-five sibling donors were treated with plerixafor at a dose of 240 µg/kg by subcutaneous injection, followed 4 hours later by leukapheresis. Successful mobilization was defined as a minimum leukapheresis yield of > 2.0 x 10^6/kg CD34+ cell/kg actual recipient body weight. If the minimal yield was not achieved following first leukapheresis, the identical procedure of plerixafor administration and repeat leukapheresis was attempted on day 3. One donor receiving plerixafor never underwent leukapheresis because of vaso-vagal episodes associated with peripheral line placement. Of the remaining 24 donors, 16 (66%) mobilized at least the minimum required number of CD34+ cells after first leukapheresis. Seven out of the 8 donors who did not collect sufficient quantity of CD34+ cells underwent repeat plerixafor administration on day 3, with 6 such donors mobilizing the target CD34+ cell dose. Overall, of the 24 donors undergoing 1 or 2 days of leukapheresis following plerixafor, two did not achieve a minimum CD34+ dose of 2.0 x 10^6/kg, for a failure rate of 8.3%. None of the donors experienced any grade 3-4 toxicities. Common grade 1 toxicities were lightheadedness, nausea, bloating, flatulence, injection site discomfort, perioral paresthesias, loose stools, and headaches. A total of 20 patients received allografts mobilized by plerixafor. All recipients engrafted promptly, with median time to neutrophil and platelet recovery of 10 and 12 days, respectively. In this study plerixafor mobilized grafts contained significantly greater number of CD3+ cells, compared to G-CSF mobilized grafts. However, despite the increased CD3+ content of the allograft, the rate of grade II-IV acute GVHD in the recipients (42%) was not more than expected. Interestingly, the cumulative incidence of chronic GVHD at 18 months was about 30%, suggesting a possible lowering of the risk of chronic GVHD compared to G-CSF mobilized grafts. The group at Washington University then performed a larger dose finding study and determined that the 240 µg/kg dose of plerixafor and subcutaneous route of administration possessed the best combination of safety and efficacy in normal donors.[52]

In 2019, Chen et al reported a phase II study (n=64) of subcutaneous plerixafor to mobilize matched related donors for allogeneic transplant for hematologic malignancies.[53] The primary objective was to determine the proportion of donors who were successfully mobilized: defined as collection of ≥ 2.0 x 10^6 $CD34^+$ cells per kg recipient weight in up to 2 apheresis sessions. Recipients subsequently received reduced intensity (RIC; n=33) or myeloablative (MAC; n=30) conditioning. Sixty-three of 64 (98%) donors achieved the primary objective. The median $CD34^+$ cell dose per kilogram recipient weight collected within 2 days was 4.7 (0.9-9.6). Plerixafor was well tolerated with only grade 1 or 2 drug-related AEs noted. Bone pain was not observed. Plerixafor-mobilized grafts engrafted promptly. One-year progression-free and overall survivals were 53% (95% confidence interval [CI], 36-71%) and 63% (95% CI, 46-79%) for MAC and 64% (95% CI, 47-79%) and 70% (95% CI, 53-84%) for RIC recipients, respectively. Donor toxicity was reduced relative to G-CSF mobilized related donors. This study confirmed the feasibility of using single agent plerixafor for mobilization, but only 27% of donors achieved the target of 4 x 10^6 $CD34^+$ cells/kg in one apheresis session. Five percent of donors required 3

apheresis sessions. Although feasible, there is opportunity to improve on the mobilization efficacy of plerixafor mobilization.

2.2.11 Clinical studies evaluating safety of MGTA-145

Please see the Investigator's Brochure (IB) for comprehensive safety information.

Safety of MGTA-145 was evaluated in the phase I 145-HV-101 study in which 79 healthy volunteers were dosed with MGTA-145 out of 107 volunteers enrolled in the study in 4 parts: Part A: single dose MGTA-145 monotherapy or placebo; Part B: single dose MGTA-145 + plerixafor or placebo; Part C: 2 consecutive daily doses of MGTA-145 + plerixafor or placebo; Part D: single dose MGTA-145 + plerixafor followed by apheresis cell collection.

Treatment emergent adverse events (TEAEs) overall were generally mild, without an apparent trend across dose levels or study part. The most consistently observed adverse event associated with MGTA-145 infusion was Grade 1 bone pain, most often occurring in the back that begins during the 10-minute infusion and generally ends 10-15 minutes later. Specifically, 48 of 102 subjects overall experienced a TEAE of back pain. All AEs of back pain were considered to be mild (grade 1) in severity with the exception of one AE of back pain, reported as moderate (grade 2) in severity. In Part A of the study, grade 1 back pain was reported for 19 of the 24 subjects in the cohorts administered MGTA-145 alone; the event was not reported for any subject in the pooled placebo group. In Part B of the study, a total of 22 subjects in the MGTA-145 + plerixafor group and 2 subjects in the pooled placebo + plerixafor group experienced an AE of back pain. One subject who received MGTA-145 0.075 mg/kg + plerixafor 240 µg/kg, experienced grade 2 (moderate) back pain after initiation of the infusion. MGTA-145 was administered 2 hours following plerixafor. Treatment was interrupted after 5 minutes and the AE of back pain resolved shortly after stopping the infusion. Of note, grade 2 back pain was not seen with MGTA-145 doses of 0.07 and 0.15 mg/kg in combination with plerixafor or at monotherapy doses up to 0.3 mg/kg.

The known toxicities of plerixafor were observed and generally assessed as mild. Overall, MGTA-145, when given in combination with plerixafor, showed no increase in severity or frequency of adverse effects expected with plerixafor.

Safety was also evaluated in study 145-RI-102, an open-label, single-arm, single-dose study to evaluate the PK and safety and tolerability of MGTA-145 in subjects with normal estimated glomerular filtration rate (GFR) and varying degrees of renal impairment. MGTA-145 was administered at the 0.07 mg/kg dose level without plerixafor. The study (n=23) evaluated 6 subjects with normal renal function, 8 subjects with mildly decreased GFR, and 9 subjects with moderately decreased GFR. Eighteen subjects experienced a TEAE of back pain. Nine of 18 (50%) subjects experienced an AE of back pain which was moderate in severity. Although no subjects experienced an AE that led to early study discontinuation, study treatment was withdrawn in 4 subjects who experienced an AE of back pain during the 10-minute infusion. All study subjects recovered from the AE of back pain. The incidence of AEs of back pain was similar across groups regardless of the baseline GFR status.

2.2.12 Rationale for studying MGTA-145 + plerixafor mobilized allografts following myeloablative conditioning

Establishing proof of concept for successful engraftment is a key objective of the first allogeneic transplant study with MGTA-145 + plerixafor mobilized HSCs. Although the use of RIC has become a standard procedure in most transplant centers across the country, following engraftment and preliminary GVHD outcomes in a heterogeneous group of RIC and MAC transplants will increase variability of these outcomes for a relatively small proof of concept study. Proof of principle that a plerixafor-mobilized allograft can lead to prompt recovery in recipients receiving RIC has already been established in the Chen et al study.[54] The present study should permit us to generate sufficient safety and efficacy data of MGTA-145 + plerixafor mobilized allografts that may be generalizable to other allogeneic transplant

donors and provide a rationale for comparison to G-CSF based mobilization. At the present time, this study will not evaluate the use of MGTA-145 + plerixafor-mobilized allografts in recipients scheduled to receive non-myeloablative (NMA) conditioning since these recipients will be more difficult to evaluate for neutrophil recovery. Hence, we propose a single stratum phase II study of MGTA-145 at 15 µg/kg intravenous infusion plus plerixafor administered at 240 µg/kg subcutaneously for mobilization in healthy sibling donors of recipients undergoing MAC allogeneic transplantation.

2.2.13 Rationale for post-transplant growth factor administration

We will administer G-CSF beginning day +7 in recipients of MAC transplantation since G-CSF was used in all recipients in the original Washington University study and in most recipients in the Chen et al study.[51,53] While the use of myeloid growth factors following allogeneic transplantation varies widely between centers, a recent CIBMTR study did show acceleration of neutrophil recovery without any increase in the risk of acute or chronic GVHD.[54]

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

The most commonly encountered AEs observed in subjects treated with MGTA-145 and plerixafor were back pain/musculoskeletal pain, diarrhea, nausea, dizziness, abdominal pain and headache. Clinically, an important risk during administration of MGTA-145 includes AEs of back pain occurring within 10 minutes of study treatment administration.

There is no known risk for the combination of MGTA-145 and plerixafor. Results following co-administration of MGTA-145 and plerixafor did not demonstrate any additive toxicological effect, indicating no further risk posed by the addition of MGTA-145 to plerixafor administration despite the synergistic pharmacological effect.

2.3.2 Known Potential Benefits

Mobilization with MGTA-145 + plerixafor offers the potential for same-day mobilization and apheresis cell collection, as compared to 4-5 days of G-CSF for mobilization. The shorter duration of mobilization has the potential to cause less interference with usual activities. G-CSF causes bone pain in a majority of donors for up to one week. Although MGTA-145 causes bone pain, it generally lasts < 15 minutes. Thus, there is the potential for a reduction in the cumulative pain morbidity associated with mobilization. The combination of less interference with daily life combined with decrease total pain may increase donor willingness to undergo mobilization and apheresis, thereby increasing the pool of potential allogeneic donors.

2.3.3 Assessment of Potential Risk and Benefits

The overall safety profile of MGTA-145 is acceptable, and combination therapy does not substantially increase the risks of side effects. Thus, the potential additional benefits of combination therapy are likely to outweigh the risk of AEs experienced during MGTA-145 treatment. Back pain is an important risk for MGTA-145 because it has led to discontinuation of infusion in phase I studies. Based on the available safety data for MGTA-145, the benefit-risk profile of the medicinal product remains favorable.

3 OBJECTIVES

3.1 Primary Objective

To determine the proportion of donors whose cells can be successfully mobilized and collected with a sufficient CD34+ cell dose using same-day, single-dose MGTA-145 + plerixafor as the mobilizing agents. Donor mobilization following MGTA-145 + plerixafor will be considered successful if ≥ 2.0×10^6 CD34+ cells/kg actual recipient weight are collected in one leukapheresis collection. All donors receiving MGTA 145 + plerixafor will be included in the analysis of the primary objective.

3.2 Secondary Objectives

3.2.1 Donor Related

3.2.1.1 To determine the proportion of donors whose cells can be successfully mobilized and collected with a target CD34+ cell dose of at least 4.0 x 10^6 CD34+ cells/kg actual recipient weight in one apheresis collection

3.2.1.2 To ascertain the incidence and severity of acute adverse events (AEs) before and during apheresis experienced by donors receiving MGTA-145 + plerixafor

3.2.1.3 To characterize the adverse effects experienced by donors receiving MGTA-145 + plerixafor

3.2.2 Recipient Related

3.2.2.1 To determine the incidence of and kinetics of neutrophil and platelet recovery after transplantation of hematopoietic cells mobilized with MGTA-145 + plerixafor

3.2.2.2 To determine the incidence of primary and secondary graft failure after transplantation of hematopoietic cells mobilized with MGTA-145 + plerixafor

3.2.2.3 To determine the incidence and severity of acute and chronic graft versus host disease (GVHD) after transplantation of hematopoietic cells mobilized with MGTA-145 + plerixafor

3.2.2.4 To determine the incidence of treatment-related mortality and disease relapse/progression after transplantation of hematopoietic cells mobilized with MGTA-145 + plerixafor

3.2.2.5 To determine the probability of progression-free and overall survival after transplantation of hematopoietic cells mobilized with MGTA 145 + plerixafor

3.2.2.6 To characterize the adverse effects experienced by recipients receiving grafts mobilized by MGTA-145 + plerixafor

3.3 Exploratory Objectives

3.3.1 Graft Related

3.3.1.1 To describe the cellular composition of allografts mobilized with MGTA-145 + plerixafor (stem/progenitor cells, T/B/NK-cells, colony forming units)

3.3.2 Recipient Related

3.3.2.1 To describe T-cell (CD3+) and myeloid chimerism after transplantation of hematopoietic cells mobilized with MGTA-145 + plerixafor

3.3.2.2 To assess the rate and quality of immune reconstitution as evidenced by peripheral blood immunophenotype after transplantation of hematopoietic cells mobilized with MGTA-145 + plerixafor

3.3.2.3 To determine the incidence of CMV reactivation after transplantation of hematopoietic cells mobilized with MGTA-145 + plerixafor in cytomegalovirus (CMV) seropositive recipients

3.3.3 Donor Related

3.3.3.1 To characterize the PK of MGTA-145

3.3.3.2 To assess treatment related Anti-drug Antibody (ADA)

3.3.3.3 To describe donation experience of PBSC donors mobilized with MGTA-145 + plerixafor

4 STUDY DESIGN

4.1 Overall Design

This is a Phase II, open-label, multicenter, prospective study of MGTA-145 + plerixafor-mobilized HLA-matched sibling and matched unrelated donor allografts for myeloablative HSCT in recipients with hematological malignancies. This study will establish the safety and efficacy of the combination of MGTA-145 infusion and subcutaneous plerixafor for HSC mobilization. Donor-recipient pairs will be recruited for this study. Collection and transplant outcomes will be assessed. AEs will be reported using event terms and grading for severity per the Common Terminology Criteria for Adverse Events (CTCAE) version 5. Safety monitoring rules related to donor and recipient AEs are in place, which may result in a Data Safety Monitoring Board (DSMB) evaluation as detailed in Section 8.2.

4.2 Justification for Dose

Optimal doses from the 145-HV-101 Phase I study were 0.015 mg/kg and 0.03 mg/kg. The dose in humans of 0.03 mg/kg represents a 1500-fold for C_{max} and 2300-fold for AUC relative to exposures in the NOAEL for macaques in the definitive repeat-dose toxicology study. In Study 145-HV-101, 6 dose cohorts of MGTA-145 infusion alone were evaluated in Part A, and no dose limiting toxicities (DLTs) were observed with dosing up to 0.3 mg/kg. In Part B of the study, MGTA-145 was administered in conjunction with plerixafor. When administered immediately after plerixafor, there were no DLTs observed at the 0.03, 0.07, and 0.15 mg/kg doses. When MGTA-145 was dosed 2 hours after plerixafor, the maximum tolerated dose (MTD) was 0.07 mg/kg, with an MTD defined as a single CTCAE grade 2 event. Pharmacodynamic assessment of CD34 cell mobilization showed apheresis collection yields of CD34+ and CD34+CD90+CD45RA- cells were highest with the 0.03 and 0.015 mg/kg doses, respectively. The 0.015 mg/kg dose was selected since it is the lowest dose that maximizes apheresis cell yield.

4.3 End of Study Definition

The study is considered complete when the last subject has completed their last study visit.

5 STUDY POPULATION

The donor population for the study includes those subjects undergoing peripheral blood mobilization and collection of grafts for allogeneic HSCT.

The recipient population for the study includes those subjects with AML, ALL or MDS receiving a hematopoietic stem cell transplant using the product obtained from a donor who underwent mobilization using MGTA-145 in combination with plerixafor.

Once the recipient has qualified for the study, the intended donor (related or unrelated) must meet all eligibility criteria for the study in order for the recipient to complete enrollment. The recipient will remain as ‘screening’ until the donor is enrolled on the study. The recipient may commence conditioning after a clinically successful allograft has been collected from the donor.

