Magenta Therapeutics

MGTA-456

CLINICAL TRIAL PROTOCOL IMD-001

A Phase 2, Single-arm, Open-label Study to Evaluate the Safety and Efficacy of MGTA-456 in Patients with Inherited Metabolic Disorders (IMD) Undergoing Hematopoietic Stem Cell (HSC) Transplantation (HSCT)

Sponsor:	**Magenta Therapeutics, Inc. (Magenta)**
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Notification of Serious Adverse Events

Refer to Section 8.2 of the protocol for definitions and complete reporting requirements for serious adverse events (SAEs).

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

INVESTIGATOR'S AGREEMENT

I have read the Study IMD-001 Protocol Version 08 10/Jan/2020 and agree to conduct the study as outlined.

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

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

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Printed Name of Investigator

_____

Signature of Investigator

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Date

SPONSOR SIGNATURE

[redacted]

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ABW	actual body weight
AE	adverse event
aGVHD	acute graft versus host disease
AHR	aryl hydrocarbon receptor
AIBW	adjusted ideal body weight
AIC	autoimmune cytopenia
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ALD	Adrenoleukodystrophy
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATG	antithymocyte globulin
AUC_{cum}	cumulative area under the plasma concentration-time curve
AUC	area under the plasma concentration-time curve
AUC_{∞}	area under the plasma concentration-time curve from time zero to infinity
AUC_{last}	area under the plasma concentration-time curve from time zero to time of last measurable concentration
BLA	Biologics License Application
BMT	bone marrow transplant
BU	busulfan
BUN	blood urea nitrogen
cALD	cerebral adrenoleukodystrophy
CBU	cord blood unit
CFR	Code of Federal Regulations
cGVHD	chronic graft versus host disease
CLIA	Clinical Laboratory Improvement Amendment
C_{max}	maximum observed concentration
CMV	Cytomegalovirus
CNS	central nervous system
CsA	cyclosporine A
CSF	cerebrospinal fluid
CTCAE	Common Toxicity Criteria Adverse Event
CY	cyclophosphamide
DNA	deoxyribonucleic acid
DMC	data monitoring committee

Abbreviation	Definition
DUCBT	double umbilical cord blood transplantation
ECG	Electrocardiogram
eCRF	electronic case report form
ERT	enzyme replacement therapy
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
GAG	Glycosaminoglycan
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GGT	gamma-glutamyl transferase
GLD	globoid cell leukodystrophy
GM-CSF	macrophage-colony stimulating factor
GVHD	graft versus host disease
HR	hazard ratio
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HNA	human neutrophil antigen
HSC	hematopoietic stem cells
HSCT	hematopoietic stem cell transplantation
HSV	herpes simplex virus
HTLV1/2	human T cell lymphotropic virus ½
IB	Investigator's Brochure
IBW	ideal body weight
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IMD	inherited metabolic disorders
IRB	institutional review board
IUD	intrauterine device
IUS	intrauterine system
IV	intravenous

Abbreviation	Definition
IVIg	intravenous immunoglobulin
LDH	lactate dehydrogenase
LFT	liver function test
LLOQ	lower limit of quantification
LMW	low molecular weight
LVEF	left ventricular ejection fraction
MAC	myeloablative conditioning
Magenta	Magenta Therapeutics, Inc.
MFI	mean fluorescence intensity
MedDRA	medical dictionary for regulatory activities
MLD	metachromatic leukodystrophy
MMF	mycophenolate mofetil
MP	Methylprednisolone
MRI	magnetic resonance imaging
MPS-HAQ	Mucopolysaccharidosis-Health Assessment Questionnaire
MPS-IH	mucopolysaccharidosis-IH
MSD	matched sibling donor
NFS	neurological function score
NMAC	non-myeloablative conditioning
NOAEL	no observed adverse effect level
NRE	non-reducing-end
PES	pre-engraftment syndrome
PFT	pulmonary function test
PK	pharmacokinetic
PMBC	peripheral blood mononuclear cells
PO	oral(ly) (per oral)
SAB	single antigen bead
SAE	serious adverse event
SOP	standard operating procedure
SR-1	StemRegenin-1
SUCBT	single umbilical cord blood transplantation
TEAE	treatment-emergent adverse events
TID	three times a day
TRALI	transfusion-related acute lung injury
TNC	total nucleated cell
TREC	T cell receptor excision circles

Abbreviation	Definition
TRSALI	transfusion-related acute lung injury
TRM	transplant-related mortality
UCB	umbilical cord blood
UCBT	umbilical cord blood transplant
ULN	upper limit of normal
US	United States
VLCFA	very long chain fatty acids
WHO	World Health Organization

SYNOPSIS

Protocol number	**IMD-001**
Title	A Phase 2, single-arm, open-label study to evaluate the safety and efficacy of MGTA-456 in patients with selected inherited metabolic disorders (IMD) undergoing hematopoietic stem cell (HSC) transplantation (HSCT)
Brief title	MGTA-456 in patients with inherited metabolic disorders undergoing HSCT
Sponsor and Clinical Phase	Magenta Therapeutics, Inc.; Phase 2
Intervention type	Intravenous (IV) administration of HSC therapy product
Study type	Interventional
Purpose and rationale	To evaluate the safety and efficacy of MGTA-456 after myeloablative conditioning to induce rapid and sustained hematopoietic engraftment with replacement of the specific protein product missing or defective in the patient with an IMD. The study aims to enhance the efficacy of umbilical cord blood (UCB) transplantation (UCBT), to preserve neurodevelopment in patients with selected IMDs. Since MGTA-456 offers increased numbers of HSCs over standard UCB, it is expected to reduce the risks of prolonged neutropenia and thrombocytopenia and graft failure, and potentially transplant-related mortality (TRM).
Primary Objective(s)	To evaluate the effect of MGTA-456 on the rate and incidence of neutrophil recovery in patients with IMD undergoing HSCT
Secondary Objectives	• To evaluate the safety of MGTA-456 in patients with IMD undergoing HSCT • To characterize engraftment following transplantation with MGTA-456 and to evaluate the effect of MGTA-456 on chimerism in the CD3 and CD33/66 (or CD15) hematopoietic compartments • To assess the incidence of acute and chronic graft versus host disease (GVHD) • To assess transplant-related mortality (the incidence of TRM)
Study design	This is a Phase 2, open-label, single-arm study in which patients with IMDs will receive MGTA-456 as a stand-alone HSC graft after MAC. Approximately 12 patients with IMD will be enrolled and followed for one year, with the option to include up to approximately 15 additional patients in an expansion cohort.
Population	Children age < 2.5 years with Hurler syndrome, age 2-17 years with cerebral adrenoleukodystrophy (cALD), age <16 years with metachromatic leukodystrophy (MLD) and age ≤ 10 years with globoid cell leukodystrophy (GLD) (also referred to as Krabbe).
Inclusion criteria	Male and female, age < 2.5 years with Hurler syndrome, age 2-17 years with cerebral adrenoleukodystrophy (cALD), age < 16 years with metachromatic leukodystrophy (MLD) and age ≤ 10 years with globoid cell leukodystrophy (GLD) (also referred to as Krabbe). Diagnosed with one of the following IMDs: • Hurler syndrome (Mucopolysaccharidosis I Hurler [MPS-IH]) • MLD: asymptomatic late-infantile, or asymptomatic/minimally symptomatic juvenile onset patients • GLD, or early attenuated disease • cALD with Loes score ≤10, and with neurologic functional score (NFS) ≤1.