5.1 Eligibility Criteria

5.1.1 Donor Inclusion Criteria

1. Donor medical suitability and eligibility will be determined following Institution or National Marrow Donor Program (NMDP)/Be The Match standards
2. Age 18-65 years old at the time of signing informed consent
3. 8/8 (HLA- A, B, C, and DRB1) HLA-matched sibling or volunteer unrelated donor
4. Fulfill Institution or NMDP/Be The Match criteria to serve as a mobilized blood cell donor

5. Serum creatinine < 1.5 x institution ULN or estimated creatinine clearance (CRCL) > 50 mL/min using the Modification of Diet in Renal Disease Study (MDRD) equation or similar method

5.1.2 Donor Exclusion Criteria

1. Donor unwilling or unable to give informed consent, or unable to comply with the protocol including required follow-up and testing
2. Donor already enrolled on another investigational agent study
3. Pregnant or breastfeeding females, sexually active female or male donors not willing or able to use adequate contraception, or males who do not agree to refrain from donating sperm, from the time of consent through 3 months after treatment with MGTA-145 + plerixafor

5.1.3 Recipient Inclusion Criteria

1. At least 18 years old at the time of signing informed consent
2. Has an available 8/8 (HLA- A, B, C, and DRB1) HLA-matched sibling or volunteer unrelated donor willing to donate peripheral blood stem cells (PBSC) for transplant
3. Fulfill additional individual Transplant Center Criteria for transplant beyond NMDP/Be The Match criteria
4. One of the following diagnoses:
    - Acute myelogenous leukemia (AML) in 1st remission or beyond with ≤ 5% marrow blasts and no circulating blasts. Documentation of bone marrow assessment will be accepted within 45 days prior to the date of consent.
    - Acute lymphoblastic leukemia (ALL) in 1st remission or beyond with ≤ 5% marrow blasts and no circulating blasts. Documentation of bone marrow assessment will be accepted within 45 days prior to the date of consent.
    - Patients with myelodysplasia (MDS) with no circulating blasts and with less than 10% blasts in the bone marrow (higher blast percentage allowed in MDS due to lack of differences in outcomes with < 5% or 5-10% blasts in MDS). Documentation of bone marrow assessment will be accepted within 45 days prior to the date of consent.
5. Cardiac function: Left ventricular ejection fraction at least 45% based on most recent echocardiogram or MUGA results obtained via standard of care
6. Estimated creatinine clearance acceptable per local institutional guidelines
7. Pulmonary function: diffusing capacity of the lungs for carbon monoxide (DLCO) corrected for hemoglobin at least 50% and forced expiratory volume in first second (FEV1) predicted at least 50% based on most recent DLCO results obtained via standard of care
8. Liver function acceptable per local institutional guidelines
9. Karnofsky performance status (KPS) of 70% or greater (See Appendix A)
10. Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) score of 4 or less (See Appendix B)

5.1.4 Recipient Exclusion Criteria

1. Subject unwilling or unable to give informed consent, or unable to comply with the protocol including required follow-up and testing
2. Subject whose donor does not meet the eligibility criteria and is a screen fail

3. Subjects with a prior allogeneic transplant
4. Subjects with active, uncontrolled infection at the time of the transplant preparative regimen
5. Pregnant or breastfeeding females, sexually active female or male subjects not willing or able to use adequate contraception, or males who do not agree to refrain from donating sperm, from the time of consent through 3 months after PBSC infusion
6. Subjects with clinical evidence of active Central Nervous System (CNS) tumor involvement as evidenced by documented disease on examination of spinal fluid or MRI within 45 days of start of conditioning
7. A condition, which, in the opinion of the clinical investigator, would interfere with the evaluation of primary and secondary endpoints
8. Planned treatment with a new investigational agent from the time of transplant through 30 days post-transplant

5.2 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information may be collected, such as demographics, screen failure details, eligibility criteria, and any SAEs.

5.3 Strategies for Recruitment and Retention

Potential subjects will be identified at participating transplant centers in the course of clinical care for allogeneic HSCT.

5.3.1 Related Donors

Transplant centers will be responsible for managing study procedures for related donors. Potential donors must be evaluated for suitability and eligibility.

5.3.2 Unrelated Donors

Be The Match will manage all unrelated donor contact, informed consent sessions, donor medical suitability and eligibility determinations, donor sample collections and donor hematopoietic progenitor cell apheresis (HPC(A)) collections. Only donors who provide written informed consent and who meet the protocol requirements will be permitted to donate an HPC(A) product for this protocol.

6 SUBJECT ACCOUNTABILITY

6.1 Point of Enrollment

A donor subject is considered enrolled when the informed consent form has been signed and the subject is confirmed to meet eligibility criteria for the study. A recipient subject is considered enrolled when the informed consent form has been signed, the subject is confirmed to meet eligibility criteria for the study, and the intended donor has met the criteria for enrollment on the study. Recipient subjects will remain in screening status until intended donor has been successfully enrolled on the study. Subjects with documented informed consent to participate in research and meeting all eligibility criteria for the study must be enrolled in the Medidata Rave® electronic data capture (EDC) application prior to initiating any study-specific activity.

6.2 Withdrawal

Subjects have the right to withdraw consent for study participation at any time and for any reason. Subject data collected up to withdrawal of consent will be retained and included in the analysis of the study. An explanation of why the subject is withdrawing from the study must be documented in a Study Exit form in the Medidata Rave® EDC application. All subjects who withdraw from the study with ongoing

SAEs or AEs of at least possible relatedness must be followed until resolution of the event, death, or until the site Principal Investigator concludes that the event is stable with no further improvement anticipated. Subjects lost to follow-up must be reported on the Study Exit form in the Medidata Rave® EDC application (see Section 8.3).

6.3 Subject Status and Classification

The following subject classifications will be utilized for this protocol:

Important: Once the recipient has qualified for the study, the intended donor (related or unrelated) must meet all eligibility criteria for the study in order for the recipient to complete enrollment. The recipient will remain as 'screening' until the donor is enrolled on the study. The recipient may commence conditioning after a clinically successful allograft has been collected from the donor.

- Screening: A subject who is being evaluated for study participation.
- Screen Failure: A subject who has signed the informed consent but is found to not meet eligibility criteria. These subjects do not count against the enrollment ceiling.
- Consented, Eligible, Enrolled but not Treated: A subject who signs the informed consent, meets eligibility criteria but then does not undergo the main study procedure. The original Informed Consent form and screening documentation for these subjects should be maintained in the site's files. There are no follow-up requirements for these subjects. These subjects do not count against the enrollment ceiling.
- Enrolled, treated: A donor subject who is consented, meets eligibility and receives treatment per the study protocol. A recipient subject who is consented, meets eligibility and whose intended donor has met the criteria for enrollment on the study. Both donor and recipient subjects are followed in accordance with the follow-up schedule and included in all analyses of safety and efficacy.
- Early Terminated: A subject who enrolled on the study and subsequently met a criterion for discontinuation from the study.
- Completed: A donor subject who receives treatment and completes the 6-month follow-up visit or contact, or a recipient subject who receives treatment and completes the 1-year follow-up visit or contact

7 STUDY INTERVENTION

7.1 Study Intervention(s) Administration

7.1.1 Donor Treatment Plan

7.1.1.1 Plerixafor and MGTA-145 Administration

Plerixafor

On the first day of mobilization, the donor will arrive in the morning and the following procedures will be performed prior to study drug administration:

- Review of medical history and current medications
- Physical exam
- Measurement of weight in kg
- Vital signs including blood pressure, pulse, respiratory rate, and temperature
- Serum pregnancy test for female donors of childbearing potential; Note: pregnancy test can be performed up to 48 hours prior to dosing

- Complete blood count (CBC) with automated differential and platelet count
- Peripheral blood sample to be collected for CD34+ cell analysis by flow cytometry
- Anti-drug Antibody (ADA) sample collected
- Plerixafor will be administered subcutaneously at 240 µg/kg actual donor weight approximately 2 hours prior to planned leukapheresis. Donors will be observed for 15-30 minutes after dosing. Only administer plerixafor in a monitored setting when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions.

The following procedures will be performed after dosing of plerixafor:

- Vital signs monitored post plerixafor injection at 30 minutes (±10 minutes), 60 minutes (±10 minutes) and per local institutional guidelines
- Monitor donor for hypersensitivity reactions including anaphylaxis.
- Monitor donor for vasovagal reaction. The majority of vasovagal events occur within an hour of plerixafor administration.
- It is suggested that donors remain recumbent for the first hour after plerixafor administration with access to a bedside commode. The investigator should consider the clinical status and relevant laboratory parameters of each donor and consider extending the observation and recumbent period as warranted on a case-by-case basis.
- If donors choose to get up during the observation period after plerixafor administration when recumbency is recommended, it is suggested that orthostatic (supine, sitting and standing) blood pressure and pulse be collected before they get up, and also at any time donors experience symptoms consistent with a vasovagal reaction (e.g., orthostatic hypotension, bradycardia, lightheadedness, fainting). Should syncope, bradycardia, orthostasis or lightheadedness occur, an electrocardiogram (ECG) should be obtained.
- Should symptomatic orthostasis occur (a decrease in > 20 mm Hg systolic or > 10 mm Hg diastolic within 3 minutes of standing), it is recommended that the donor remain recumbent until orthostasis resolves and hydration should be administered if clinically acceptable.
- Donors will be assessed by clinic and/or apheresis staff for evidence of AEs related to plerixafor during the injection and at 30 minutes (±10 minutes) and 60 minutes (±10 minutes) following administration of plerixafor. Any AEs observed will be noted in the Medidata Rave® EDC application by the staff assessing the donor. If any CTCAE grade 3 or greater AE is observed, the clinical staff (e.g. attending physician, site Principal Investigator, mid-level providers) will be contacted immediately for further instruction. If an AE requires any type of intervention, the requirement for and nature of that intervention should be clearly documented in the Medidata Rave® EDC application.

<u>MGTA-145</u>

- PK sample to be collected prior to MGTA-145 infusion (within 60 minutes of the start of the infusion)
- Vital signs monitored prior to MGTA-145 dosing, during infusion and 30 minutes (±10 minutes), 60 minutes (±10 minutes, 120 minutes (±20 minutes), and 240 minutes (±20 minutes) following start of infusion
- MGTA-145 will be administered at a dose of 0.015 mg/kg intravenously over 3 minutes, starting approximately 2 hours after plerixafor. The infusion time may range from 1 to 10 minutes as clinically indicated.

- PK sample to be collected 15-30 minutes after start of infusion
- Donors will be assessed by clinic and/or apheresis staff for evidence of AEs related to MGTA-145 during the infusion and at 30 minutes (±10 minutes), 60 minutes (±10 minutes, 120 minutes (±20 minutes), and 240 minutes (±20 minutes) following start of infusion. Any AEs observed will be noted in the Medidata Rave® EDC application by the staff assessing the donor. If any CTCAE grade 3 or greater AE is observed, the clinical staff (e.g. attending physician, site Principal Investigator, mid-level provider) will be contacted immediately for further instruction. If an AE requires any type of intervention, the requirement for and nature of that intervention should be clearly documented in the Medidata Rave® EDC application.
- After MGTA-145 infusion but prior to leukapheresis, a peripheral blood sample for CD34+ cell analysis by flow cytometry will be collected.
- As soon as feasible after MGTA-145 infusion (approximately 30 minutes following the administration of MGTA-145), begin leukapheresis procedure to process at least 4 times blood volume, but no more than the institutional limit.
- Following the completion of leukapheresis, the following will be done:
    - Vital signs
    - Collect sample for CBC with automated differential and platelet count
    - Collect sample for CD34+ cell analysis by flow cytometry from the apheresis product
    - Collect sample for graft immunophenotyping from the apheresis product
    - Collect sample for colony forming unit testing from the apheresis product
- Both during and immediately following completion of leukapheresis, donor will be assessed for evidence of AEs. Any AEs observed will be noted on the day of collection form by the staff assessing the donor. If any CTCAE grade 3 or greater AE is observed, the clinical staff (attending physician, site Principal Investigator, mid-level provider) will be contacted immediately for further instruction. It is possible that grade 3 or greater AE could be entirely related to the leukapheresis procedure rather than MGTA-145 or plerixafor, but this will ultimately be determined by the investigator at the site. Otherwise, the donor may be discharged from the leukapheresis center.
- Leukapheresis product must be cryopreserved until the recipient is ready to receive the product.

7.1.1.2 Target Collection

The target CD34+ cell dose for the donor allograft collected following MGTA + plerixafor is ≥ 4.0 x 10^6/kg actual recipient weight. The leukapheresis should target 4-5 blood volumes.

If the target CD34+ cell dose of ≥ 4.0 x 10^6/kg actual recipient weight is met after the first leukapheresis, no further collections will be performed. Otherwise, the donor will return the following morning and the same procedures described above will be repeated in order to achieve the target CD34+ cell dose. The second leukapheresis session should also be targeted to process 4-5 blood volumes just as with the first leukapheresis session, as long as it can be done safely. If the sum of the two collected leukapheresis products is ≥ 2.0 x 10^6 CD34+ cells/kg actual recipient weight, collection will be completed.

If the donor mobilizes ≥ 2.0 x 10^6 CD34+ cells/kg actual recipient weight after one or two days of MGTA-145 + plerixafor administration, the treating centers are strongly encouraged to use this as the sole graft for the recipient in order to keep the recipient on study and evaluate for important secondary endpoints.

In the event that the donor fails to mobilize at least 2.0 x 10^6 CD34+ cells/kg actual recipient weight after two days of treatment with MGTA-145 + plerixafor, the center will be allowed to use that graft (regardless of the total CD34+ cell dose) at their discretion, and the recipient will be followed. Alternatively, in this scenario the treating center may choose to remobilize the donor with G-CSF or collect bone marrow for transplantation as a supplement or replacement for the MGTA-145 + plerixafor mobilized graft.

Each leukapheresis product (that is, from each day of collection) must be analyzed for CD34+ and CD3+ cell content, normalized to recipient actual body weight, prior to cryopreservation. In addition, exploratory immunophenotypic analysis and colony forming unit assays will be performed. Following thawing, an analysis of CD34+ cell viability must also be performed.

7.1.1.3 Monitoring donors for adverse events

Adverse Events will be monitored and collected on donors beginning from the time of signing informed consent and up to 72 hours following dosing with MGTA-145 and plerixafor. The donor will be closely monitored during treatment and mobilization with MGTA-145 + plerixafor for AEs. Refer to Section 9.8 for Adverse Event Reporting Requirements.

To date in Magenta studies, the most commonly encountered AEs observed in plerixafor treated healthy donors include injection site erythema, headache, paresthesias, nausea, diarrhea, and flatulence. The CTCAE grade of toxicities observed have been mild (grade 1) or moderate (grade 2). The most commonly encountered AEs observed in subjects treated with MGTA-145 and plerixafor were back pain/musculoskeletal pain, diarrhea, nausea, dizziness, abdominal pain and headache as well as transient bone pain, predominantly in the lower back, that begins during infusion and lasts < 20 minutes. The CTCAE grade has been mild (grade 1) or moderate (grade 2).

7.1.1.4 Cryopreservation and Thawing of Collected Product

To ensure that an adequate Hematopoietic Progenitor Cells (HPC) product is available prior to admission of the recipient and start of the preparative regimen, the HPC products must be collected and cryopreserved according to the local institutional guidelines. Collection by apheresis and cryopreservation are performed using validated facility procedures. A sample adequate to perform post-thaw viability testing must also be cryopreserved. Cryopreserved products and samples must be stored in the liquid or vapor phase of liquid nitrogen freezers until completion of the required product testing. HPC products must be tested at the time of collection for total nucleated cell count (TNC), CD34, CD3 and red blood cell count (RBC) content according to local procedures. The subject may commence conditioning as long as a CD34+ dose of ≥ 2.0 x 10^6/kg actual recipient weight has been collected. Since the cellular content (e.g., neutrophils) of HPC products has the potential to impact how well cells survive the cryopreservation process, a sample of the cryopreserved product must be thawed and tested to determine the percent recovery of viable CD34+ cells. Upon thawing of the cryopreserved sample, it is recommended that the sample contain at least a viable CD34+ count of 2.0 x 10^6/kg actual recipient weight cells to proceed with the transplant.

Products are to be thawed for infusion according to validated facility procedures. Due to the potential for hemolysis due to both the freeze thaw process and major ABO incompatibility, sites should consider either washing products at the time of thaw or splitting the infusion over multiple days or morning and evening if the volume of RBCs to be infused exceeds the institutional RBC maximum, regardless of ABO compatibility.

7.1.1.5 Transport and Shipment of Product

If product transportation or shipment is required, product may be shipped fresh and cryopreserved at the transplant center destination. Product shipment will follow NMDP standard shipping procedures.

7.1.2 Recipient Treatment Plan

7.1.2.1 Administration of conditioning to the subject

The following conditioning regimens can be used for subjects enrolled on this trial:

Myeloablative (one of five general regimens):

- Busulfan (≥ 9 mg/kg orally (PO) or intravenously (IV) total) with fludarabine
- Busulfan (≥ 9 mg/kg orally (PO) or intravenously (IV) total) with cyclophosphamide

- Total body irradiation (≥ 1000 cGy) plus etoposide
- Total body irradiation (≥ 500 cGy) plus cyclophosphamide
- Melphalan 140 mg/m^2 with fludarabine

Details of the conditioning regimen are at the treating center's discretion as long as the backbone requirements for the regimen as specified above are met. Centers using pharmacokinetically targeted busulfan dosing should target an AUC of at least 4,000 +/-10% µM*min per day for 4 days.

7.1.2.2 GVHD Prophylaxis

All recipients must receive pharmacological GVHD prophylaxis. Choice of agents for GVHD prophylaxis will also be left to the discretion of the treating center provided no monoclonal (e.g., alemtuzumab) anti-T-cell antibodies or any form of ex vivo T-cell depletion is employed. GVHD prophylaxis may include post-transplant cyclophosphamide or a calcineurin phosphatase inhibitor in combination with methotrexate, mycophenolate mofetil, or sirolimus in accordance with local institutional guidelines. Tapering of immunosuppressive agents will be per local institutional guidelines. In general, it is recommended that tapering of immunosuppression not be started, in the absence of disease progression, until days 90-100 post-transplant since the risks for and tempo of GVHD following MGTA-145 + plerixafor-mobilized allografts are not completely understood.

7.1.2.3 Stem Cell Transplantation (Day 0)

Recipients who have a clinically successful allograft (≥ 2.0 x 10^6 CD34+ cells/kg actual recipient weight) collected following mobilization with MGTA-145 + plerixafor will undergo the testing described below and will receive the MGTA-145 + plerixafor mobilized allograft on Day 0.

- Physical examination
- CBC with differential and platelet count
- Serum creatinine/AST/ALT/LDH/Total bilirubin
- Vital signs will be monitored 1 hour prior to the allograft infusion and then approximately 15 minutes, 30 minutes, 1 hour, 2 hours, and 4 hours post infusion

7.1.3 Supportive Care

Supportive care will be given in keeping with local institutional guidelines.

7.1.3.1 Growth Factors

G-CSF will be administered at a dose of 5 µg/kg/day actual recipient weight (may be rounded to the nearest vial size) by subcutaneous injection starting day +7 and continuing until the absolute neutrophil count (ANC) is > 1.5 x 10^9/L for 2 consecutive days.

7.1.3.2 Blood Products

Transfusion thresholds for blood product support will be consistent with local institutional guidelines. All cellular blood products will be irradiated. Recipients who are CMV negative will receive CMV negative or leuko-reduced blood products from study entry. Blood products will be recorded as a concomitant medication.

7.1.3.3 Prophylaxis Against Infections

Prophylaxis against infections during the peritransplant period will be done according to local institutional guidelines.

7.1.3.4 Intravenous Immune Globulin (IVIG)

IVIG administration will be left to local institutional guidelines.

7.1.3.5 ABO Incompatibility

All recipients with ABO incompatibility should be evaluated and treated per local institutional guidelines.

7.1.3.6 Anti-seizure Prophylaxis

Phenytoin, levetiracetam (Keppra), or a benzodiazepine may be used with busulfan in accordance with local institutional guidelines.

7.1.4 Dosing Administration

Donors will be administered both investigational interventions, plerixafor and MGTA-145, described below.

7.2 Study Drugs

7.2.1 Description

7.2.1.1 Plerixafor

Plerixafor (injection) is a sterile, preservative-free, clear, colorless to pale yellow, isotonic solution for subcutaneous 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.

7.2.1.2 MGTA-145

MGTA-145 (Gro-beta truncate or GROβT) is a synthetically manufactured naturally occurring four amino acid-truncated variant of the immunomodulatory protein CXCL2.

MGTA-145 is formulated at 20 mg/mL in 20 mM sodium acetate, 150 mM sodium chloride, 0.02% (w/v) Polysorbate 80 at pH 4.0. MGTA-145 is supplied in a single-dose 2 mL Type I amber glass vial. Each vial contains not less than 1 mL.

7.2.2 Packaging and Labeling

7.2.2.1 Plerixafor

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

7.2.2.2 MGTA-145

MGTA-145 is manufactured, packaged, and labelled according to Good Manufacturing Practice guidelines and applicable laws or regulations. The study drug is suitably packaged in such a way as to protect it from deterioration during transport and storage.

MGTA-145 is supplied in single-use amber vials packaged in cartons. Each vial is labeled as required per country requirements. Each vial is filled to deliver 1.0 mL of 20 mg/mL solution containing 20 mg MGTA-145.

7.2.3 Product Storage and Stability

7.2.3.1 Plerixafor

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

7.2.3.2 MGTA-145

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

7.2.4 Preparation and Administration

7.2.4.1 Plerixafor

Plerixafor is supplied as a ready-to-use formulation. The contents of the vial must be transferred to a suitable syringe for administration. Vials should be inspected visually for particulate matter and discoloration prior to administration and should not be used if there is particulate matter or if the solution is discolored.

Plerixafor should be administered subcutaneously per the manufacturer's instructions. Plerixafor will be administered subcutaneously at 240 µg/kg actual donor weight approximately 2 hours prior to planned leukapheresis. Plerixafor will be administered up to two times, once on each of two consecutive days.

7.2.4.2 MGTA-145

Vials of MGTA-145 should be thawed overnight at 2°C – 8°C prior to use and are stable at 2°C – 8°C for up to 30 days. Once thawed, MGTA-145 should not be refrozen.

Vials should be inspected visually for particulate matter and discoloration prior to administration and should not be used if there is particulate matter or if the solution is discolored.

MGTA-145 should be diluted in 0.9% saline in accordance with the study protocol and Pharmacy Manual. Once prepared, MGTA-145 may be stored for no more than 8 hours at room temperature prior to administration.

Approximately 2 hours after plerixafor administration MGTA-145 will be administered intravenously at 0.015 mg/kg actual donor weight over 3 minutes. The infusion time may range from 1 to 10 minutes as clinically indicated. MGTA-145 will be administered up to two times, once on each of the two consecutive days.

The Investigator or designee is responsible for recording the details of the intravenous infusion of MGTA 145 in the Medidata Rave® EDC application.

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only subjects enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

7.3 Concomitant therapy

Donors may continue all medications in compliance with local apheresis center mobilization and apheresis local institutional guidelines. Premedication and/or treatment for possible AEs related to MGTA-145 and plerixafor are permitted and should be documented in the Medidata Rave® EDC application.

Prohibited medications for donors include concomitant use of Granulocyte-macrophage colony-stimulating factor (GM-CSF), G-CSF and investigational products.

There are no prohibited medications for recipients.

8 STUDY INTERVENTION DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

8.1 Discontinuation of Study Intervention

In the event that the donor fails to mobilize at least 2.0 x 10^6 CD34+ cells/kg actual recipient weight after two days of treatment with MGTA-145 + plerixafor, the center will be allowed to use that graft (regardless of the total CD34+ cell dose) at their discretion, and the recipient will be followed. Alternatively, in this scenario the treating center may choose to remobilize the donor with G-CSF or collect bone marrow for transplantation as a supplement or replacement for the MGTA-145 + plerixafor mobilized graft.

8.2 Study-wide Safety Monitoring Rules

Monitoring of Donor safety: Donors will be monitored closely for AEs up to 72 hours following infusion. If a CTCAE grade 3 or greater AE believed to be at least possibly related to plerixafor or MGTA-145 is observed in any of the donors, the AE must be entered in Medidata Rave® EDC application within 24 hours of learning of the event. This will notify the CIBMTR Medical Monitor who will consult with Magenta, the NMDP Protocol Chair and the DSMB Study Chairperson. At that time, a decision will be made as to whether the DSMB needs to meet to review the AE further and whether the study enrollment should be suspended, at least temporarily until the DSMB meeting. Refer to Section 9.8 for Adverse Event Reporting Requirements.

Monitoring of Recipient safety: Three safety monitoring rules will be utilized to monitor recipient safety. The CIBMTR Medical Monitor will review the relevant data on a weekly basis to assess whether any stopping rules have been met. If a stopping rule as described below is triggered, the DSMB will be notified, and enrollment will be paused while the DSMB conducts a review of the safety data. The safety monitoring rules serve as a trigger for consultation with the DSMB for additional review and would not mandate automatic closure of study enrollment. Since all events being monitored are expected to occur with some frequency in the general transplant population, a sequential hypothesis testing framework will be utilized to identify whether the event rate is exceeding what is expected. The following safety endpoints and null hypothesis values will be used for sequential testing.

- The first monitoring rule is based on primary graft failure, which is expected to be no higher than 3% of recipients by Day 28.
- The second monitoring rule is based on treatment-related mortality (TRM), which is expected to be no higher than 15% of recipients by Day 100.
- The third monitoring rule is based on grades 3-4 acute GVHD (aGVHD), which is expected to be no higher than 10% of recipients by Day 100.

Monitoring rules for recipients and their operating characteristics were obtained using the R package ‘clinfun’, using a 5% one-sided type I error rate across the sequential tests for each event. These are described in Table 8.2.

Graft Failure at day 28						
Number of recipients (n)	2-9	10-23	24-28			
Stopping boundary (x)	2	3	4			
TRM by day 100						
Number of recipients (n)	4-8	9-11	12-15	16-19	20-24	25-28
Stopping boundary (x)	4	5	6	7	8	9
aGVHD grade 3-4						
Number of recipients (n)	3-6	7-11	12-17	18-22	23-28	
Stopping boundary (x)	3	4	5	6	7	

Table 8.2 Monitoring Guidelines among Recipients Receiving Allografts Successfully Mobilized by MGTA-145 + Plerixafor

*Stopping guideline is triggered if ≥ x recipients out of n experience events described

The graft failure pausing rule has a 5% chance of being triggered if the true graft failure rate is 3%, and an 85% chance of being triggered if the true graft failure rate is 18%. If the true graft failure rate is 18%, the stopping rule will be triggered on average after approximately 13 subjects are evaluable for the graft failure endpoint. Similarly, the TRM pausing rule has a 5% chance of being triggered if the true TRM rate is 15%, and an 89% chance of being triggered if the true TRM rate is 40%. If the true TRM rate is 40%, the stopping rule will be triggered on average after approximately 14 subjects are evaluable for the TRM endpoint. Finally, the grade 3-4 aGVHD pausing rule has a 5% chance of being triggered if the true rate is 10%, and an 83% chance of being triggered if the true rate is 30%. If the true grade 3-4 aGVHD rate is 30%, the stopping rule will be triggered on average after approximately 15 subjects are evaluable for the grade 3-4 aGVHD endpoint.

Triggering a safety monitoring rule does not mean discontinuation from the study for subjects currently enrolled, and remaining study procedures should be completed as indicated by the study protocol, especially for efficacy and safety endpoints, namely, to capture AE, SAE, and unanticipated problems (UPs). Refer to Appendix G and Appendix H for more information. If a clinically significant finding is identified after enrollment, the investigator or qualified designee will determine if any change in subject management is needed.

8.3 Subject Discontinuation/Withdrawal from the Study

Subjects are free to withdraw from participation in the study at any time upon request. If the subject wishes to withdraw, data collected up to that time point for inclusion in the study will be retained. If a subject withdraws prematurely after HSCT, all data normally collected at the end of study visit should be gathered at the time of premature discontinuation and reported in the forms in the Medidata Rave® EDC application.

Off-study criteria: The subject is no longer followed. No study-specific evaluations, procedures, or tests are performed after date the subject was considered to have met off-study criteria.

An investigator may discontinue or withdraw a subject from the study for the following reasons:

- Concerns for recipient or donor safety
- Noncompliance with study procedures or obligations
- Required use of a prohibited medication
- Transplant is cancelled, subject (recipient) reason
- Transplant is cancelled (recipient), insufficient number of cells obtained
- A subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- The subject is lost to follow-up
- Discontinued per medical discretion of the site Principal Investigator or Medical Monitor, such as if any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject
- Subject withdraws consent
- Death

Off-protocol criteria: The subject is followed for clinical endpoint data capture only. No study-specific evaluations, procedures, or tests will be performed after date the subject was considered to have met off-protocol criteria.

- Subject received a subsequent HSCT and/or donor cellular infusion (DLI)
- Subject experiences disease relapse

The reason for subject discontinuation or withdrawal from the study will be recorded in the Medidata Rave® EDC application and documented in the medical record. All subjects who withdraw from the study with ongoing SAEs or AEs of at least possible relatedness must be followed until resolution of the event,

death, or until the site Principal Investigator concludes that the event is stable with no further improvement anticipated.

Subjects who sign the informed consent form but do not receive the study medications may be replaced. Subjects who sign the informed consent form, and receive the study medications, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

8.4 Lost to Follow-Up

A subject will be considered lost to follow-up if the subject fails to be available for or return for a scheduled visit and is unable to be contacted by the study site staff. Subjects lost to follow-up must be reported in the Medidata Rave® EDC application.

The following actions must be taken if a subject fails to be available for a virtual visit or return to the clinic or laboratory for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost-to-follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods).These contact attempts should be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

Post-collection donor survey assessments are administered centrally by the CIBMTR Survey Research Group. If the Survey Research Group is unable to contact a subject for a specific survey time point, after several phone and email contact attempts, they will code that survey assessment as Lost to Follow-Up. The subject will not be exited from the study and the Survey Research Group will continue attempting to reach the subject for subsequent survey time points.

9 STUDY ASSESSMENTS AND PROCEDURES

9.1 Donor Screening

Within 30 days prior to start of stem cell mobilization with plerixafor and MGTA-145, the donor will undergo inclusion/exclusion criteria testing to include the following:

- Written informed consent covering the complete study procedures must be obtained before any study procedure is performed.
- Medical history review and collection of any current medications
- Physical exam including vital signs (blood pressure, pulse, respiratory rate, and temperature), height, weight
- KPS
- Electrocardiogram
- CBC with differential and platelet count
- Serum Creatinine
- Prothrombin Time (PT)/ Partial thromboplastin time (PTT)
- Serum pregnancy for female donors of childbearing potential
- Urinalysis (dipstick and microscopic examination)
- Infectious disease markers as required by FDA
- ABO/Rh Typing
- Chimerism sample (e.g. VNTR or other method in use at treating institution)

9.1.1 Unrelated Donors

Be The Match will manage all aspects of volunteer unrelated donor participation on the study. Standard operating procedures for approaching and evaluating potential donors for HSC donation will be followed. Volunteer unrelated donors will participate in an information session with a Be The Match Donor Services representative via telephone regarding HSC donation and will be approached for participation in this study. If the donor is willing to proceed, the donor will participate in an informed consent session with a Be The Match Medical Services representative. Verbal consent will be obtained to proceed with the Be The Match donor eligibility evaluations. Study specific screening assessments will not start until the donor signs the study specific informed consent form and returns the consent to Be The Match, where the signed consent form will be retained.

If the donor at any point does not meet the requirements for donation, they will be withdrawn from the study and the reason will be documented.

Donors that are determined to be acceptable to continue participation will be scheduled for an HPC(A) collection at a study-qualified Be The Match apheresis center.

9.2 Donor Follow-up

Donors will be contacted for a virtual visit (with telephone backup if video is not available) by study site staff (clinic or apheresis center) for related donors, or by a Be The Match Donor Services representative for unrelated donors, at Week 1, Month 1, and Month 6. At the Week 1 visit, the Donors will be asked non-leading questions about whether any AEs have occurred and whether any new medications were required. At the Week 1, Month 1, and Month 6 visits. Donors will be asked whether any SAEs have occurred. Donors will also be instructed to report any important safety events throughout the study to the clinic where the donation procedure occurred.