	Patient must have a minimum life expectancy of 6 months in the judgment of the Investigator. Recipients must meet the following criteria: • Lansky score ≥50% • Renal: serum creatinine ≤2.5 × upper limit of normal (ULN) corrected for age • Hepatic: total bilirubin and alanine aminotransferase (ALT) ≤3 × ULN corrected for age • Pulmonary function: oxygen saturation ≥92% without an oxygen requirement; an exception may be made as documented in the medical record for patients with abnormal sleep studies (such as Hurler patients) • Cardiac: left ventricular ejection fraction ≥30. Required graft characteristics: • The UCB unit must be at least 6/8 HLA-A, HLA-B, HLA-C, and HLA-DRB1 matched with the recipient at the allele level. This is based upon a recent publication which showed that allele-level matching at HLA-A, HLA-B, HLA-C and HLA-DRB1 between the UCB unit and its recipient is associated with best survival and lowest occurrence of graft failure in children with non-malignant diseases. • The UCB units must come from a qualified UCB bank(s) per institutional standard operating procedures (SOPs). Any matched unit not from a qualified UCB bank must be pre-approved for use by the Sponsor. If the UCB unit is "unlicensed" (most commonly based on location [e.g., European countries], testing by non-CLIA (Clinical Laboratory Improvement Amendment) approved laboratories, or collection before May 25, 2005), the Sponsor will make the final decision on patient eligibility based on the reason why the UCB unit is unlicensed • The minimal total nucleated cell (TNC) count for the selected UCB unit is to be 1.0×10^7/kg of the recipient's body weight • In a case where there is a better HLA-matched UCB unit with a lower cell dose, it may be selected over a less well-matched unit with a higher cell dose • The patient must not have donor-specific anti-HLA antibodies considering HLA A, B, C, DRB1, DQ and DP (Mean Fluorescence Intensity [MF]I >1000). • A suitable back-up HSC source (UCB unit or unaffected haploidentical donor) must be available. • Cord blood grafts require genetic testing and/or demonstration of enzyme activity for patients with Hurler syndrome, MLD or GLD and are tested for very long chain fatty acids (VLCFA) to confirm there is no evidence of VLCFA consistent with ALD
Exclusion criteria	• Availability of 8/8 HLA-matched related donor who is not a carrier of the same genetic defect. • Active infection at Screening (defined as requiring parenteral antibiotics because of persistent changes consistent with infection based on imaging studies and/or positive cultures) including active infection with Aspergillus or other fungus within 30 days prior to screening, or severe concomitant diseases which in the judgment of the Investigator would lead to the patient's inability to tolerate the protocol specified conditioning regimen. • Prior myeloablative conditioning.

	• Prior use of an investigational study drug or procedure within 3 months before screening that might confound study outcomes. Except for approved Enzyme Replacement Therapy (ERT), use of investigational study drugs is prohibited throughout the course of the study unless approved by Magenta.
	• Females of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception from the day of transplant and for 1 year after infusion.
	• Highly effective contraception methods include:
	  • Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception)
	  • Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
	• Sexually active male patients unless they are using condoms as contraception starting on the first day of conditioning regimen (Day -9) until 1 year after infusion or completion of immune suppressive therapy, whichever comes last.
	• History of HIV infection.

Investigational therapy	[redacted]
Primary Endpoints	• Incidence of engraftment with MGTA-456, engraftment defined as achieving an absolute neutrophil count (ANC) $\geq 0.5 \times 10^9$/L for 3 consecutive days • Time to neutrophil recovery, defined as the first day of 3 consecutive days with an ANC $\geq 0.5 \times 10^9$/L
Secondary Endpoints	• Incidence of infusion toxicities (incidence of MGTA-456-related AEs that limit MGTA-456 administration) • Incidence of treatment-emergent adverse events (TEAEs) • Incidence of late hematological graft failure defined as meeting 1 of the following 3 criteria: (1) <5% donor whole blood or myeloid chimerism in peripheral blood or bone marrow beyond Day 42 post-transplant in patients with prior hematopoietic recovery with ≥5% donor cells by Day 42 post-transplant; (2) Sustained decline in the ANC to <500/mm^3 for 3 consecutive measurements on different days, unresponsive to growth factor therapy after initial hematopoietic recovery by Day 42; (3) Subsequent bone marrow aplasia identified after initial hematopoietic recovery by Day 42 • Number of days with neutropenia from the day of transplant through Day 42 • Contribution of MGTA-456 to myeloid and lymphoid engraftment as determined by percent chimerism in CD33/66 (or CD15) and CD3 cells at Days 7, 14, 21, 28, 60, 84, 100, 180, 360

	• Incidence of platelet recovery as defined in 2 ways: (1) $\geq 20 \times 10^9$/L for 3 consecutive laboratory measurements on different days without transfusion in the prior 7 days (2) $\geq 50 \times 10^9$/L for 3 consecutive laboratory measurements on different days without transfusion in the prior 7 days • Time to platelet recovery as defined in 2 ways: (1) the first of 3 consecutive laboratory measurements on different days with a platelet count $\geq 20 \times 10^9$/L without transfusion in the prior 7 days (2) the first of 3 consecutive laboratory measurements on different days with a platelet count $\geq 50 \times 10^9$/L without transfusion in the prior 7 days • Incidence of Grade II - IV acute GVHD by Day 100 • Incidence of chronic GVHD by 1 Year • Probability of survival by 1 year • Incidence of TRM by Day 100 and 1 year of MGTA-456 infusion
Data analysis	The primary variables are incidence of neutrophil recovery with MGTA-456, and time to neutrophil recovery. Secondary variables are incidence of infusion toxicities, TEAEs, and late hematological graft failure. Each incidence will be summarized with a 95% confidence interval. Additional secondary variables are incidence of and time to platelet recovery, percent chimerism, incidence of acute and chronic GVHD, and death, which will be summarized using Kaplan-Meier time to event methods. Each variable will be displayed graphically and the number of patients experiencing the events by relevant time windows will be presented. [redacted]
Key words	Inherited metabolic disorders (IMD), hematopoietic stem cell transplantation (HSCT), umbilical cord blood (UCB), conditioning regimen, Hurler syndrome, cerebral adrenoleukodystrophy (cALD), metachromatic leukodystrophy (MLD), globoid cell leukodystrophy (GLD, or Krabbe).

1. INTRODUCTION

1.1 Background

1.1.1 Inherited Metabolic Disease

Inherited metabolic diseases (IMD), including cerebral adrenoleukodystrophy (cALD), globoid cell leukodystrophy (GLD or Krabbe), metachromatic leukodystrophy (MLD), and Hurler syndrome are a group of rare, inherited disorders that result in a progressive loss of neuromotor and cognitive abilities. Untreated, these disorders are progressive and lethal. Enzyme replacement of lysosomal disorders cannot correct the central nervous system (CNS) defects due to lack of penetration of the blood-brain-barrier. The only effective neurologic therapy for MLD, GLD, cALD, and Hurler syndrome is allogeneic hematopoietic stem cell transplantation (HSCT), after which immature cells of hematopoietic origin migrate to tissues, including the CNS (Orchard et al 2007; Prasad et al 2008).