At Month 1, laboratory sample collections will be ordered by CIBMTR staff. Study sites will be responsible for communicating visit requirements with subjects. Donors will be given instruction by the study site on where to go to have samples collected.

At Days 3-4, and Month 1, donor survey assessments will be conducted by the CIBMTR Survey Research Group staff, as described in Section 9.7.

9.3 Recipient Screening

Within 45 days of the start of the conditioning regimen, the subject will undergo inclusion/exclusion criteria testing to include the following:

- Written informed consent covering the complete study procedures must be obtained before any study procedure is performed. In order for the recipient to continue on the study, the intended donor will have to consent as well (see Section 9.1).
- Medical history review and collection of any current medications
- Physical exam including vital signs (blood pressure, pulse, respiratory rate, and temperature)
- Height and Weight
- KPS
- CBC with differential and platelet count
- Blood chemistries to assess renal/hepatic function per local institutional guidelines, including serum creatine, AST, ALT, LDH and total bilirubin
- Serum pregnancy for female subjects of childbearing potential
- Urinalysis
- Assessment of HCT-CI score
- Disease specific staging and assessment
- Bone marrow assessment if not done within 45 days prior to the date of consent

The following tests are required but may be performed earlier than 45 days prior to the start of the conditioning regimen:

- Infectious disease markers as required by FDA
- ABO/Rh Typing
- Chimerism sample (e.g. VNTR or other method in use at treating institution)
- Most recent echocardiogram or MUGA results obtained via standard of care
- Most recent DLCO results obtained via standard of care

9.4 Recipient Follow-up

The following assessments should be made at the time points listed. The study visits reflect standard follow-up for an allogeneic HSCT subject.

Day + 1 through neutrophil recovery or Day + 21 (whichever is first):

- Daily physical exam with vital signs (blood pressure, pulse, respiratory rate, and temperature)
- CBC with differential and platelet count: daily until neutrophil recovery occurs (neutrophil recovery is defined in Section 9.6.6) Note: in the event that neutrophil recovery occurs but not platelet recovery, a CBC should continue to be obtained daily until platelet count recovery or Day + 21 (whichever is first)
- Blood chemistries (serum creatinine, AST, ALT, LDH, total bilirubin) twice weekly
- Daily acute GVHD assessment
- Recipients will receive G-CSF 5 µg/kg/day subcutaneously starting day +7 until ANC > 1.5 x 10^9/L for 2 consecutive days
- Daily assessment for AEs
  Note: Only AEs with relatedness of possible, probable, or definite need to be entered in Medidata Rave® EDC application

Day 28 (± 3 days):

- Physical exam including vital signs (blood pressure, pulse, respiratory rate, and temperature)
- CBC with differential and platelet count
  Note: If platelet and/or neutrophil recovery has not occurred at this time, continue testing three times weekly until recovery
- Blood chemistries (serum creatinine, AST, ALT, LDH, total bilirubin)
- Chimerism sample
- Immune reconstitution sample
- Assessment for adverse events
- Acute GVHD assessment
- **Note:** Only AEs with relatedness of possible, probable, or definite need to be entered in Medidata Rave® EDC application

Day 56 (± 7 days):

- Physical exam including vital signs (blood pressure, pulse, respiratory rate, and temperature)
- CBC with differential and platelet count
  Note: If platelet and /or neutrophil recovery has not occurred, continue testing two times weekly until recovery
- Blood chemistries (serum creatinine, AST, ALT, LDH, total bilirubin)
- Acute GVHD assessment
- Assessment for adverse events
  Note: Only AEs with relatedness of possible, probable, or definite need to be entered in Medidata Rave® EDC application

Day 100 (± 7 days):

- Physical exam with vital signs (blood pressure, pulse, respiratory rate, and temperature)
- CBC with differential and platelet count
  Note: If platelet and /or neutrophil recovery has not occurred, continue testing two times weekly until recovery
- Blood chemistries (serum creatinine, AST, ALT, LDH, total bilirubin)
- Acute and/or chronic GVHD assessment
- Chimerism sample
- Immune reconstitution sample
- Assessment for adverse events
  Note: Only AEs with relatedness of possible, probable, or definite need to be entered in Medidata Rave® EDC application

Day 180 (± 14 days):

- Physical Exam including vital signs (blood pressure, pulse, respiratory rate, and temperature)
- KPS
- CBC and differential with platelet count
- Blood chemistries (serum creatinine, AST, ALT, LDH, total bilirubin)
- Acute and/or chronic GVHD assessment
- Chimerism sample
- Immune reconstitution sample
- Assessment for adverse events
  Note: Only AEs with relatedness of possible, probable, or definite need to be entered in Medidata Rave® EDC application

Day 365 (± 14 days):

- Physical Exam including vital signs (blood pressure, pulse, respiratory rate, and temperature)
- KPS
- CBC and differential with platelet count
- Blood chemistries (serum creatinine, AST, ALT, LDH, total bilirubin)
- Acute and/or chronic GVHD assessment
- Chimerism sample
- Immune reconstitution sample
- Disease appropriate staging reevaluation is recommended
- Bone marrow aspirate and biopsy required if leukocyte count is outside of the normal laboratory range at the transplant center and/or platelet count is < 100 x 10^9/L
- Assessment for adverse events
  Note: Only AEs with relatedness of possible, probable, or definite need to be entered in Medidata Rave® EDC application

9.5 Criteria for engraftment failure and transplantation of second stem cell allograft

If any recipient receiving the MGTA-145 + plerixafor mobilized allograft does not have evidence of an ANC of at least 0.5 x 10^9/L by Day + 28 following myeloablative conditioning and transplantation, plans for a second allograft should be made (e.g., G-CSF mobilized allograft, bone marrow harvest) unless there is a clear reason for failure to achieve an ANC > 0.5 x 10^9/L such as CMV viremia, an active bacterial, other viral, or fungal infection, or the concomitant use of myelosuppressive drugs believed to be a likely cause of the neutropenia. If these plans are being made, the Medical Monitor should be notified.

9.6 Definitions for Safety, Efficacy and PK Assessments

9.6.1 Primary Endpoint: Clinically adequate allograft within one apheresis collection

For the purposes of this study, a clinically adequate allograft is defined as a graft that contains ≥ 2.0 x 10^6 CD34+ cells/kg recipient weight collected. The primary endpoint is defined as achieving this clinically adequate allograft in one apheresis session.

9.6.2 Secondary Endpoint: Clinically desirable allograft in one apheresis collection

This secondary endpoint is defined as achieving a graft that contains ≥ 4.0 x 10^6 CD34+ cells/kg recipient weight collected in one apheresis session.

9.6.3 Secondary Endpoint: Clinically adequate allograft overall

This secondary endpoint is defined as achieving a graft that contains ≥ 2.0 x 10^6 CD34+ cells/kg recipient weight collected across all apheresis sessions.

9.6.4 Secondary Endpoint: Assessment of AE in Donors

Assessment of AE in donors will be done during the infusion and 30 minutes (±10 minutes), 60 minutes (±10 minutes) after the administration of plerixafor and 30 minutes (±10 minutes), 60 minutes (±10 minutes, 120 minutes (±20 minutes), and 240 minutes (±20 minutes) following start of MGTA-145 infusion. In addition to monitoring the donor on the days of collection, donors will be contacted at Week 1, Month 1, and Month 6 to assess the donor's medical condition.

Back pain is an AE of special interest, and information on the date and time of onset, date and time of resolution, concomitant medications and supportive care used to treat the back pain, action taken with study drug, peak severity of the pain on a 0-10 numeric rating scale, relationship to study drug will be assessed and documented in Medidata Rave® EDC application.

9.6.5 Secondary Endpoint: Assessment of AEs related to Allograft

Assessment of AEs related to the allograft will include measurement of the recipient's blood pressure, pulse, respiration rate and temperature one hour prior to the allograft infusion and then approximately 15 minutes, 30 minutes, 1 hour, 2 hours, and 4 hours post infusion.

9.6.6 Secondary Endpoint: Neutrophil Recovery

Time to neutrophil recovery is measured by determining the first of 3 consecutive daily measurements of neutrophil count ≥ 0.5 x10^9/L following conditioning regimen induced nadir. Although unlikely, recipients who do not experience a drop in the neutrophil count < 0.5 x10^9/L will not be evaluable for neutrophil recovery but will be evaluable for graft failure based on the degree of donor cell chimerism at Day +28.

9.6.7 Secondary Endpoint: Platelet Recovery

Platelet recovery is defined as the first day when the platelet count is ≥ 20 × 10^9/L measured by at least 3 consecutive laboratory values that show that level was achieved and maintained. The recipient should not have any platelet transfusions in the 7 days prior to the date selected for achieving ≥20 × 10^9/L and the date should be the first of 3 consecutive lab values tested on different days.

9.6.8 Secondary Endpoint: Graft Failure

Primary graft failure is defined as failure to experience neutrophil recovery by Day +28 following a conditioning regimen induced neutrophil nadir < 0.5 x10^9/L. For recipients not experiencing a fall in the neutrophil count to < 0.5 x10^9/L following conditioning, graft failure will be defined as < 5% donor cell chimerism in the myeloid and CD3+ cell compartments by Day +28. Secondary graft failure will be defined as a fall in the neutrophil count after primary engraftment to < 0.5 x10^9/L sustained for more than three days that cannot be attributed to other causes such as drugs, infection, GVHD, etc., is not

responsive to G-CSF or GM-CSF, and is associated with a fall in donor chimerism to < 5%. Fall in donor chimerism to less than 5% following primary engraftment will also be considered secondary graft failure even in the absence of a fall in the peripheral blood counts.

9.6.9 Secondary Endpoint: Acute GVHD

Mount Sinai Acute GVHD International Consortium (MAGIC) clinical criteria (see Appendix C) and histological grading of skin, liver or gastrointestinal pathology and confidence levels where possible will be used to establish and grade acute GVHD. In the first 100 days after transplantation recipients will be assessed by a transplant physician or designee (e.g. mid-level provider) for the development of acute GVHD approximately weekly.

9.6.10 Secondary Endpoint: Chronic GVHD

Chronic GVHD will be diagnosed and graded according to the NIH consensus criteria (Appendix D) and treated with standard or experimental immunosuppressive therapy as deemed appropriate by the transplant center. Recipients will be assessed for chronic GVHD at Days 100, 180, and 365, and more frequently if clinically indicated.

9.6.11 Secondary Endpoint: Treatment-Related Mortality (TRM)

TRM is defined as death in recipients without relapse or progression of their disease. Non-medical, accidental causes of death, e.g. natural disasters, are not considered TRM.

9.6.12 Secondary Endpoint: Overall Survival

Survival will be measured by assessing if the recipient remains alive by visual observation or telephone call. For recipients lost to follow-up, public means of assessing survival may be employed such as the National Death Index.

9.6.13 Secondary Endpoint: Determination of Relapse or Disease Progression

Disease relapse occurs in subjects who entered HSCT in complete remission (CR); progression occurs in those with existing disease at transplant who meet criteria for progressive disease post-HSCT. A recipient will be considered relapsed when there is a recurrence of the original malignant disease after transplantation. This will be determined locally by tests and procedures in place at each participating institution. Date of relapse/progression is defined as the date at which the first observation of hematologic, radiographic, or cytogenetic changes which herald progression/relapse is made. See Appendix E for definitions.

9.6.14 Secondary Endpoint: Progression-Free Survival

Death or relapse/disease progression will be an event, and the time to the event will be determined as the time from transplant to the first event. Patients alive and relapse/progression-free will be censored at last contact.

9.6.15 Exploratory Endpoint: Graft composition

Graft composition will be defined phenotypically by molecular cell markers to stratify leukocyte subsets.

9.6.16 Exploratory Endpoint: Colony Formation Assay

Colony formation assay is defined as number of functional progenitor cells that form colonies in methylcellulose.

9.6.17 Exploratory Endpoint: Chimerism

Chimerism is defined as leukocyte subset percentages that are donor vs. recipient over time.

9.6.18 Exploratory Endpoint: Immune Reconstitution

Immune reconstitution is defined as counts of leukocyte subsets over time, with respect to normal ranges.

9.6.19 Exploratory Endpoint: CMV Reactivation

CMV reactivation will be defined as a positive test for CMV viremia as determined by an antigenemia assay or quantitative PCR (whichever is in use at each individual institution) that results in the administration of antiviral treatment directed against CMV.

9.6.20 Exploratory Endpoint: MGTA-145 PK

A validated assay will be used to determine MGTA-145 plasma concentrations. The exact date and time (hours and minutes) of the sampling time and infusion start and end times will be recorded.

9.6.21 Exploratory Endpoint: Immunogenicity

A validated assay to determine the formation of ADA will be used.

9.6.22 Exploratory Endpoint: Donor Experience

Donor survey assessments are described in more detail in Section 9.7.

9.7 Donor Survey Assessments

The CIBMTR Survey Research Group (SRG) centrally administers all donor survey assessments. At the time a donor consents to participate in the study, the SRG is notified and then adds that subject to CIBMTR's electronic Patient Reported Outcomes (ePRO) system for data collection tracking. Contact information for unrelated donor subjects is accessed in NMDP databases. Contact information for related donor subjects will be obtained from transplant centers and maintained in a confidential manner.

The SRG will contact the donor by phone to confirm contact information, remind them of survey assessment time points and confirm how they want to receive surveys going forward (paper or electronic). The same method of survey collection (paper or electronic) will be used for each Donor throughout the study.

Up to 14 days prior to Day 1, the SRG will contact the donor to administer the baseline survey assessments.

For the Day 1 donor survey assessments, donors will be asked to complete the surveys anytime from 60 minutes after the apheresis process is completed until the end of that day (e.g., midnight). Unique links and an email template for electronic survey administration and PDFs of paper versions of the survey will be provided by SRG to HSC collection centers, if needed. Day 1 survey assessments will be repeated if there is a second day of collection. HSC collection center staff will securely email or fax completed paper surveys to SRG for data entry, as applicable.

The SRG will contact the donor via email, phone and/or mail to collect donor survey assessments at Day 3-4 and Month 1. The SRG will follow-up with non-responders to minimize missing surveys.

Table 9.7: Schedule of Donor Survey Assessments

Survey[1]	Items	Minutes to complete	Baseline Day -14 to Day 0	Post-treatment Day 1[2, 3]	Day 3-4[4]	Month 1 Day 28 (+/-7)
Brief Pain Inventory	15	5	X	X	X	X
PROMIS Fatigue	8	1-2	X	X	X	X
PROMIS (Gastrointestinal, Diarrhea)	6	1-2	X	X	X	X
PROMIS Phys. Function	10	1-2	X	X	X	X
PROMIS Anxiety	4	1-2	X	X		X
PROMIS Depression	4	1-2	X	X		X
PROMIS Sleep disturbance	4	1-2	X	X	X	X
EQ-5D	5	1	X	X	X	X
Work Productivity and Activity Impairment	6	1			X	
Healthcare Resource Use (HRU) utilization	6	1-2			X	
Donor Experience	6	1-2				X
Total items			*46-86*	*46-86*	*50-74*	*52-92*
Total minutes			*12-18*	*12-18*	*13-17*	*14-21*

1- To be completed in the order listed
2- Repeat if 2 days of mobilization and donation
3- To be completed from 60 minutes after apheresis is completed until the end of that day (e.g., midnight)
4- 72-96 hours after last donation

9.7.1 Brief Pain Inventory

The 15-item Brief Pain Inventory (BPI) assesses severity of pain and its impact on functioning. The BPI will be included on the donor assessment survey at baseline, post-treatment (Day 1), Day 3-4, and Day 28.

9.7.2 PROMIS domains

Six PROMIS domains – Fatigue, Gastrointestinal (Diarrhea), Sleep disturbance, Physical function, Anxiety and Depression - will be used to measure detailed functioning and symptom burden for donors. They will be evaluated at Baseline, post-treatment (Day 1), Day 3-4 and Day 28. Note: Anxiety and Depression will not be collected at Day 3-4.

When delivered on paper, the domains will be delivered in 8-item (Fatigue), 10-item (Physical Function), 6-item (Gastrointestinal), and 4-item (Anxiety, Depression, Sleep disturbance) short forms. When delivered electronically, most domains will be delivered as Computer Adaptive Tests (CAT), in which the questions a person answers are tailored to that person. Each response is used to further refine the questions a participant receives, and thus the participant's score, for that domain. The PROMIS CAT item banks for a domain typically involve 4-12 items. The first item administered is usually in the middle of the range of function or severity for that domain. After a participant responds, an estimated score is calculated. The PROMIS CAT algorithm then selects the best item in the item bank for refining the estimated score and recalculates the participant's score as they continue responding. The PROMIS CAT continues to administer items until a specified level of measurement precision is reached, or the maximum number of 12 items per measure have been administered. Studies have shown that the average number of items delivered in a CAT domain is 5-8.[55] The Gastrointestinal domain is not available in CAT format.

The Gastrointestinal, Fatigue and Sleep Disturbance domains have a 7-day recall period. At the 3-4 day post-treatment time point, these domains will be delivered as short forms, and modified to a 24-hour recall period.

9.7.3 EQ-5D

The EQ-5D is a 5-domain questionnaire measuring mobility, self-care, usual activities, pain/discomfort and anxiety/depression. This questionnaire will be used to measure donors' overall quality of life at baseline, post-treatment (Day 1), Day 3-4 and Day 28.

9.7.4 Work Productivity and Activity Impairment (WPAI)

The 6-item Work Productivity and Activity Impairment (WPAI) Questionnaire measures work productivity and activity impairment during a 7-day recall period. It yields four scores: absenteeism (proportion of work hours missed), presenteeism (degree that health is affected productivity while working), overall work impairment (linear combination of absenteeism and presenteeism), and activity impairment (degree to which health is affected regular activities). The WPAI will be collected at Day 3-4.

9.7.5 Healthcare Resource Use (HRU)

A donor survey assessment will include a questionnaire of healthcare resource use at Day 3-4 to capture healthcare resources utilized.

9.7.6 Donor Experience

A donor experience questionnaire that asks about time and travel burden and overall satisfaction with the donation experience will be collected at Day 28. This questionnaire will be used to understand travel burden and donation satisfaction.

9.8 Adverse Events and Serious Adverse Events

9.8.1 Definition of Adverse Events (AE)

An adverse event (AE) is any untoward medical occurrence regardless of causality assessment. An adverse event can be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom, syndrome or disease associated with or occurring during the use of an investigational product whether or not considered related to the investigational product.

Medical conditions present at screening (i.e., before the study treatment is administered) are not AEs. These medical conditions should be adequately documented on the subject study chart and in Medidata Rave® EDC application as Medical History. However, medical conditions present at baseline that worsen in intensity or frequency during the treatment or post treatment periods should be considered and recorded as AEs in the Medidata Rave® EDC application.

For Donors, all AEs and SAEs will be collected beginning from the signing of the informed consent form. AEs will then be collected through 72 hours post infusion of MGTA-145 and SAEs will be collected through the 6-month follow-up time point as outlined in the schedule of assessments.

For Recipients, all SAEs and all related AEs, will be collected from Day 0 through the 1-year follow-up time point as outlined in the schedule of assessments.

9.8.2 Definition of Serious Adverse Events (SAE)

A **serious adverse event (SAE)** is any medical occurrence at any dose that meets the following criteria:

1. Death.
2. Life-threatening situation.
3. In patient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
5. Congenital anomaly/birth defect.
6. A significant medical condition which, without urgent medical intervention, would lead to one of the above outcomes.

Clarification on SAEs:

- All deaths, regardless of cause, must be reported for subjects on study and for deaths occurring within 30 days of last study evaluation, whichever is longer.
- "Immediately life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs hospitalization, it is an SAE. Note that the hospital prolongation should be clearly and directly attributable to the event.
- "Inpatient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. This does not refer to evaluation in an Emergency Department without admission to the hospital. This does not include planned inpatient hospitalizations for transplant or other elective procedures.
- Subjects undergoing HSCT are frequently hospitalized after the initial transplant hospitalization. Subsequent hospitalizations for reasons that meet criteria for SAEs should be reported as an SAE.

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 and not the individual signs/symptoms.

9.8.3 Classification of an Adverse Event

The site Principal Investigator will assess each AE for duration, severity, seriousness, and relatedness of the event to the investigational products.

9.8.3.1 Severity of Event

AEs will be reported using event terms and grading for severity per the CTCAEv5.0. The CTCAE includes a grading (severity) scale for each AE term:

Grade

- 0 – No AE or within normal limits
- 1 – Mild AE
- 2 – Moderate AE
- 3 – Severe AE
- 4 – Life-threatening or disabling AE
- 5 – Fatal AE

9.8.3.2 Relationship to Study Product

Attribution of the event to the investigational product may be characterized as follows:

- Definite – The AE is **clearly related** to the study procedure/treatment(s).
- Probable – The AE is **likely related** to the study procedure/treatment(s).
    - The AE is not likely to be caused by the subject's underlying medical condition or other concomitant therapy, and the nature of the AE or the temporal relationship between the onset of the AE and study procedure/treatment administration lead the investigator to believe that there is a reasonable chance of causal relationship.
- Possible – The AE **may be related** to the study procedure/treatment(s).
    - The AE could be attributed to the subject's underlying medical condition or other concomitant therapy, but the nature of the AE or the temporal relationship between the onset of the AE and study procedure/treatment administration lead the investigator to believe that there could be a causal relationship.
- Unlikely – The AE is **doubtfully related** to the study procedure/treatment(s).
- Unrelated – The AE is **clearly NOT related** to the study procedure/treatment(s).
    - The AE is most plausibly explained by the subject's underlying medical condition or other concomitant therapy, or the AE has no plausible biological relationship to study procedure/treatment.

For reporting purposes, an AE should be regarded as definitely or probably related to the regimen if the investigator believes that at least one of following criteria are met:

- There is a clinically plausible time sequence between onset of the AE and the administration of the study treatment;
- There is a biologically plausible mechanism for the treatment causing or contributing to the AE;
- The AE cannot be attributed solely to concurrent/underlying illness, other drugs, or procedures

9.8.3.3 Expectedness

- **Expected Adverse Events** are those listed in the Reference Safety Information of the Investigators Brochure for MGTA-145 or in the Package Insert for Plerixafor.
- **Unexpected Adverse Events** are those events the nature of which, severity, or frequency are not consistent with the known or foreseeable risk of AEs associated with the research procedures described in the protocol-related documents. Adverse events that are reflective of the patient's pre-existing condition need not be reported.

9.8.4 Time Period and Frequency for Adverse Event Assessment and Follow-Up

Safety events for donors and recipients will be reported and collected as indicated in Table 9.8.

Table 9.8: Reporting Adverse Events

Subject	Category	Severity Grade	Relatedness	Reporting Timelines	Study Site Reporting Requirement
Donor	SAE	All grades	All attributions	From time of informed consent through 6-months post mobilization	Within 24 hours of learning of the event; Site is to report to Sponsor using SAE form[1]
	AE	≥ Grade 3 AEs	All attributions	From time of informed consent through 72 hours post mobilization	Within 24 hours of learning of the event; Site is to enter AE in Medidata Rave® EDC application
	AE	Grade 1, Grade 2	All attributions	From time of informed consent through 72 hours post mobilization	Site is to enter AE in Medidata Rave® EDC application within standard timeline
Recipient	SAE	All grades	All attributions	From Day 0 through 1-year post-transplant	Within 24 hours of learning of the event; Site is to report to Sponsor using SAE form[1]
	AE	All grades	Possible, Probable, or Definite[2]	From Day 0 through 1-year post-transplant	Site is to enter AE in Medidata Rave® EDC application within standard timeline

[1]Submit death summaries and/or autopsy reports when SAE is Fatal along with the SAE form, which should include potential contributing causes of death; AE form should include potential contributing causes of death. Study site must also complete all follow up forms through date of death, and study exit form.

[2]AEs that are attributed as Unlikely or Unrelated to study product do not need to be reported.

All treatment related SAEs or AEs and Adverse Events of Special Interest (AESIs) should be followed until resolution of the event, death, or until the investigator concludes that the event is stable with no further improvement anticipated. Any SAE occurring after the reporting period must be promptly reported if a causal relationship to the study drugs is suspected.

The CIBMTR Medical Monitor will be notified by the Medidata Rave® EDC application if any CTCAE grade 3 or greater AE believed to be at least possibly related to plerixafor or MGTA-145 is observed in any of the donors.

The CIBMTR Medical Monitor will review reported AEs, GVHD, infection, and primary graft failure events on a weekly basis to assess whether any safety monitoring rules have been met that should be referred to the DSMB (See Section 8.2).

9.8.5 Adverse Event Reporting

AEs occurring in donors and recipients will be reported using event terms and grading for severity per the CTCAE v5.0 (See Appendix G).

All SAEs, regardless of relationship to study treatment, must be reported to the Sponsor within 24 hours of the Investigator becoming aware of the event. Initial and Follow up SAE notification should be made by emailing or faxing the SAE report form to the email or fax number provided on the SAE report form.

The Sponsor is responsible for submitting reports of SAEs associated with the use of the study drugs to the appropriate Regulatory Authority (i.e., US Food and Drug Administration) and Investigators in accordance with applicable regulations and guidelines.

It is the responsibility of the Investigator to notify the IRB of all SAEs that occur at his or her site. Investigators will be notified of all Suspected Unexpected Serious Adverse Reactions (SUSARs 7/15 Day Safety Reports) that occur during any clinical studies that are using the investigative compound. Each site is responsible for notifying their IRB of these additional SUSARs in accordance with local regulations.

9.8.6 Adverse Events of Special Interest

An **Adverse Event of Special Interest (AESI)** is a category of adverse event specific to this trial. Back pain occurring within 24 hours of administration of MGTA-145, regardless of severity or relationship to study drug, will be captured as an AESI. The location, severity based on CTCAE v5.0, time of onset, duration of back pain, relationship to study drug, action taken with study drug, outcome, and any treatment administered will be captured in the Medidata Rave® EDC application.

9.8.7 Reporting of Pregnancy

All donors must agree to an effective means of birth control while on study treatment and for at least 3 months following plerixafor and MGTA-145 treatment (including both female subjects of childbearing potential and male subjects with partners of childbearing potential). All recipients must agree to an effective means of birth control for at least 3 months following PBSC infusion (including both female subjects of childbearing potential and male subjects with partners of childbearing potential).

Female subjects of childbearing potential are defined as women who have not undergone hysterectomy or bilateral oophorectomy or are not naturally postmenopausal (defined as ≥ 12 consecutive months without menstrual bleeding). Effective birth control includes: (a) vasectomy or vasectomized partner (b) hormonal contraception (for example, birth control pills, intravaginal birth control, transdermal birth control injectable birth control or implantable birth control) or an intrauterine device plus one barrier method; or (c) two barrier methods. Effective barrier methods are male and female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm). All male subjects will refrain from sperm donation from the time of signing this consent form until 3 months after treatment with MGTA-145 and plerixafor (Donors) or until 3 months after PBSC infusion (Recipients). For subjects using a hormonal contraceptive method, information about any interaction of plerixafor or MGTA-145 with hormonal contraceptives is not known.

During the study, all women of childbearing potential and female partners of male subjects should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g. missed or late menstrual cycle). If a pregnancy occurs, the pregnant woman should be referred to an obstetrician/ gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The Pregnancy must be reported to the Sponsor within 24 hours of the Investigator’s knowledge of the pregnancy using a Pregnancy Report Form.

The Investigator will follow the pregnant woman until completion of the pregnancy and must notify the Sponsor of the outcome within 24 hours of the Investigator’s knowledge of the pregnancy outcome using a Pregnancy Outcome Form. This notification includes pregnancies resulting in live, “normal” births.

10 LABORATORY ASSESSEMENTS

The following tables list the laboratory tests that will be performed for the donors and recipients on the study.

Table 10.1 (Donor)

HEMATOLOGY[1]	**CHEMISTRY[1]**
Hemoglobin Hematocrit Erythrocyte Count (Red Blood Cells [RBC]) Mean Cell Volume Leukocytes (White Blood Cells [WBC]) Absolute Counts Of: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils • Platelets	Serum Creatinine
OTHER[1]	**URINALYSIS[1]**
PT/PTT	Microscopic evaluation
Serum pregnancy test	
Infectious disease markers	**EXPLORATORY[2]**
ABO/Rh Typing	PK
Chimerism analysis	ADA
Flow cytometric analysis for CD34+ cells[3]	Colony Forming Unit
	Graft Immunophenotyping

1- Samples sent to local laboratory for analysis; the hematology samples collected at Month 1 may be analyzed at a laboratory coordinated by CIBMTR staff
2- Samples sent to central laboratory for analysis
3- Samples sent to local laboratory and central laboratory for analysis

Table 10.2 (Recipient)

HEMATOLOGY[1]	**CHEMISTRY[1]**
Hemoglobin Hematocrit Erythrocyte Count (Red Blood Cells [RBC]) Mean Cell Volume Leukocytes (White Blood Cells [WBC]) Absolute Counts Of: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils • Platelets Leukoblasts	Serum Creatinine Aspartate Aminotransferase (AST) Alanine Aminotransferase (ALT) Lactate Dehydrogenase (LDH) Total Bilirubin
OTHER[1]	**URINALYSIS[1]**
Serum pregnancy test	Microscopic evaluation
Infectious disease markers	
ABO/Rh Typing	**EXPLORATORY[2]**
Chimerism analysis	Immune Reconstitution

1- Samples sent to local laboratory for analysis
2- Samples sent to central laboratory for analysis

11 STATISTICAL CONSIDERATIONS

11.1 Statistical Hypotheses

The study is designed as a Phase II, multicenter, prospective trial to evaluate the safety and efficacy of subcutaneous plerixafor and MGTA-145 for the mobilization and transplantation of HLA-matched sibling and matched unrelated donor allografts in recipients with hematological malignancies. This study is designed as a Simon minimax two-stage trial.[56]

The target enrollment is 28 donors receiving at least one dose of the combination regimen of MGTA-145 + plerixafor. The number of recipients may vary if the mobilization is unsuccessful in some donors.

1. Accrual

It is estimated that 18 months of accrual will be necessary to enroll the targeted sample size. The trial will remain open until the last recipient enrolled has been followed for one year.

2. Randomization

There will be no randomization in this study. At enrollment, each center will declare whether or not a recipient is intended to receive a myeloablative regimen.

3. Primary Endpoint

The primary endpoint of this study is the collection of sufficient CD34+ cells using MGTA-145 + plerixafor as the mobilizing agent. A donor is considered successful for this endpoint if ≥ 2.0 x 10^6 CD34+ cells/kg recipient weight are collected in one leukapheresis collection using MGTA-145 + plerixafor.

11.2 Sample Size Determination

The sample size for this study is 28 donors receiving at least one dose of the combination regimen of MGTA-145 + plerixafor. It is expected that 90% of donors treated with MGTA-145 + plerixafor will mobilize ≥ 2.0 x 10^6 CD34+ cells/kg within one leukapheresis collection. MGTA-145 + plerixafor is considered an unacceptable mobilizing agent if fewer than 70% of donors achieve this cell-dose threshold within one leukapheresis collection.

Using a two-stage Simon minimax design, assuming the true successful collection probability of 90%, 28 donors provide 85% power to reject the probability of successful collection of 70% or lower using a one-sided Type I error α=0.05. This is equivalent to testing the null hypothesis H_0: p ≤ 0.70 against the alternative hypothesis H_1: p > 0.70 with 85% power to contrast a successful collection probability of 90% vs. 70%.