In cALD, mutations in the *ABCD1* gene cause a defect in peroxisome membrane transport and lead to accumulation of VLCFA. High levels of VLCFA in turn cause inflammation and demyelination within the CNS white matter resulting in progressive disease. Microglia derived from allogeneic bone marrow progenitors are hypothesized to ameliorate the defect by processing VLCFA. One general mechanism known as cross-correction has been shown in Hurler syndrome where microglia capable of providing the α-L-iduronidase enzyme to the CNS of Hurler patients supply the defective enzyme and serve as a permanent source of cellular enzyme replacement (Krivit et al 1995). This same mechanism is thought to provide clinical benefit to those with early and/or attenuated MLD and GLD.

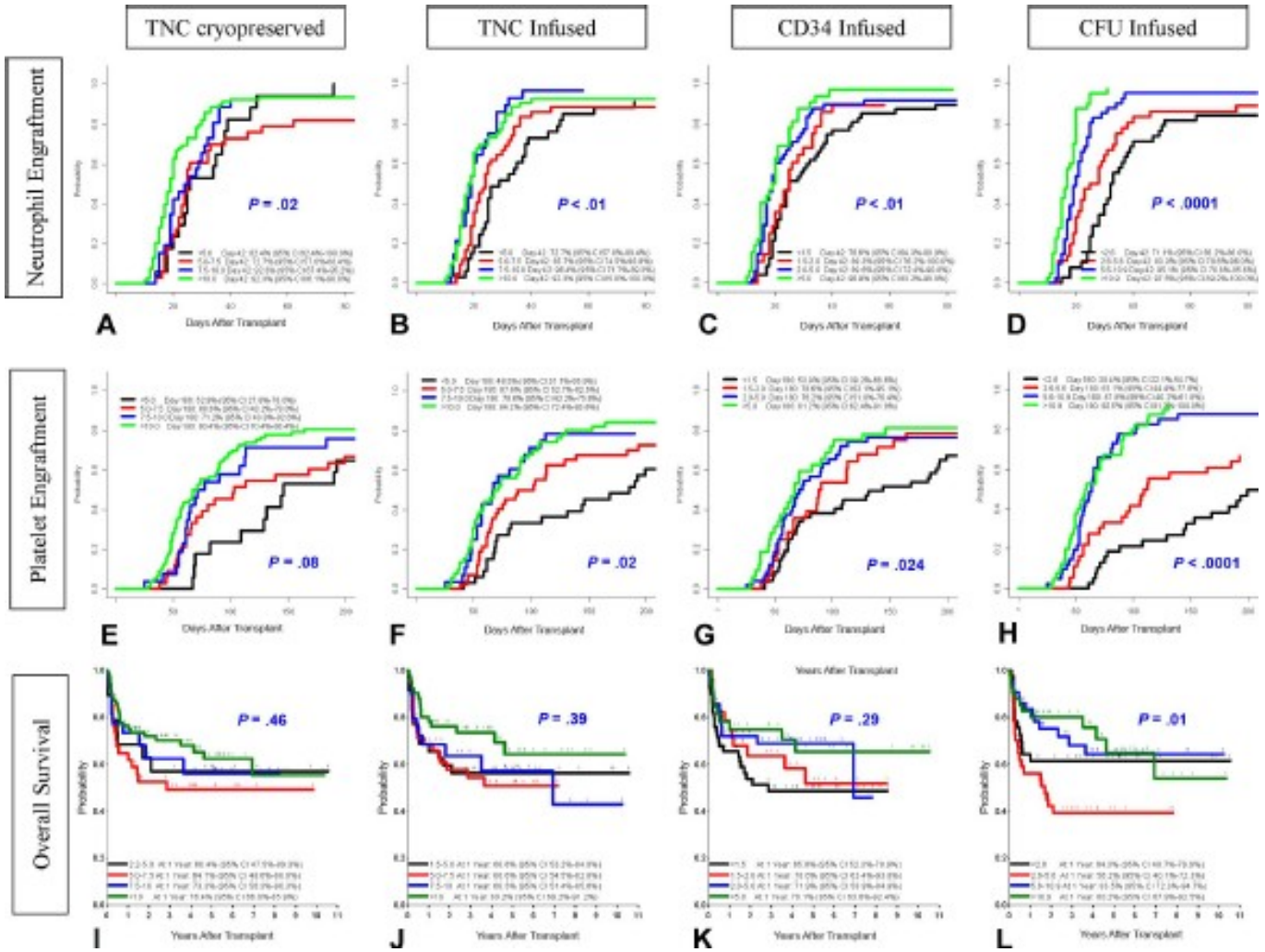
While allogeneic HSCT is considered the standard of care for these diseases, the morbidity and mortality of transplantation are significant, with peri-transplant mortality reported as 20% to 30% (Prasad et al 2008; Boelens et al 2013). Transplant-related mortality (TRM) is in part caused by the conditioning regimen, which traditionally has included myeloablative doses of chemotherapy and/or radiation and was independent of the specific indication. Reducing TRM is a high priority in this patient population.

Most of the mortality in patients with IMD occurs within the first 6 months of HSCT, most often secondary to transplant-related complications. The best outcomes are achieved in patients receiving a genotypic-identical sibling donor bone marrow transplant (BMT) or a human leukocyte antigen (HLA)-matched, unrelated UCB transplant (UCBT) prior to the onset of irreversible neurologic complications (Boelens et al 2013).

UCB has become a preferred choice for patients lacking a HLA matched related donor due to its rapid availability and permissiveness for HLA allele mismatching. In one center, an outcome study of 159 patients with IMDs undergoing UCBT (Prasad et al 2008; Figure 1), overall survival was 71.8% at 1 year. Median time to neutrophil engraftment was 22 days with a cumulative incidence by Day 42 of 87%. Platelet engraftment occurred in a median of 87 days with a cumulative incidence of 71% at 180 days. Factors significantly affecting neutrophil engraftment included HLA match of at least 5/6 (hazard ratio [HR] 1.4, p=0.04), higher CD34+ cell dose (HR 1.76, p<0.01) and higher TNC (HR 1.78, p<0.01) (Figure 1). In terms of GVHD, the incidence of grade II-IV acute graft versus host disease (aGVHD) was approximately 41% and grade II-IV was 10.2%. Chronic GVHD was observed in 20.9% at 1 year. Graft failure

occurred in 8.2% of patients; however additional studies have reported higher rates of approximately 20% (Miller et al 2011; Martin et al 2006; Beam et al 2007).

Figure 1: Impact of Graft Characteristics on the Probability of Engraftment and Overall Survival



MSD=matched sibling donor; CB=cord blood; MUD=matched unrelated donor; MMUD=mismatched unrelated donor; OS=overall survival; TNC=total nucleated cell. Event-free survival is defined as alive with donor-derived engraftment.