In this design, 13 donors are accrued in the first stage. If 9 or fewer donors mobilize sufficient cells within one leukapheresis collection, the study will be terminated due to inadequate response. Otherwise, accrue 15 additional donors in stage 2. At the end of this stage, if at least 24 out of 28 donors successfully mobilize ≥ 2.0 x 10^6 CD34+ cells/kg within one leukapheresis collections, it will be concluded that MGTA-145 + plerixafor is effective and can be recommended for further investigation.

Table 11.2 shows the power to reject successful collection probability of 70% or lower for other plausible true probability of successful collection using the same design.

True probability of successful collection (p1)	Power
0.85	58%
0.90	85%
0.95	99%

Table 11.2 Power and Operating Characteristics for Plausible Combinations of Primary Endpoint

11.2.1 Planned Interim Analyses

There will be no interim analysis for efficacy. Interim analyses for futility will be induced by the two-stage design as described in Section 11.2. Safety monitoring is described in Section 8.2.

11.3 Populations for Analyses

- Donor treated Population: Includes all donors receiving any exposure to both parts of the combination regimen of MGTA-145 + plerixafor. This population will be used for the primary donor efficacy analysis and for safety analyses of the donor.
- Donor Per Protocol Population: Includes all donors receiving both products of the combination regimen at the right doses and who meet the requirement of the apheresis volume collected. Donors who have major protocol deviations that impact the primary or secondary objectives of the study will be excluded from this population. This population will be used for a per protocol analysis of the donor outcomes.
- Plerixafor-only Population: Includes all donors receiving exposure to plerixafor and did not receive any MGTA-145. This population will be followed for safety purposes.
- Recipient Analysis Population: Includes all enrolled subjects receiving a MGTA-145 + plerixafor-mobilized allograft. This will be used for the primary analysis of the recipient outcomes
- Recipient Eligible Analysis Population: Includes all subjects receiving a MGTA-145 + plerixafor-mobilized allograft who continue to meet eligibility requirements at the time of infusion. This will be used for a sensitivity analysis of the recipient outcomes, in the event that more than 10% of the subjects has changed eligibility between enrollment and transplant so that they would no longer be eligible if reassessed.

11.4 Statistical Analyses

11.4.1 General Approach

Counts and percentages will be used to describe categorical variables, while the number of subjects (N), median, mean, standard deviation, and range will be used to summarize continuous variables. Missing data will not be imputed due to the small sample size of this study. Unless otherwise specified, confidence intervals will be done using 95% confidence level, and hypothesis testing will be done using a two-sided 5% significance level. All individual data will be presented in listings.

11.4.2 Baseline Descriptive Statistics

Demographic and baseline characteristics will be summarized for all donors and recipients. Donor characteristics to be examined are: age, gender, weight, race/ethnicity, CMV status. Recipient characteristics to be examined are: age, gender, weight, race/ethnicity, KPS, disease status at transplant, time from diagnosis to transplantation, cytogenetics at diagnosis, conditioning regimen, GVHD prophylaxis, graft source and recipient CMV status.

11.4.3 Analysis of the Primary Efficacy Endpoint(s)

The primary endpoint of this study is the collection of a clinically adequate allograft in one apheresis session. A donor is considered successful for this endpoint if ≥ 2.0 x 10^6 CD34+ cells/kg actual recipient weight are collected in one leukapheresis collection using MGTA-145 + plerixafor.

A test of the null hypothesis that the rate of providing a clinically adequate allograft within one apheresis collection is ≤ 70% will be done using the Simon 2-stage design as described in Section 11.2, with a one-sided type I error of 5%. The proportion of donors who mobilize ≥ 2.0 x 10^6 CD34+ cells/kg actual recipient weight in one leukapheresis collection will be estimated along with a 90% confidence interval for consistency with the one-sided type I error rate of 5%. A 95% confidence interval will also be provided. The primary analysis will use the Donor Treated Population, where donors who do not undergo apheresis will be considered a failure for this endpoint. A secondary analysis of this outcome in the donor per protocol population will also be conducted using similar methods.

11.4.4 Analysis of the Secondary Endpoint(s)

Clinically desirable allograft in one apheresis collection

The proportion of donors who mobilize ≥ 4.0 x 10^6 CD34+ cells/kg actual recipient weight in one leukapheresis collection will be estimated along with both 90% and 95% confidence intervals. The analysis will use the Donor Treated Population, where donors who do not undergo apheresis will be considered a failure for this endpoint. A secondary analysis of this outcome in the donor per protocol population will also be conducted using similar methods.

Clinically adequate allograft overall

The proportion of donors who mobilize ≥ 2.0 x 10^6 CD34+ cells/kg actual recipient weight across all leukapheresis collection will be estimated along with both 90% and 95% confidence intervals. The analysis will use the Donor Treated Population, where donors who do not undergo apheresis will be considered a failure for this endpoint. A secondary analysis of this outcome in the donor per protocol population will also be conducted using similar methods.

Incidence of Donor AEs

Type and severity of AEs experienced at various timepoints during and after infusion of plerixafor and after administration of MGTA-145, during apheresis, and at one week, one, and six months post donation will be tabulated in the donor treated population. Incidence of AEs will be summarized along with both 90% and 95% confidence intervals. Adverse Events of Special Interest (AESI) will also be summarized and detailed in a listing. AEs experienced in the plerixafor only population will also be listed.

Time to Neutrophil Recovery

Incidence of neutrophil recovery will be estimated using the cumulative incidence function treating death and relapse prior to recovery as the competing risk. Probability of neutrophil recovery at Day 28 will be calculated along with both 90% and 95% confidence intervals for the recipient analysis population.

Time to Platelet Recovery

Incidence of platelet recovery will be estimated for the recipient analysis population using the cumulative incidence function treating death prior to platelet recovery as the competing risk. 90% and 95% confidence intervals will be provided.

Primary and Secondary Graft Failure

The frequency and proportion of recipients experiencing graft failure by Day 28 and the proportion of recipients who have engrafted who subsequently experience secondary graft failure will be described with 90% and 95% confidence intervals for the recipient analysis population.

Acute Graft versus Host Disease of Grades 2-4 and 3-4

Incidence of aGVHD will be estimated using the cumulative incidence function treating death prior to aGVHD as the competing risk. The incidence of aGVHD with 90% and 95% confidence intervals will be estimated at Day 100 for the recipient analysis population.

Chronic Graft versus Host Disease

Incidence of cGVHD will be estimated using the cumulative incidence function treating death prior to cGVHD as the competing risk. The incidence of cGVHD with 90% and 95% confidence intervals will be estimated at Day 100, 6 and 12 months for the recipient analysis population.

Treatment Related Mortality (TRM)

The event is death without disease relapse or progression. Incidence of TRM will be estimated using the cumulative incidence function treating relapse/progression as the competing risk. The incidence of TRM with 90% and 95% confidence intervals will be estimated at Day 100 for the recipient analysis population.

Relapse/Progression

The event is relapse or progression. Incidence of relapse/progression in subjects receiving grafts mobilized with MGTA-145 + plerixafor will be estimated using the cumulative incidence function treating death in remission as the competing risk. Estimates and 90% and 95% confidence intervals will be provided at 1 year for the recipient analysis population.

Progression-Free Survival

The event is relapse/progression or death. The time to this event is the time from transplant to relapse/progression, death, loss to follow-up, or end of study whichever comes first. Progression–free survival will be estimated using the Kaplan-Meier estimator for the recipient analysis population. Estimates and 90% and 95% confidence intervals will be provided at 1 year.

Overall Survival

The event is death from any cause. The time to this event is the time from transplant to death, loss to follow-up, or end of study whichever comes first. Overall survival will be estimated using the Kaplan-Meier estimator for the recipient analysis population. Estimates and 90% and 95% confidence intervals will be provided at 1 year.

Incidence of AEs related to the Allograft

Type and severity of AEs experienced by the recipient related to the allograft will be tabulated in the recipient analysis population. Incidence of AEs related to the allograft will be summarized along with the 90% and 95% confidence intervals.

11.4.5 Exploratory Analyses

Donor Chimerism

Donor and host cells will be measured at Day 28, 100, 180 and at one-year post-transplant. The degree of donor chimerism will be summarized at each time point using descriptive statistics. The proportions of recipients with mixed (5-95% donor cells), full (> 95%), or graft rejection (< 5%) will be summarized. This analysis will be conducted in the recipient analysis population.

Colony Formation

Number of functional progenitor cells that form in methylcellulose (defined as total CFU-GM, CFU-GEMM, CFU-E, and BFU-E) will be measured. Data will be summarized using descriptive statistics.

Immunologic Reconstitution

Immune reconstitution assays which will include a quantitation of absolute numbers of CD3+, CD3+CD4+, CD3+CD8+, CD19+ and CD3-CD56+ cells in recipients on Day 28, 100, 180 and at one-year post-transplant. These will be summarized at each time point using descriptive statistics for the recipient analysis population.

Incidence of CMV Reactivation

Incidence of CMV reactivation will be estimated using the cumulative incidence function with death prior to CMV reactivation as the competing risk, in the recipient analysis population.

Cellular Composition of Allografts

The proportions of CD34+, CD3+, CD3+CD8+, CD3+CD4+, CD19+, CD34+C90+CD45RA- and CD3-CD56+ cells in the allografts collected will be summarized using descriptive statistics for grafts mobilized with MGTA-145 + plerixafor.

PK Analysis

Individual Concentration-time data will be listed. Summary statistics of concentration data will be presented at each timepoint. Noncompartmental analyses will not be performed. Data will be analyzed as collected in the donor treated population.

Immunogenicity

The number and percentage of positive ADAs will be presented at Day 28 for the donor treated population.

Donor Survey Assessments

Donor survey assessments (BPI, PROMIS and EQ-5D) will be described longitudinally using means and SDs. Linear mixed models will be used to describe the trajectory of recovery over time. The WPAI, HRU and donor experience surveys will be presented descriptively.

12 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

12.1 Regulatory, Ethical, and Study oversight Considerations

12.1.1 Institutional Review Board Approval

Prior to gaining Approval-to-Enroll status, the investigational site will provide to the Sponsor/Sponsor representative documentation verifying of IRB approval.

A copy of the written IRB approval and Informed Consent Form (ICF), must be received by the Sponsor before recruitment of subjects into the study and shipment of investigational product.

Annual IRB approval and renewals will be obtained throughout the duration of the study as required by local/central IRB requirements. Copies of the Investigator's reports and the IRB continuance of approval must be provided to the sponsor.

12.1.1.1 Recipients and Related Donors

The IRB of Record for each site (whether sites are relying on a local IRB or central IRB, such as the National Marrow Donor Program IRB) will be responsible for the review and continuing oversight of protocol procedures that relate to recipient and related donor subjects consented to the study.

12.1.1.2 NMDP Unrelated Donors

The National Marrow Donor Program IRB will have sole responsibility for the review and continuing oversight of protocol procedures that relate only to NMDP unrelated donors, including unrelated donor consent forms. Local IRB's do not hold any jurisdiction over unrelated donors obtained through the

NMDP, as NMDP Donor Centers participating in this protocol rely on NMDP IRB for this research oversight.

12.1.2 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Subject participation is voluntary. Informed Consent is required from each subject or his/her legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to any study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, any applicable national regulations, or Regulatory authority body, as applicable. The ICF must be approved by the IRB of Record.

The ICF must be in a language understandable to the subject. Privacy language for compliance with Health Insurance Portability and Accountability Act (HIPAA) regulations shall be included in the body of the form or as a separate form, as applicable.

12.1.2.1 Consent Procedures and Documentation

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- Be conducted by the site Principal Investigator or designee authorized/delegated to conduct the process, or a Be The Match Donor Services representative,
- Include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- Avoid any coercion of or undue influence of subjects to participate,
- Not waive or appear to waive subject's legal rights,
- Use native language that is non-technical and understandable to the subject or his/her legal representative,
- Provide ample time for the subject to consider participation and ask questions if necessary,
- Ensure important new information is provided to new and existing subjects throughout the clinical study.

Consent forms describing in detail the study procedures and possible risks and benefits of the research are given to the subject. The investigator will explain the research study to the subject and answer any questions that may arise, and the subject will sign the informed consent document prior to any procedures being done specifically for the study. The subject may withdraw consent at any time throughout the course of the trial, and a copy of the informed consent document will be given to the subject. The rights and welfare of the subject will be protected by emphasizing that the quality of medical care will not be adversely affected by declining to participate in this study. A copy of the signed consent form and documentation of the informed consent discussion will be filed in the subject's medical record.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in site Principal Investigator, administrative changes, or following annual review by the IRB. The new version of the ICF must be approved by the IRB. The IRB will determine the subject population to be re-consented.

12.1.3 Study Discontinuation and Closure

The study may be discontinued early by the Sponsor for valid scientific or administrative reasons and reasons related to the protection of subjects. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigators, IRBs and regulatory authorities, as applicable. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule.

12.1.4 Investigator Responsibilities

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the clinical study agreement/rider, applicable sections of 21 CFR, the clinical study protocol, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following:

- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship) every adverse event as applicable per the protocol.
- Allow the sponsor/sponsor representative to perform monitoring and auditing activities and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the IRB when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and IRB requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the ICF.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.

12.1.5 Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

12.1.6 Confidentiality and Privacy

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party, without prior written approval of the sponsor.

The study monitor, or other authorized representatives of the sponsor, may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

12.1.7 Future use of Stored Specimens and Data

Donors will be provided with an optional ICF for an additional blood sample to be obtained during the Day 28 blood draw. This blood sample will be stored and used for future medical and/or scientific research projects that are outside of the current study purpose and objectives.

12.1.8 Safety Oversight

12.1.8.1 Data Safety Monitoring Board

Safety oversight will be under the direction of the RCI BMT DSMB composed of individuals with the appropriate expertise. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. All DSMB recommendations will be communicated to the appropriate representatives of Magenta and NMDP as defined in the charter.

The DSMB will meet per requirements of its charter to assess safety data and determine whether any subject safety problems necessitate protocol modifications or discontinuation of the trial. The DSMB will also meet on an *ad hoc* basis if safety monitoring rules are met (see Section 8.2) or if unexpected safety events occur that may necessitate study suspension or closure. The DSMB will determine if additional review is required and make recommendations to the study team concerning continuation of the study. The DSMB will discontinue the review of outcomes when this protocol is closed to accrual.

12.1.9 Clinical Monitoring

The Investigator will permit study-related on-site, remote, and/or centralized monitoring visits by representatives of CIBMTR or designees, and regulatory inspection(s) to ensure proper conduct of the study and compliance with the protocol. Access will be provided to the facilities where the study took place, to source documents, to data collection forms, and to all other study documents. It is important that the site Principal Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

The monitor should have access to laboratory test reports and other subject records needed to verify the entries in the Medidata Rave® EDC application. The investigator [or designee] agrees to cooperate with

the monitor to ensure that any problems detected in the course of these monitoring visits are resolved. Details regarding monitoring can be found in the study monitoring plan.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

12.1.10 Data Handling and Record Keeping

12.1.10.1 Data Collection and Management Responsibilities

Database backups are performed regularly.

Protocol-specific study data will be collected within Medidata Rave® EDC application. Medidata Rave® software and database have been designed to meet regulatory compliance (21 CFR Part 11) as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. All changes made to the clinical data will be captured in an electronic audit trail and available for review by the sponsor or its representative. For each subject enrolled, appropriate electronic case report forms (eCRFs) will be completed. These include study-specific eCRFs within the study specific electronic data capture system. The Investigator or delegate provides his/her electronic signature on the appropriate eCRFs in compliance with local regulations. Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents.

The data collection forms for the subjects enrolled on this study include the standard CIBMTR data collection forms in the FormsNet3 Recipient module, and study-specific CIBMTR data collection forms in the study specific electronic data capture system, Medidata Rave. Monitoring for this study is limited to source document verification (SDV) of the data within Medidata Rave.

Many important data elements for the study are collected on the standard reporting forms within FormsNet3 and therefore timely and accurate completion of these forms is essential. Centers must continue to do standard CIBMTR follow-up reporting on these subjects beyond the study time point of 6 months post-HSCT, per CIBMTR reporting requirements. Recipient subjects will be approached for co-enrollment to the CIBMTR Outcomes Database protocol. If consented, CIBMTR comprehensive report forms (CRF-track) will be required in FormsNet3.

12.1.10.2 Study Records Retention

The Investigator must maintain, at the investigative site, all essential study documentation relating to the study for a period of 3 years after the last marketing application approval or, if not approved, 3 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.

The Principal Investigator or his/her designee will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and Magenta must receive written notification of this custodial change. Sites are required to inform Magenta in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

12.1.11 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or ICH GCP. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions may be developed by the site and implemented promptly.

These practices are consistent with Good Clinical Practice (GCP ICH E6) Sections:

- Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- Quality Assurance and Quality Control, section 5.1.1
- Noncompliance, sections 5.20.1, and 5.20.2

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An Investigator shall notify the sponsor and the reviewing IRB (per local requirements) of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency and those deviations which affect the scientific integrity of the clinical investigation.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions will be put into place by the sponsor.

12.1.12 Publication and Data Sharing Policy

Following completion of the study, the study team may publish research results in a scientific journal with any interim analysis presented as experience is gained. The International Committee of Medical Journal Editors (ICMJE) member journals has adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as www.ClinicalTrials.gov, which is sponsored by the National Library of Medicine.

12.1.13 Conflict of Interest Policy

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the RCI BMT has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

12.2 Additional Considerations

12.2.1 Donor Product Qualification

Any processes covered by the FDA's 21 CFR part 1271, including donor qualification and good tissue practice, are the responsibility of the transplant center, and are out of the scope for this study.

12.3 Publication Policy

Magenta assures that the key design elements of this protocol will be posted in a publicly accessible database such as www.ClinicalTrials.gov. In addition, upon study completion and finalization of the study report, the results of this study (regardless of study outcomes) will be either submitted for publication and/or posted in a publicly accessible database of clinical study results. Magenta requires disclosures of its involvements as a sponsor or financial supporter in any publication or presentation relating to a Magenta study or its results.

12.4 Abbreviations

ABO/RH	Blood type
ADA	Anti-drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
aGVHD	Acute graft versus host disease
ALL	Acute Lymphoblastic Leukemia
ALT	Alanine aminotransferase
AML	Acute Myelogenous Leukemia
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase
AUC	Area under the curve
BM	Bone Marrow
CBC	Complete blood count
CFR	Code of Federal Regulations
CIBMTR	Center for International Blood and Marrow Transplant Research
CRCL	Creatinine Clearance
CMV	Cytomegalovirus
CNS	Central Nervous System
CR	Complete Remission
CTCAE	Common Terminology Criteria for Adverse Events
CVC	Central Venous Catheter
DLCO	Diffusing capacity of the lungs for carbon monoxide
DLI	Donor Cellular Infusion
DLT	Dose limiting toxicities
DSMB	Data Safety Monitoring Board
EBMT	European Bone Marrow Transplant group
ECG	Electrocardiogram
eCRF	Electronic Case Report Forms
EDC	Electronic Data Capture
FEV1	Forced expiratory volume in first second
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GFR	Glomerular filtration rate
GLP	Good Laboratory Practices
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GMP	Good Manufacturing Practices
GVHD	Graft versus host disease
HCT-CI	Hematopoietic Cell Transplantation-Comorbidity Index
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HLA	Human Leukocyte Antigen
HPC	Hematopoietic Progenitor Cells
HPC(A)	Hematopoietic Progenitor Cell Apheresis
HRU	Healthcare Resource Utilization
HSC	Hematopoietic Stem Cells
HSCT	Hematopoietic Stem Cell Transplantation

HSPC	Hematopoietic Stem and Progenitor Cells
IB	Investigators Brochure
IBMTR	International Blood and Marrow Transplant Registry
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
IVIG	Intravenous Immune Globulin
KPS	Karnofsky performance status
LA	Leukapheresis
LDH	Lactate dehydrogenase
MAC	Myeloablative Conditioning
MDRD	Modification of Diet in Renal Disease
MDS	Myelodysplastic Syndrome
MPB	Mobilized Peripheral Blood
MTD	Maximum tolerated dose
NHL	Non-Hodgkin lymphoma
NMA	Non-myeloablative Conditioning
NMDP	National Marrow Donor Program
PB	Peripheral Blood
PBSC	Peripheral Blood Stem Cells
PK	Pharmacokinetic
PT	Prothrombin Time
PTT	Partial thromboplastin time
RBC	Red blood cell count
RIC	Reduced Intensity Conditioning
SAE	Serious Adverse Event
SOA	Schedule of Activities
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAEs	Treatment emergent adverse events
TNC	Total Nucleated Cell count
TRM	Treatment-Related Mortality
UCB	Umbilical cord blood
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell
WPAI	Work Productivity and Activity Impairment

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14 APPENDICES

A. Karnofsky Performance Scale

KARNOFSKY SCALE, ≥ 16 YEARS
100% – Normal, no complaints, no evidence of disease
90% – Able to carry on normal activity
80% – Normal activity with effort
70% – Cares for self, unable to carry on normal activity or to do active work
60% – Requires occasional assistance but is able to care for most needs
50% – Requires considerable assistance and frequent medical care
40% – Disabled, requires special care and assistance
30% – Severely disabled, hospitalization indicated, although death not imminent
20% – Very sick, hospitalization necessary
10% – Moribund, fatal process progressing rapidly

* Report performance score only as multiples of 10.

B. Hematopoietic Cell Transplant Comorbidity Index (HCT-CI) Scoring

The following table can be used to calculate the HCT-CI as developed by Sorror, *Blood, 2013 Apr 11; 121(15): 2854-2863.*

Comorbidities	**HCT-CI scores**
Arrhythmia	1
Cardiovascular comorbidity	1
Inflammatory bowel disease	1
Diabetes or steroid-induced hyperglycemia	1
Cerebrovascular disease	1
Psychiatric disorder	1
Mild hepatic comorbidity	1
Obesity	1
Infection	1
Rheumatologic comorbidity	2
Peptic ulcer	2
Renal comorbidity	2
Moderate pulmonary comorbidity	2
Prior malignancy	3
Heart valve disease	3
Moderate/severe hepatic comorbidity	3
Severe pulmonary comorbidity	3
	Total score = _____

C. Acute GVHD Grading

The following target organ staging and overall clinical grading criteria should be used when completing acute GVHD assessments, utilizing the Mount Sinai Acute GVHD International Consortium (MAGIC).

Harris AC, Young R, Devine S, et al. International, Multicenter Standardization of Acute Graft-versus-Host Disease Clinical Data Collection: A Report from the Mount Sinai Acute GVHD International Consortium. *Biol Blood Marrow Transplant*. 2016;22(1):4-10. doi:10.1016/j.bbmt.2015.09.001

Target Organ Staging				
Stage	**Skin (active erythema only)**	**Liver (bilirubin)**	**Upper GI**	**Lower GI (stool output/day)[3]**
0	No active (erythematous) GVHD rash	< 2 mg/dl	No or intermittent nausea, vomiting or anorexia	Adult: < 500 ml/day or <3 episodes/day Child: < 10 ml/kg/day or <4 episodes/day
1	Maculopapular rash <25% BSA[1]	2-3 mg/dl[2]	Persistent nausea, vomiting or anorexia[4]	Adult: 500–999 ml/day or 3–4 episodes/day Child: 10–19.9 ml/kg/day or 4–6 episodes/day
2	Maculopapular rash 25-50% BSA[1]	3.1-6 mg/dl[2]	-	Adult: 1000–1500 ml/day or 5–7 episodes/day Child: 20 – 30 ml/kg/day or 7–10 episodes/day
3	Maculopapular rash >50% BSA[1]	6.1-15 mg/dl[2]	-	Adult: >1500 ml/day or >7 episodes/day Child: > 30 ml/kg/day or >10 episodes/day
4	Generalized erythroderma (>50% BSA[1]) plus bullous formation and desquamation >5% BSA[1]	>15 mg/dl[2]	-	Severe abdominal pain with or without ileus, or grossly bloody stool (regardless of stool volume).
Overall Clinical Grade [5]				
0	None	None	None	None
I	Stage 1-2	None	None	None
II	Stage 3	Stage 1	Stage 1	Stage 1
III	—	Stage 2-3	Stage 1	Stage 2-3

IV[6]	Stage 4	Stage 4		Stage 4
Confidence Levels				
	Pathologic evidence	**Clinician assessment**	**Treatment for acute GVHD**	**Comments**
Confirmed	Unequivocal pathologic evidence of GVHD	GVHD is the etiology for symptoms	Not applicable	GVHD is clearly present even if other etiologies may co-exist simultaneously
Probable	Not required	GVHD most likely etiology for symptoms (as evidenced by treatment being provided)	Yes	GVHD is most likely present but other etiologies may also explain the symptoms and there is insufficient evidence to make a confirmed diagnosis
Possible	Not required	GVHD in differential diagnosis (but no treatment is being provided)	No	GVHD may be present, but other etiologies are favored to the degree that GVHD treatment is not initiated
Negative	Unequivocal evidence of a diagnosis other than GVHD (e.g., drug rash)	GVHD is not considered as an explanation for the symptoms	No **and** the symptoms resolve without GVHD treatment	A “negative” biopsy (e.g., normal skin) is not unequivocal evidence of a diagnosis other than GVHD

[1] Use “Rule of Nines” or burn chart to determine extent of rash.
[2] Range given as total bilirubin. Downgrade one stage if an additional cause of elevated bilirubin has been documented.
[3] Downgrade one stage if an additional cause of diarrhea has been documented.
[4] Persistent nausea with or without histologic evidence of GVHD in the stomach or duodenum.
[5] Criteria for grading given as minimum degree of organ involvement required to confer that grade.
[6] Grade IV may also include lesser organ involvement with an extreme decrease in performance status

D. Chronic GVHD Grading

NIH Consensus Criteria will be used for GVHD diagnosis and grading.

Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant*. 2015;21(3):389-401.e1. doi:10.1016/j.bbmt.2014.12.001

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capabl of self-care, >50% of waking hours ou of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† **SCORE % BSA** ☐ *GVHD features to be scored by BSA*: **Check all that apply**: ☐ Maculopapular rash/erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like GVHD	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply**: ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration

Other skin GVHD features (NOT scored by BSA)
Check all that apply:
☐ Hyperpigmentation
☐ Hypopigmentation
☐ Poikiloderma
☐ Severe or generalized pruritus
☐ Hair involvement
☐ Nail involvement
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* ☐ **Yes** ☐ **No** ☐ **Not examined**	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GI Tract ***Check all that apply:*** ☐ Esophageal web/ proximal stricture or ring ☐ Dysphagia ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Weight loss ≥5%* ☐ Failure to thrive	☐ No symptoms	☐ Symptoms without significant weight loss* (<5%)	☐ Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	☐ Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
LIVER	☐ Normal total bilirubin and ALT or AP < 3 x ULN	☐ Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	☐ Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	☐ Elevated total bilirubin > 3 mg/dL
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
GENITAL TRACT (*See Supplemental figure*‡) ☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐ No signs	☐ Mild signs‡ and females with or without discomfort on exam	☐ Moderate signs‡ and may have symptoms with discomfort on exam	☐ Severe signs‡ with or without symptoms
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

☐ Ascites (serositis)___	☐ Myasthenia Gravis___	
☐ Pericardial Effusion___	☐ Peripheral Neuropathy___	☐ Eosinophilia > 500/µl___
☐ Pleural Effusion(s)___	☐ Polymyositis___	☐ Platelets <100,000/µl ___
☐ Nephrotic syndrome___	☐ Weight loss>5%* without GI symptoms ___	☐ Others (specify):_____

Overall GVHD Severity *(Opinion of the evaluator)*	☐ **No GVHD**	☐ **Mild**	☐ **Moderate**	☐ **Severe**

E. Determination of Relapse or Disease Progression

Acute Myelogenous Leukemia (AML) Response Criteria:

Complete Remission (CR)
Hematologic complete remission is defined as meeting all of the following response criteria for at least four weeks.

- < 5% blasts in the bone marrow
- No blasts with Auer rods
- Normal maturation of all cellular components in the bone marrow
- No extramedullary disease (e.g., CNS, soft tissue disease)
- Neutrophils ≥ 1 $x10^9$/L
- Platelets ≥ 100 $x10^9$/L
- Transfusion independent

Complete Remission with Incomplete Hematologic Recovery (CRi)
Hematologic complete remission with incomplete hematologic recovery is defined as meeting all of the following response criteria for at least four weeks:

- < 5% blasts in the bone marrow
- No blasts with Auer rods
- Normal maturation of all cellular components in the bone marrow
- No extramedullary disease (e.g., CNS, soft tissue disease)
- Transfusion independent (Please note, if the physician documents transfusion dependence related to treatment and not the patient's underlying AML, CRi can be reported)

Primary Induction Failure (PIF)
The patient received treatment for AML but **never achieved CR or CRi at anytime**. PIF is not limited by the number of unsuccessful treatments; this disease status only applies to recipients who have *never been in CR or CRi*.

Relapse (REL)
Relapse is defined as the recurrence of disease after CR, meeting one or more of the following criteria:

- ≥ 5% blasts in the marrow or peripheral blood
- Extramedullary disease
- Disease presence determined by a physician upon clinical assessment

No Treatment
The recipient was diagnosed with acute leukemia and never received therapeutic agents; include patients who have received only supportive therapy, including growth factors and/or blood transfusions.

Acute Lymphoblastic Leukemia (ALL) Response Criteria:

Complete Remission (CR)
Hematologic complete remission is defined as meeting all of the following response criteria for at least four weeks.

- < 5% blasts in the bone marrow
- Normal maturation of all cellular components in the bone marrow
- No extramedullary disease (e.g., CNS, soft tissue disease)
- ANC (absolute neutrophil count) ≥ 1 x 10^9/L
- Platelets ≥ 100 x 10^9/L
- Transfusion independent

Complete Remission with Incomplete Hematologic Recovery (CRi)
Hematologic complete remission with incomplete hematologic recovery is defined as meeting all of the following response criteria for at least four weeks:

- < 5% blasts in the bone marrow
- Normal maturation of all cellular components in the bone marrow
- No extramedullary disease (e.g., CNS, soft tissue disease)
- Transfusion independent (Please note, if the physician documents transfusion dependence related to treatment and not the patient's underlying ALL, CRi can be reported)

Primary Induction Failure (PIF)
The patient received treatment for ALL but **never achieved CR or CRi at anytime**. PIF is not limited by the number of unsuccessful treatments; this disease status only applies to recipients who have *never been in CR or CRi*.

Relapse (REL)
Relapse is defined as the recurrence of disease after CR, meeting at least one of the following criteria:

- ≥ 5% blasts in the marrow or peripheral blood
- Extramedullary disease
- Disease presence determined by a physician upon clinical assessment

No Treatment
The recipient was diagnosed with acute leukemia and never received therapeutic agents; include patients who have received only supportive therapy, including growth factors and/or blood transfusions.