Note: Probability plots are shown for the each of the 4 quartiles. Panels A, E, and I depict the impact of cryopreserved TNCs (x 10^7/kg recipient weight) on neutrophil engraftment, platelet engraftment, and OS, respectively. Panels B, F, and J depict the impact of infused TNCs (x 10^7/kg recipient weight) on neutrophil engraftment, platelet engraftment, and OS, respectively. Panels C, G, and K depict the impact of infused CD34 cells (x 10^5/kg recipient weight) on neutrophil engraftment, platelet engraftment, and OS, respectively. Panels D, H, and L depict the impact of infused CFUs (x 10^4/kg recipient weight) on neutrophil engraftment, platelet engraftment, and OS, respectively. *P* values are shown with each plot for the quartile analysis.
Source: Prasad et al 2018

While UCB has the advantages of rapid availability and relatively less HLA restriction as compared to hematopoietic stem cells (HSC) from adult volunteer donors, the use of UCB is substantially limited by the low finite number of hematopoietic stem and progenitor cells, resulting in prolonged periods of neutropenia and thrombocytopenia and suboptimal engraftment, particularly with increasing degrees of HLA mismatch. Therefore, the identification of a strategy to expand the number of CD34+ cells from a single UCB unit could enhance engraftment and reduce TRM, as well as more rapidly stabilize the underlying disease in patients with IMD.

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1.1.3 MGTA-456 in IMD Patients

In the proposed study, Magenta plans to test MGTA-456 in patients with the following IMD diagnoses: Hurler syndrome (mucopolysaccharidosis-IH, or MPS-IH), MLD (late-infantile and juvenile onset patients), pre-symptomatic Globoid cell leukodystrophy (sometimes referred to as Krabbe), and cALD. The targeted population was chosen based on their eligibility to receive HSCT under international guidelines (The EBMT Handbook 2008-Chapter 41) and published literature (Boelens et al 2014; Prasad, 2010; de Ru, 2011; Aldenhoven, 2015; Eisengart, 2018, Poe, 2014; Scarpa, 2017, Engelen, 2012; Page, 2019; Raymond, 2019; Kuhl, 2017; Boucher, 2015; van den Broek, 2018; Kwon, 2018); Duffner, 2012). Since MGTA-456 contains increased numbers of CD34+ stem and progenitor cells (approximately 300-fold more than a standard UCB unit), it is expected to result in rapid and consistent engraftment rates, as observed in prior studies of MGTA-456 in patients with malignancy, and potentially lower TRM. In addition, transplantation with large numbers of progenitor cells should result in an increased probability of donor-derived engraftment even with HLA-mismatched UCB after a lower toxicity conditioning regimen, and potentially more rapid stabilization of neuromotor and neurocognitive dysfunction.

In addition to providing cell doses high enough for consistent engraftment in IMD, the use of MGTA-456 also has the potential to increase the availability of better HLA-matched UCB units. A recent report shows that only 19% of Hurler patients had a 6/6 HLA-matched UCB unit of sufficient HSC dose available for transplantation (Boelens et al 2013). Another recent publication showed that allele-level matching at HLA-A, HLA-B, HLA-C, and HLA-DRB1 between the UCB unit and its recipient is associated with best survival and lowest occurrence of graft failure in children with non-malignant diseases (Eapen 2014). Because HLA match is significantly related to long-term survival of IMD patients (Figure 1), the use of MGTA-456 is especially promising in IMD as it permits the use of better matched UCB units with smaller cell doses.

1.1.5 Human Safety and Tolerability Data in Adults and Children

Twenty-seven patients were treated in Study CHSC835X2201.

In the double UCB (DUCBT) cohort of CHSC835X2201, the incidence of neutrophil recovery was 100% for both adult (n=15) and pediatric patients (n=3) occurring at a median of 16 days (6-30) and 7 days, respectively. The incidence of platelet recovery was 73% and 67% for adult and pediatric patients at a median of 59 days for adults (range, 28 to 108 days) and 22 and 59 days for the 2 of 3 pediatric patients. Of the 18 patients, 1 had transient hypotension 4 hours after the infusion of MGTA-456 which was subsequently demonstrated to be due to an occult bacterial contamination of the MGTA-456 product. Otherwise, no infusional toxicities were noted and no other adverse effects were attributed to MGTA-456. Grade III aGVHD was diagnosed in 3 adult patients and Grade IV aGVHD was reported in one patient. None of the pediatric patients developed Grade III or IV aGVHD. The adverse event (AE) profiles between day 0 and day 30 were comparable to those commonly observed after UCB transplantation. In addition, no patient had late graft failure with the longest follow-up of 687+ days. In terms of other transplant outcomes, overall survival for adult and pediatric patients combined (10/18, 55.6%) was similar to the historical cohort. Primary causes of death were acute GVHD (n=4), alveolar hemorrhage (n=2), idiopathic pneumonia (n=1), and relapse (n=1).

In the single UCB (SUCBT) cohort of CHSC835X2201 (n=9), there were 8 adults and 1 pediatric patient. The incidence of neutrophil recovery was 100%, at a median of 17 days (range: 7-32 days) for the adults and day 8 for the single pediatric patient. For adults transplanted with MGTA-456 as a stand-alone product, the incidence of platelet recovery was 63% at Day 180 at a median of 50.5 days (range 42 to 181 days). The single pediatric patient had platelet recovery after 97 days.

The primary endpoint of the SUCBT clinical trial was to determine the safety of MGTA-456. There were no infusional toxicities noted within the first 24 hours after transplant and no other adverse effects were observed that could be attributed to the product infusion. In addition, no patient had late graft failure within the follow-up period. In terms of other transplant outcomes, Grade II-IV and Grade III-IV aGVHD occurred in 4 and 2 of 9 patients, respectively, at a median of 34.5 days after transplant. Thus far, TRM has been low with 1 of 9 dying due to non-disease related reasons.

The median follow-up is 6 months (range: 1 to 38 days). At time of the last data cut off, 6 of 9 were alive with deaths due to relapse (n=2), alveolar hemorrhage (n=1).

Overall, the median time to engraftment for the 27 patients in the study was 14 days (range 6 to 32 days), which compares favorably with the time to neutrophil recovery reported for DUCBT patients at the University of Minnesota receiving the same conditioning regimen and GVHD immune prophylaxis, which was 26 days (Brunstein et al 2010). The pace of hematopoietic recovery was remarkably rapid in patients where MGTA-456 with a CD34 cell dose >10 million/kg could be administered. Similarly, the fraction of patients achieving platelet recovery was greater in patients receiving MGTA-456 and the pace of platelet recovery was accelerated relative to DUCBT patients (for details see the published results of the DUCBT patients enrolled in this study (Wagner et al 2016). Of note, the length of hospitalization was significantly reduced in recipients of MGTA-456 (median of 27 days compared to 46 days in the control population, $p<0.001$).

Study CHSC835X2202 was a single-arm, open-label study evaluating the safety and tolerability of MGTA-456 as single stand-alone graft (SUBCT) in patients with hematologic malignancies undergoing a reduced dose conditioning to minimize TRM in an older population or those with

pre-existing comorbidities. Nine patients received TBI 200 cGy, CY 50 mg/kg (total dose) and FLU 200 mg/m2 (total dose) followed by MGTA456 as stand-alone graft. All patients had lympho-hematopoietic malignancy.

Neutrophil recovery was achieved in all (100%) patients at a median of 7 days (range: 5 to 14 days) and platelets recovery at median 106 days (range: 28 to 106 days). No infusional toxicities were noted within the first 24 hours after transplant and no other adverse effects were observed that could be attributed to the product infusion. In addition, no patient had late graft failure within the follow-up period (note: 1 patient had loss of engraftment, occurring with leukemia relapse). In terms of other transplant outcomes, Grade II-IV and Grade III-IV aGVHD occurred in 6 and 4 of 9 patients, respectively. At the time of last study report, TRM was low with 1 of 9 dying due to non-disease related reasons (N=1 GVHD); 3 patients died from relapse during the study period (1 other patient died of relapse after the end of study period). Most importantly, late hematological graft failure has not occurred.

At last data cutoff, the median follow-up was 6 months (range: 1 to 38 months). Four of 9 were alive with deaths due to relapse (n=4) and GVHD (n=1).

The principal conclusion of the clinical existing experience with MGTA-456 as stand-alone unit are that MGTA-456 supports rapid hematopoietic recovery with stable, long-term engraftment regardless of conditioning intensity.

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1.1.8 Risk and Benefit Summary

Based on the available safety data from CHSC835X2201 and CHSC835X2202 and the published clinical outcome data on UCBT in IMD patients, the benefit-risk assessment for the inclusion of IMD patients in this clinical study investigating the enhanced cord blood product MGTA-456 is considered acceptable. As the increased numbers of hematopoietic stem and progenitor cells in response to MGTA-456 are expected to enable rapid and sustained engraftment despite the use of a reduced intensity conditioning, the proposed treatment holds out the prospect of direct benefit for the individual patient in the study.

1.2 Study Purpose

The purpose of this study is to assess the safety and efficacy of MGTA-456, an expanded UCB product, with efficacy defined as inducing rapid and sustained donor-derived hematopoietic engraftment. Protein replacement in IMD and other disease specific outcomes will also be assessed in an exploratory manner. The study will contribute to our understanding of the MGTA-456 product with regards to engraftment efficacy after conditioning in patients who are fully immune-competent and have not received cytoreductive or immunosuppressive treatment prior to conditioning for transplant.

2. OBJECTIVES AND ENDPOINTS

	Objective	Endpoint
Primary	To evaluate the effect of MGTA-456 on the rate of neutrophil recovery in patients with IMD undergoing HSCT	Incidence of engraftment with MGTA-456, engraftment defined as achieving an absolute neutrophil count (ANC) $\geq 0.5 \times 10^9$/L for 3 consecutive days
		Time to neutrophil recovery defined as the first day of 3 consecutive days with an ANC $\geq 0.5 \times 10^9$/L
Secondary	To evaluate the safety of MGTA-456 in patients with IMD undergoing HSCT	Incidence of infusion toxicities (incidence of MGTA-456-related AEs that limit MGTA-456 administration)
		Incidence of TEAEs
	To characterize engraftment following transplantation with MGTA-456 and to evaluate the effect of MGTA-456 on chimerism in the CD3 and CD33/66 (or CD15) hematopoietic compartments	Incidence of late hematological graft failure defined as meeting 1 of the following 3 criteria: (1) <5% donor whole blood or myeloid chimerism in peripheral blood or bone marrow beyond Day 42 post-transplant in patients with prior hematopoietic recovery with ≥5% donor cells by Day 42 post-transplant; (2) Sustained decline in the ANC to $<500/mm^3$ for 3 consecutive measurements on different days, unresponsive to growth factor therapy after initial hematopoietic recovery by Day 42; (3) Subsequent bone marrow aplasia identified after initial hematopoietic recovery by Day 42
		Number of days with neutropenia from the day of transplant through Day 42

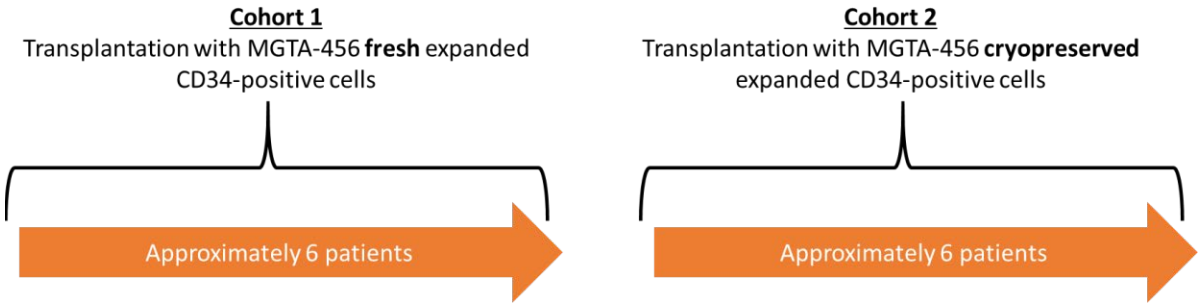
		Contribution of MGTA-456 to myeloid and lymphoid engraftment as determined by percent chimerism in CD33/66 (or CD15) and CD3 cells at days 7, 14, 21, 28, 60, 84, 100, 180, 360
		Incidence of platelet recovery as defined in 2 ways: (1) $\geq 20 \times 10^9$/L for 3 consecutive laboratory measurements on different days without transfusion in the prior 7 days (2) $\geq 50 \times 10^9$/L for 3 consecutive laboratory measurements on different days without transfusion in the prior 7 days
		Time to platelet recovery as defined in 2 ways: (1) the first of 3 consecutive laboratory measurements on different days with a platelet count $\geq 20 \times 10^9$/L without transfusion in the prior 7 days (2) the first of 3 consecutive laboratory measurements on different days with a platelet count $\geq 50 \times 10^9$/L without transfusion in the prior 7 days
	To assess the incidence of acute and chronic graft versus host disease (GVHD)	Incidence of Grade II - IV aGVHD by Day 100
		Incidence of chronic GVHD by Year 1
	To assess transplant-related mortality (the incidence of TRM)	Probability of survival by 1 year
		Incidence of TRM by Day 100 and 1 year of MGTA-456 infusion
Exploratory	[redacted]	[redacted]

3. INVESTIGATIONAL PLAN

3.1 Study Design

This is a Phase 2, open-label, single-arm study in which patients with IMD will receive MGTA-456 as a stand-alone HSC graft after MAC. Approximately 12 patients will be enrolled into 1 of 2 sequential cohorts, with the option to include up to approximately 15 additional patients in an expansion cohort following dosing of Cohort 2. Cohort 1 will comprise approximately 6 patients who will receive MGTA-456 fresh expanded CD34+ cells and Cohort 2 will comprise approximately 6 patients who will receive MGTA-456 cryopreserved expanded CD34+ cells. Up to approximately 15 additional patients may be included in an expansion cohort following dosing of Cohort 2; these patients will receive MGTA-456 cryopreserved expanded CD34+ cells. All patients will be followed up to the end of study visit at 1 year after post-transplant. The design is presented in Figure 3.

Figure 3: Study Design



Note: Up to approximately 15 additional patients may be included in the study following dosing of Cohort 2 and will receive cryopreserved MGTA-456 product.

For each patient in Cohort 1 (see Section 3.1.1) and Cohort 2 (see Section 3.1.2), the study will consist of an approximately 50-day screening period (Day -60 to Day -10). The patient must meet all eligibility criteria before the expansion culture will be initiated. Following MGTA-456 manufacturing, patients will be admitted to begin the transplant conditioning regimen (Day -9 to Day -1 [see Section 5.1.2 for details]). The day of MGTA-456 administration will be considered Day 0 and will consist of the infusion of the expanded CD34+ fraction followed by the infusion of the CD34-depleted fraction of the cord blood unit (CBU). Infusional toxicity will be assessed within 48 hours after transplant. Each patient will remain hospitalized until neutrophil recovery is achieved (refer to Section 7.3.1 for neutrophil recovery definition). The patient will be monitored with protocol-specific procedures for 1 year following transplant to assess engraftment, graft failure, and late hematological graft failure (refer to Section 7.3.1 for definitions) and other study endpoints.