Myelodysplastic Syndrome (MDS) Response Criteria

Complete Remission (CR)

Requires all of the following maintained for a minimum of four weeks:

Bone marrow evaluation:

- < 5% myeloblasts with normal maturation of all cell lines

Peripheral blood evaluation:

- Hemoglobin ≥ 11 g/dL untransfused without erythropoietic support
- ANC ≥ 1 x 10^9/L without myeloid growth factor support
- Platelets ≥ 100 x 10^9/L without thrombopoietic support
- 0% blasts in blood

Hematologic Improvement (HI)

Requires one measurement of the following maintained for at least eight weeks without ongoing cytotoxic therapy:

Hematologic improvement – erythropoietic (HI-E):

- Hemoglobin increase of ≥ 1.5 g/dL untransfused
  or
- For RBC transfusions performed for hemoglobin ≤ 9.0: reduction in RBC units transfused in 8 weeks by ≥ 4 units compared to the number of units transfused in the 8 weeks prior to treatment

Hematologic improvement – platelets (HI-P):

- For pre-treatment platelet count of ≥ 20 ×10^9, platelet absolute increase of ≥ 30 ×10^9
- For pre-treatment platelet count of < 20 ×10^9, platelet absolute increase of ≥ 20 ×10^9 and ≥ 100% increase from pre-treatment level

Hematologic improvement – neutrophils (HI-N):

- Neutrophil count increase of ≥ 100% from pre-treatment level and an absolute increase of ≥ 0.5 x 10^9/L

No Response (NR)/Stable Disease (SD)

Does not meet the criteria for at least HI, but no evidence of disease progression to AML

Progression from Hematologic Improvement (Prog from HI)

Requires at least one of the following in the absence of another explanation (e.g., infection, bleeding, ongoing chemotherapy, etc.):

- ≥ 50% reduction from maximum response levels in granulocytes or platelets
- Reduction in hemoglobin by ≥ 1.5 g/dL
- Transfusion dependence

Note: declining donor chimerism does not meet the criteria for progression. If the above criteria for progression have been met, but a hematologic improvement was not previously achieved, status is "No Response (NR) / Stable Disease (SD)."

Relapse from Complete Remission (Rel from CR)
Requires at least one of the following:

- Return to pre-treatment bone marrow blast percentage
- Decrease of ≥ 50% from maximum response levels in granulocytes or platelets
- Transfusion dependence or hemoglobin level ≥ 1.5 g/dL lower than prior to therapy

Note: declining donor chimerism does not meet the criteria for relapse.

Progression to AML

- ≥ 20% blasts in the blood or bone marrow

F. Donor Survey Assessments

Presented here are examples of potential donor survey assessment questions. Not all questions are asked at each donor survey time point. Section 9.7 lists the donor survey assessment domains included at each time point.

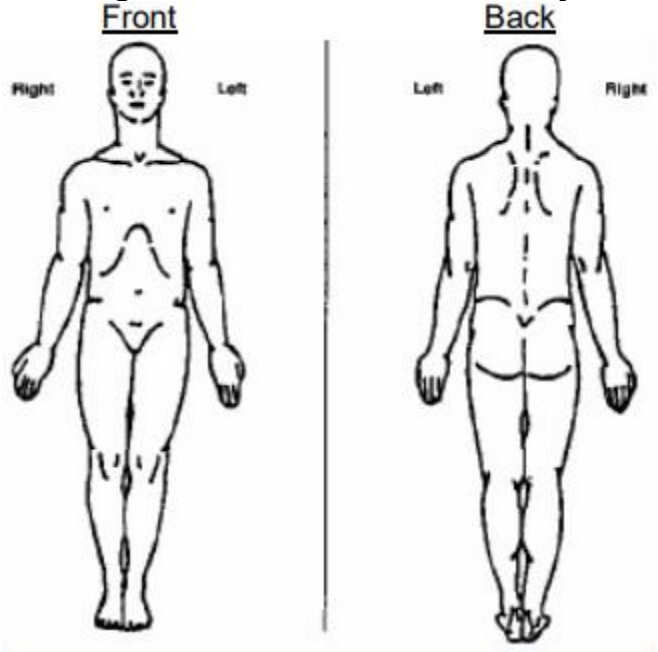
The PROMIS questions presented here represent the short forms that would be included on any paper donor survey assessment. If a donor subject completes their surveys online, the PROMIS questionnaires will be administered via Computer Adaptive Testing, as described in section 9.7.2 of this protocol. In Computer Adaptive Testing, each subject is presented with different questions within each domain, that are tailored to how they feel.

Brief Pain Inventory (Short Form)

Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kind of pains today?

- ☐ Yes
- ☐ No

On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



Please rate your pain by selecting the one number that best describes your pain at its <u>worst</u> in the last 24 hours.

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Please rate your pain by selecting the one number that best describes your pain at its <u>least</u> in the last 24 hours.

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Please rate your pain by selecting the one number that best describes your pain on the <u>average</u>.

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Please rate your pain by selecting the one number that tells how much pain you have <u>right now</u>.

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

What treatments or medications are you receiving for your pain?

_____

_____

_____

In the last 24 hours, how much relief have pain treatments or medications provided? Please select the one percentage that shows how much <u>relief</u> you have received.

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

Select the one number that describes how during the past 24 hours, pain has interfered with your:

General Activity

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

Mood

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

Walking Ability

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

Normal Work (includes both work outside the home and housework)

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

Relations with other people

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

Sleep

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

Enjoyment of life

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

PROMIS Fatigue

At Day 3-4 time point, the recall period of these questions will be changed from 7 days to 1 day.

Please respond to each question or statement by marking one box per row

During the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
I feel fatigued	☐	☐	☐	☐	☐
I have trouble starting things because I am tired	☐	☐	☐	☐	☐

Please respond to each question or statement by marking one box per row

In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
How run-down did you feel on average?	☐	☐	☐	☐	☐
How fatigued were you on average?	☐	☐	☐	☐	☐
How much were you bothered by your fatigue on average?	☐	☐	☐	☐	☐
To what degree did your fatigue interfere with your physical functioning?	☐	☐	☐	☐	☐

Please respond to each question or statement by marking one box per row

In the past 7 days…	Never	Rarely	Sometimes	Often	Always
How often did you have to push yourself to get things done because of your fatigue?	☐	☐	☐	☐	☐
How often did you have trouble finishing things because of your fatigue?	☐	☐	☐	☐	☐

PROMIS Gastrointestinal (Diarrhea)
Asked at Baseline and Day 28

In the past 7 days, how many days did you have loose or watery stools?

If 1 or more days…

How much did having loose or watery stools interfere with your day-to-day activities?

How much did having loose or watery stools bother you?

In the past 7 days, how often did you feel like you needed to empty your bowels right away or else you would have an accident?

If 1 or more days…

How much did feeling you needed to empty your bowels right away interfere with your day-to-day activities?

How much did feeling you needed to empty your bowels right away bother you?

Asked at Day 1 and Day 3-4

In the past 24 hours, did you have loose or watery stools?

☐ No
☐ Yes

If yes…

How much did having loose or watery stools interfere with your day-to-day activities?
How much did having loose or watery stools bother you?

In the past 24 hours, did you feel like you needed to empty your bowels right away or else you would have an accident?

☐ No
☐ Yes

If Yes…

How much did feeling you needed to empty your bowels right away interfere with your day-to-day activities?

PROMIS Physical Function

Please respond to each question or statement by marking one box per row

	Not at all	Very little	Somewhat	Quite a lot	Cannot do
Does your health now limit you in doing vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?	☐	☐	☐	☐	☐
Does your health now limit you in walking more than a mile (1.6 km)?	☐	☐	☐	☐	☐
Does your health now limit you in climbing one flight of stairs?	☐	☐	☐	☐	☐
Does your health now limit you in lifting or carrying groceries?	☐	☐	☐	☐	☐
Does your health now limit you in bending, kneeling, or stooping?	☐	☐	☐	☐	☐

Please respond to each question or statement by marking one box per row

	Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Cannot do
Are you able to do chores such as vacuuming or yard work?	☐	☐	☐	☐	☐
Are you able to dress yourself, including tying shoelaces and buttoning your clothes?	☐	☐	☐	☐	☐
Are you able to shampoo your hair?	☐	☐	☐	☐	☐
Are you able to wash and dry your body?	☐	☐	☐	☐	☐
Are you able to sit on and get up from the toilet?	☐	☐	☐	☐	☐

PROMIS Anxiety

Please respond to each question or statement by marking one box per row

In the past 7 days…	Never	Rarely	Sometimes	Often	Always
I felt fearful	☐	☐	☐	☐	☐
I found it hard to focus on anything other than my anxiety	☐	☐	☐	☐	☐
My worries overwhelmed me	☐	☐	☐	☐	☐
I felt uneasy	☐	☐	☐	☐	☐

PROMIS Depression

Please respond to each question or statement by marking one box per row

In the past 7 days…	Never	Rarely	Sometimes	Often	Always
I felt worthless	☐	☐	☐	☐	☐
I felt helpless	☐	☐	☐	☐	☐
I felt depressed	☐	☐	☐	☐	☐
I felt hopeless	☐	☐	☐	☐	☐

PROMIS Sleep Disturbance

At Day 3-4 time point, the recall period of these questions will be changed from 7 days to 1 day.

Please respond to each question or statement by marking one box per row

In the past 7 days…	Very poor	Poor	Fair	Good	Very good
My sleep quality was	☐	☐	☐	☐	☐

Please respond to each question or statement by marking one box per row

In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
My sleep was refreshing	☐	☐	☐	☐	☐
I had a problem with my sleep	☐	☐	☐	☐	☐
I had difficulty falling asleep	☐	☐	☐	☐	☐

EQ-5D

Please mark one box in each group below to indicate which statements best describe your state of health today.

Mobility

- ☐ I have no problems in walking about
- ☐ I have some problems in walking about
- ☐ I am confined to bed

Self-Care

- ☐ I have no problems with self-care
- ☐ I have some problems washing or dressing myself
- ☐ I am unable to wash or dress myself

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

- ☐ I have no problems with performing my usual activities
- ☐ I have some problems with performing my usual activities
- ☐ I am unable to perform my usual activities

Pain / Discomfort

- ☐ I have no pain or discomfort
- ☐ I have moderate pain or discomfort
- ☐ I have extreme pain or discomfort

Anxiety / Depression

- ☐ I am not anxious or depressed
- ☐ I am moderately anxious or depressed
- ☐ I am extremely anxious or depressed

On a scale of zero to one hundred; with the best state of health you can imagine being 100 and the worst state you can imagine being 0. Which number best describes your state of health today?

Please enter a number between 0 and 100: _____

Work Productivity and Activity Impairment (WPAI)

The following questions ask about the effect of your stem cell donation process on your ability to work and perform regular activities. *Please fill in the blanks or select a response as indicated.*

Are you currently employed (working for pay)?

☐ No

☐ Yes

If yes…

During the past seven days, how many hours did you miss from work because of problems associated with your stem cell donation process? *Include hours you missed on sick days, times you went in late, left early, etc., because of your stem cell donation process. Do not include time you missed to participate in this study.*

_____ hours

During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

_____ hours

During the past seven days, how many hours did you actually work?

_____ hours

If you have worked <u>any</u> hours during the past seven days…
During the past seven days how much did your stem cell donation process affect your productivity <u>while you were working</u>?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If your stem cell donation process affected your work only a little, choose a low number. Choose a high number if your stem cell donation process affected your work a great deal.

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10

Stem cell donation process had no effect on work

Stem cell donation process completely prevented me from working

During the past seven days, how much did your stem cell donation process affect your ability to do your regular daily activities, other than work at a job?
By regular activities, we mean the usual activities you do, such as work around the house, shopping, child care, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If your stem cell donation process affected your activities only a little, choose a low number. Choose a high number if your stem cell donation process affected your activities a great deal.

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10

Stem cell donation process had no effect on my daily activities

Stem cell donation process completely prevented me from doing my daily activities

Healthcare Resource Use (HRU)

Since completing your stem cell donation, have you sought any medical care related to your donation?
Please enter how many visits you have made for each type of medical care listed below.

For each type of medical care that you have had 1 or more visit, please indicate whether the care was related to donation, the reason for the visit/s, how far from your home the medical care was, and how much time the visit took.

Type of medical care	**Number of visits** *enter whole number*	**Was any of the care related to your donation?**	**Reasons for visit/s**	**Approximate distance from your home**	**Time spent seeking this care, including travel and waiting room time**
General practitioner	_____ visits	☐ Related to donation ☐ Not related to donation		_____ miles	_____ hours
Medical specialist	_____ visits	☐ Related to donation ☐ Not related to donation		_____ miles	_____ hours
Urgent Care	_____ visits	☐ Related to donation ☐ Not related to donation		_____ miles	_____ hours
Emergency room	_____ visits	☐ Related to donation ☐ Not related to donation		_____ miles	_____ hours
Social worker or Care manager	_____ visits	☐ Related to donation ☐ Not related to donation		_____ miles	_____ hours
Other, please describe: _____	_____ visits	☐ Related to donation ☐ Not related to donation		_____ miles	_____ hours

Donation experience

Thinking back over your entire donation journey to date, which statement best describes your overall satisfaction?

- ☐ Completely satisfied. I wouldn't change a thing.
- ☐ Moderately satisfied. Some things could have gone better, but overall, I was satisfied.
- ☐ Neither satisfied nor unsatisfied.
- ☐ Moderately unsatisfied. Some things could have gone better, but overall, I was unsatisfied.
- ☐ Extremely unsatisfied. A lot needs to change.

If called to donate again, would you? (Your answer will not affect your status on the Registry)

- ☐ Yes
- ☐ No
- ☐ Unsure

Would you recommend donation to a friend or family member?

- ☐ Yes
- ☐ No
- ☐ Unsure

Did you learn or discover anything after your donation that you wish you had known earlier?

_____

_____

Reflecting on your donation experience overall, are there any changes you would recommend?

_____

_____

Is there anything else you would like to share with the researchers about your stem cell donation experience?

_____

_____

G. Adverse Event Definitions and Grading (CTCAE v5.0)

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

H. Guidance on Reviewing and Reporting Unanticipated Problems

For more information, please see http://www.hhs.gov/ohrp/policy/advevntguid.html#Q1
Below are pertinent excerpts from the Office for Human Research Protections (OHRP) Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects.

1. **What are *unanticipated problems*?**

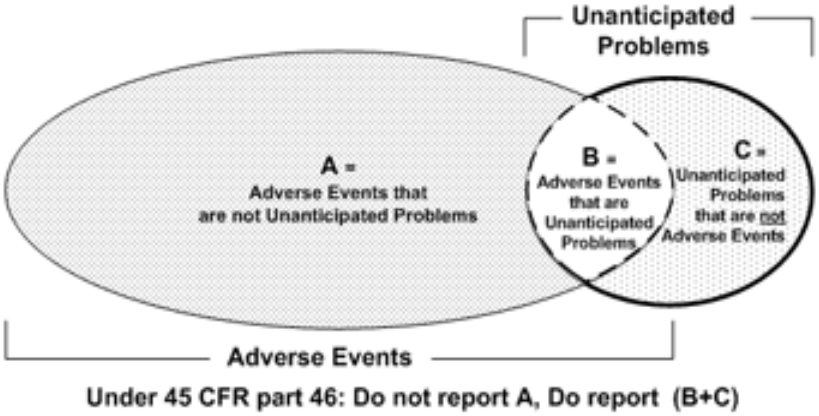
The phrase "unanticipated problems involving risks to subjects or others" is found but not defined in the HHS regulations at 45 CFR part 46. OHRP considers *unanticipated problems*, in general, to include any incident, experience, or outcome that meets **all** of the following criteria:

a. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
b. related or possibly related to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
c. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

OHRP recognizes that it may be difficult to determine whether a particular incident, experience, or outcome is unexpected and whether it is related or possibly related to participation in the research.

2. **How do you determine which *adverse events* are *unanticipated problems*?**

In OHRP's experience, most IRB members, investigators, and institutional officials understand the scope and meaning of the term *adverse event* in the research context but lack a clear understanding of OHRP's expectations for what, when, and to whom adverse events need to be reported as unanticipated problems, given the requirements of the HHS regulations at 45 CFR part 46.
The following Venn diagram summarizes the general relationship between adverse events and unanticipated problems:



Under 45 CFR part 46: Do not report A, Do report (B+C)

To determine whether an adverse event is an unanticipated problem, the following questions should be asked:

a. Is the adverse event unexpected?
b. Is the adverse event related or possibly related to participation in the research?
c. Does the adverse event suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized?

If the answer to **all three questions** is *yes,* then the adverse event is an unanticipated problem.