Any patient (or guardian) withdrawing their consent or any patient withdrawn because of an event unrelated to the study, at any time during the study, will be replaced to ensure approximately 6 evaluable patients in each cohort.

After 1 year, patients may be transferred to a separate long-term follow up study, if eligible and willing (after signature of the specific study informed consent form [ICF]).

3.1.1 Cohort 1 – Fresh MGTA-456 Cell Therapy Product

A first group of approximately 6 evaluable patients with IMD will receive MGTA-456 fresh expanded CD34+ cells. Recruitment will be sequential.

For the study to proceed to Cohort 2, none of the stopping rules regarding excessive graft failure, TRM, or Grade 3 to 4 aGVHD may be met (Section 6.4).

3.1.2 Cohort 2 – Cryopreserved MGTA-456 Cell Therapy Product

A second group of approximately 6 patients with IMD will be enrolled sequentially to receive cryopreserved MGTA-456 in a single UCBT setting. The cryopreserved MGTA-456 product will allow flexibility around planning the exact day of stem cell administration and allow the assessment of attributes like sterility that are expected to increase product quality. Up to approximately 15 additional patients may be included in an expansion cohort following dosing of the initial 6 patients in Cohort 2. These patients will receive cryopreserved MGTA-456 product.

3.2 Rationale for Study Design

An open-label, single-arm, 2-part study design, aligned to the standard of care, was chosen as a conservative approach as this is the first study to administer MGTA-456 in a younger (infant/child) IMD patient population. The outcomes for conventional HSCT in IMD patients are well-documented, and given the rare indication, it is proposed to study only the experimental treatment, without the requirement of a placebo control arm.

The considerable experience with UCBT for the treatment of IMD patients at the selected clinical center(s) will allow the assessment of the safety and efficacy in comparison to historical or concomitant patients treated with standard UCBT. The study assessments are aligned with the standard of care; thus, patients will undergo only limited additional burden assessment for research purposes only.

3.3 Rationale for Dose, Regimen, and Duration of Treatment

MGTA-456 is an allogeneic UCB cell therapy product that consists of 2 cell fractions derived from the same UCB unit.

Two formulations of MGTA-456 will be used in this study:

1. [redacted]

For both cohorts, starting on Day 0 of the study, 2 therapeutic cell preparations will be infused sequentially in the following order.

1. A minimal dose of 10×10^6 CD34+ cells per kg body weight within a range of 20×10^6 to 270×10^6 TNC per kg body weight will be administered.
2. The remaining and entire CD34-depleted fraction derived from the same UCB unit as the ex vivo expanded CD34+ cells (the CD34-depleted fraction). All available CD34-negative cells will be administered.

The MGTA-456 production process results in a median >800-fold TNC expansion and a median >300-fold CD34+ cell expansion. The absolute number of CD34+ cells in the final product is affected by the number of CD34+ cells available in the starting UCB unit and the rate of differentiation of the unit during the culture. Due to differences between UCB units, the final CD34+ cell fraction of MGTA-456 constituted a median of 31.5% of all nucleated cells (range of 19.3% to 53.7%; see Table 2 for a comparison of TNC required to achieve the target CD34 cell dose). Furthermore, the final CD34+ cell dose is also affected by the patient's body weight resulting in a range of administered TNC and CD34+ cell doses.

Overcoming the engraftment barrier in IMD patients (who have not received prior immunosuppressive or cytoreductive therapy prior to transplant conditioning as is typical in oncology patients) undergoing UCBT is challenging, and historically required fully myeloablative conditioning regimens (Prasad et al 2008; Boelens et al 2013). It is expected that the higher dose of CD34+ cells present in MGTA-456 compared to a conventional UCB unit will promote engraftment in IMD patients. The need for high doses of CD34+ cells must be balanced with potential safety risks associated with the infusion of high numbers of nucleated cells. Therefore, the study will target the administration of a CD34+ cell dose (targeting 10×10^6 CD34+ cells per kg body weight compared to typically less than 1×10^6 CD34+ cells per kg body weight in a conventional UCB unit) and allow the use of up to 270×10^6 TNC/kg body weight in the IMD pediatric population which is the upper limit of the dosing window that has been investigated and has showed a favorable safety profile in oncology patients.

The rationale for selecting the above cell doses is based on the following observations:

- Higher CD34+ cell doses speed up neutrophil engraftment and establish long term chimerism in IMD (Martin et al 2006, Boelens et al 2013).
- MGTA-456 has shown a relationship between infused cell dose and engraftment (Figure 2, Investigator Brochure attached)
- In IMD specifically, the successful use of reduced dose conditioning regimens has been impeded by a suboptimal engraftment (Aldenhoven et al 2015a). However, IMD patients, unlike malignancy patients, do not typically receive myelotoxic and immunosuppressive chemotherapy as initial therapy for malignancy prior to HSCT. Additionally, in models of IMD in mice (e.g., Hurler syndrome) the accumulation of toxic byproducts in the bone marrow leads to impaired homing of stem cells (Watson et al 2014; Aldenhoven et al 2015a).
- Even with MAC, there is a substantial risk of graft failure. In the COBLT trial report on UCBT in IMD, the median number of CD34+ cells was 0.2×10^6/kg (range: 0.04

to 1.33). With these cell doses, the incidence of engraftment by Day 42 was 78% (95% CI, 67% to 87%) (Martin et al 2006).

- In the MGTA-456 studies in hematologic malignancies, 3 adolescents received MGTA-456 at doses of 17.2, 34.8, and 25.1 × 10^6 CD34+ cells/kg and 90, 46, and 90 × 10^6 TNC/kg without safety concerns related to MGTA-456. Therefore, the next dosing window (90 to 270 × 10^6 TNC/kg) was opened in the adolescent age group in study CHSC835X2201. Based on data from the unlocked clinical databases, adults in the ongoing MGTA-456 studies in hematologic malignancies have received cell doses up to 48 × 10^6 CD34+ cells/kg and 133 × 10^6 TNC/kg without infusional toxicity considered related to MGTA-456 except for 1 patient reporting febrile neutropenia and hypotension secondary to occult bacterial contamination of the MGTA-456 product.
- In publications reporting on conventional UCBT for IMD, TNC cell doses of up to 320 × 10^6/kg (median 88 × 10^6/kg), 388 × 10^6/kg (median 87 × 10^6/kg) and 503 × 10^6/kg (median 97.3 × 10^6/kg) have been reported without relevant toxicity (Boelens et al 2013, Martin et al 2006, Prasad et al 2008). These numbers are considerably higher than the TNC doses administered to patients with malignancies undergoing conventional UCBT (e.g., COBLT trial TNC median 51 × 10^6; Prasad et al 2008).
- [redacted]

Table 2: Percentage of CD34+ Cells in MGTA-456 Product Resulting in a Total CD34+ Cell Dose of 10 × 10^6/kg[a]

	TNC dose (10^6/kg)	CD34-positive cells (10^6/kg)	Percentage of CD34+ cells in final MGTA-456 product (%)
Minimum	51.8	10	19.3
Average	32.25	10	31.5
Maximum	18.6	10	53.7

[a] Based on 21 previous expansions

4. POPULATION

The study population will include pediatric patients age < 2.5 years with Hurler syndrome, age 2-17 years with cerebral adrenoleukodystrophy (cALD), age < 16 years with metachromatic leukodystrophy (MLD) and age ≤ 10 years with globoid cell leukodystrophy (GLD) (also referred to as Krabbe) Approximately 12 patients will be enrolled in the study, with the possibility of expanding to include up to approximately 15 additional patients.

The study will enroll pediatric patients with an IMD in which enzyme replacement treatment is not effective in preventing CNS deterioration likely due to the enzyme's inability to cross the blood brain barrier. Furthermore, only those disorders will be included for which there is considerable published evidence either from registries or from single institutions demonstrating the efficacy of allogeneic HSCT in limiting disease progression. Therefore, we will recruit only patients with diseases and disease stages in which allogeneic HSCT is considered 'standard' and in which HSCT is considered a treatment option per International EBMT guidelines (The EBMT Handbook 2008-Chapter 41) and a recent publication (Boelens et al 2014). Therefore, Hurler syndrome, cALD, MLD, and GLD will be included.

Any patient (or guardian) withdrawing their consent or any patient withdrawn because of an event unrelated to the study, at any time during the study, will be replaced to ensure approximately 6 patients in each cohort.

The patient must meet all inclusion criteria before the expansion culture will be initiated.

After 1 year, patients may be transferred to a separate long-term follow up study, if eligible and willing (after signature of the specific study ICF).

4.1 Inclusion Criteria

Patients must fulfill all the following criteria to be eligible for this study:

1. Written informed consent must be obtained from the patient or parent/guardian before any assessment is performed. Study assents will also be prepared for children and adolescents to review when applicable.
2. Male and female, age < 2.5 years with Hurler syndrome, age 2-17 years with cerebral adrenoleukodystrophy (cALD), age < 16 years with metachromatic leukodystrophy (MLD) and age ≤ 10 years with globoid cell leukodystrophy (GLD) (also referred to as Krabbe)Diagnosed with 1 of the following IMD:
    a. Hurler syndrome (mucopolysaccharidosis MPS-IH)
    b. MLD; asymptomatic late-infantile, or asymptomatic/minimally symptomatic juvenile onset patients
    c. GLD; asymptomatic infants, or asymptomatic/minimally symptomatic attenuated disease
    d. ALD; with active cerebral disease as established by radiographic review of brain MRI demonstrating a Loes score ≤10 and with a neurological function score (NFS) ≤1 (Moser, Arch Neurol 2005;62:1073-1080)

3. Able to complete all study procedures, measurements and visits; and parent/guardian and patient has adequately supportive psychosocial circumstances, in the opinion of the Investigator.
4. Patient must have a minimum life expectancy of 6 months in the judgment of the Investigator.
5. Recipients must meet the following:
    - Lansky score ≥50%
    - Renal: serum creatinine ≤2.5 × upper limit of normal (ULN) corrected for age
    - Hepatic: total bilirubin and ALT ≤3 × ULN corrected for age
    - Pulmonary function: oxygen saturation ≥92% without an oxygen requirement (an exception may be made as documented in the medical record for patients with abnormal sleep studies [such as patients with Hurler syndrome])
    - Cardiac: left ventricular ejection fraction (LVEF) ≥30%.
6. Graft Characteristics
    - The unrelated UCB grafts must be at least 6/8 HLA-A, HLA-B, HLA-C, and HLA-DRB1 matched with the recipient at the allele level. This is based upon a recent publication which showed that allele-level matching at HLA-A, HLA-B, HLA-C and HLA-DRB1 between the UCB unit and its recipient is associated with best survival and lowest occurrence of graft failure in children with non-malignant diseases.
    - UCB units must come from a qualified UCB bank(s) per institutional standard operating procedures (SOPs). A matched UCB unit from an unlicensed bank must be pre-approved by the sponsor before use. If the UCB unit is unlicensed (most commonly based on location [eg, European countries], testing by non- Clinical Laboratory Improvement Amendment (CLIA)-approved laboratories, or collection before 25 May 2005), Magenta will make the final decision on patient eligibility based on the reason why the UCB unit is unlicensed.
    - The minimal TNC count for the selected UCB unit is to be 1.0×10^7/kg body weight.
    - In a case where there is a better HLA-matched UCB unit with a lower cell dose, it may be selected over a less well-matched unit with a higher cell dose
    - The patient must not have donor specific anti HLA antibodies considering HLA A, B, C, DRB1, DQ and DP (MFI >1000).
    - A suitable back-up HSC source (UCB unit or unaffected haploidentical donor) must be available.
    - Cord blood grafts require genetic testing and/or demonstration of enzyme activity for patients with Hurler syndrome, MLD or GLD and are tested for very long chain fatty acids (VLCFA) to confirm there is no evidence of VLCFA consistent with ALD.

4.2 Exclusion Criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the Investigator, to ensure that the study population will be representative of all eligible patients.

1. Availability of a HLA 8/8 matched-related donor who is not a carrier of the same genetic defect.
2. Active infection at screening (defined as requiring parenteral antibiotics because of persistent changes consistent with infection based on imaging studies and/or positive cultures) including active infection with Aspergillus or other fungus within 30 days prior to screening, or severe concomitant diseases which in the judgment of the Investigator would lead to the patient's inability to tolerate conditioning regimen.
3. Prior myeloablative conditioning.
4. Prior use of an investigational study drug or procedure within 3 months before Screening that might confound study outcomes. Use of investigational study drugs is prohibited throughout the course of the study unless approved by Magenta. Except for approved Enzyme Replacement Therapy (ERT), use of investigational study drugs is prohibited throughout the course of the study unless approved by Magenta.
5. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.
6. Females of child-bearing potential, defined as all women physiologically capable of becoming pregnant (including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partner have been sterilized by vasectomy or other means), unless they are using highly effective methods of contraception from the day of transplant and for 1 year after infusion. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception).
    - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
7. Sexually active male patients unless they are using condoms as contraception starting on the first day of conditioning regimen (Day -9) until 1 year after infusion or off immune suppression, whichever is last.
8. History of human immunodeficiency virus (HIV) infection.

5. TREATMENT

5.1 Study Treatment

Details on the management of study medication, and instructions for administration are outlined in the Site Operations Manual.

Descriptive information regarding potential treatment risks, including infusional toxicity, peri-infusion infection, and pre-engraftment syndrome (PES) may be found in the IB.

5.1.1 Investigational Treatment

Starting on Day 0 of the protocol, the day of stem cell infusion, 2 separate therapeutic cell preparations will be infused sequentially in the following order.

1. A minimal dose of 10×10^6 CD34+ cells/kg body weight within a range of 20×10^6 to 270×10^6 TNC/kg body weight.
2. The entire CD34-depleted fraction derived from the same UCB unit as the ex vivo expanded CD34+ cells (referred to as the CD34-negative fraction).

The CD34-depleted fraction will be infused approximately one hour after the CD34+ fraction when all side effects relative to the CD34+ fraction have resolved, but may be infused as late as 24 hours after the CD34+ fraction if adverse events occurred with the expanded fraction or other reason approved by the principal investigator.

Each patient will be treated only once. A back-up HSC graft must be available in the event that the MGTA-456 product does not meet release criteria.

5.1.2 Additional Study Treatment

5.1.2.1 Conditioning Regimen

The dosing scheme using busulfan (BU), CY, and rabbit antithymocyte globulin (ATG) serotherapy will be used uniformly at all clinical sites participating in this study based on Bartelink et al 2008, Bartelink et al 2009, Bartelink et al 2014, and Prasad et al 2008.

The conditioning regimen will be initiated on Day -9 and will consist of:

- BU will be administered via IV for 4 days (Days -9 to -6).

  (A) Patients will receive a total of 4 doses (recommended initial dose: 120 mg/m^2 for age >1 year and 80 mg/m^2 for age <1 year) given once daily over 3 hours and adjusted to achieve targeted dose range (see below). Initial dose may also be determined by institutional nomogram or test dose.

  OR

  (B) Patients will receive a total of 16 doses (recommended initial dose 1 mg/kg) given every 6 hours and adjusted to achieve the targeted dose range (see below). Initial dose may also be determined by institutional nomogram or test dose.

- Leveteracetam (Keppra) prophylaxis against seizures will be given starting with a loading dose on the day before the first dose of BU and continued until 24 hours after the final dose of BU.
- CY will be administered via IV for 4 days (Days -5 to -2) at a dose of 50 mg/kg each day (total dose 200 mg/kg). Mesna prophylaxis will be administered per institutional protocol. The CY dose will be adjusted if the patient's actual body weight is more than 125% of the ideal body weight (IBW). The first dose of CY will begin >24 hours after the final dose of BU.
- ATG (rabbit; Thymoglobulin-Sanofi/Genzyme) will be administered over at least 6 hours at 2.5 mg/kg/dose each day on Days -5 to -2. If no initial adverse reactions occur, the infusion rate may be increased per institutional guidelines.

GVHD prophylaxis will consist of cyclosporine A (CsA) and mycophenolate mofetil (MMF).

Pre-medications for the conditioning regimen should be administered per Section 5.8.1.

Table 3: Conditioning Regimen Scheme and GVHD Prophylaxis

Day	Conditioning Regimen	GVHD Prophylaxis
Day -9	BU[a] IV given once daily over 3 hours (A) **OR** q6h IV given over 2 hours (B)	--
Day -8	BU[a] IV given once daily over 3 hours (A) **OR** q6h IV given over 2 hours (B)	--
Day -7	BU[a] IV given once daily over 3 hours (A) **OR** q6h IV given over 2 hours (B)	--
Day -6	BU[a] IV given once daily over 3 hours (A) **OR** q6h IV given over 2 hours (B)	--
Day -5	CY 50 mg/kg once daily over 1 hour + Mesna prophylaxis ATG once daily IV over at least 6 hours[b]	--
Day -4	CY 50 mg/kg once daily over 1 hour + Mesna prophylaxis ATG once daily IV over at least 6 hours[b]	--
Day -3	CY 50 mg/kg once daily over 1 hour + Mesna prophylaxis ATG once daily IV over at least 6 hours[b]	Begin CsA and MMF
Day -2	CY 50 mg/kg once daily over 1 hour + Mesna prophylaxis ATG once daily IV over at least 6 hours[b]	--
Day -1	--	--
Day 0	MGTA-456 infusion	
Day 1	--	Begin G-CSF[c]

Abbreviations: ANC=absolute neutrophil count; CY=cyclophosphamide; BU=busulfan; ATG=antithymocyte globulin; CsA=Cyclosporine A; MMF=mycophenolate mofetil; G-CSF= granulocyte-colony stimulating factor; IV=intravenous; q6h=every 6 hours; C_{ss}=steady state concentration

a BU will be targeted to achieve cumulative AUC of 74 to 82 mg*h/L (18,050 to 20,000 μM*min/L) **OR** 770 to 850 ng/mL C_{ss}.
b If the first dose of ATG is well tolerated, subsequent doses may be administered over a shorter time frame per institutional guidelines.
c G-CSF will be started on Day+1 and continued until the ANC ≥2,500/μL for 2 consecutive days.

Dosing of BU:

Busulfan dosing will target a cumulative AUC of 74 to 82 mg*hr/L with a goal of 78 mg*hr/L (equivalent to 18,050 to 20,000 μM*min/L with a goal of 19,025 μM*min/L).

Pharmacokinetic evaluation of BU:

The BU cumulative exposure (AUC_{cum}) goal is an AUC range of 74 to 82 mg*hr/L with a target of 78 mg*hr/L for dose adjustments. This is equivalent to 18,050 to 20,000 μM*min/L with a goal of 19,025 μM*min/L.

The BU daily exposure goal is an AUC range 18 to 20 mg*hr/L with a goal of 19 mg*hr/L. This is equivalent to approximately 4500 to 5000 μM*min/L with a goal of 4570 μM*min/L.

The BU single dose goal (if dosage regimen is Q6h) is an AUC range of 4.5 to 5 mg*hr/L with a target of 4.8 mg*hr/L. This is equivalent to approximately 1100 to 1220 uM*min/L with a goal of 1160 uM*min/L.

The steady state concentration (C_{ss}) goal is 770 to 850 ng/mL with a target of 810 ng/mL.

(A) Once daily dosing: BU will be given IV over 3 hours and adjusted to maintain an AUC target or C_{ss} target as indicated above. Recommended calculation of the AUC is performed on blood samples obtained: predose, 15 minutes, 1 hour, 3 hours, 5 hours, and 7 hours after the end of infusion. Recommended calculation of C_{ss} is performed on blood samples obtained: predose, 60 minutes, 115 minutes (5 minutes before end), 150 minutes, 3 hours, 4 hours, 5 hours, and 6 hours (prior to next dose). Busulfan dose is adjusted when the predicted cumulative AUC or C_{ss} falls outside the range. If possible, an evaluation of the AUC or C_{ss} after dose adjustment may be performed on subsequent days and used to confirm that the BU exposure is within the range. Busulfan PK may alternatively be calculated based on institutional guidelines, including the use of test doses, to achieve the specified target AUC or C_{ss}. Initial starting BU doses may also be calculated according to institutional nomogram or test dose.

OR

(B) Q6h dosing: BU will be given IV over 2 hours and adjusted to achieve an AUC target or C_{ss} target as indicated above. Recommended calculation of the AUC is performed on blood samples obtained: predose, 15 minutes, 1 hour, 3 hours, 5 hours, and 7 hours after the end of infusion. Recommended calculation of C_{ss} is performed on blood samples obtained: pre dose, 60 minutes, 115 minutes (5 minutes before end), 150 minutes, 3 hours, 4 hours, 5 hours, 6 hours (prior to next dose). Busulfan dose is adjusted when the predicted cumulative AUC or C_{ss} falls outside the range. If possible, an evaluation of the AUC or C_{ss} after dose adjustment may be performed on subsequent days and used to confirm that the BU exposure is within the range.

Busulfan PK may alternatively be calculated based on institutional guidelines, including the use of test doses, to achieve the specified target AUC or C_{ss}. Initial starting BU doses may also be calculated according to institutional nomogram or test dose.

Calculations used for AUC/C_{ss} conversions are as follows:

- AUC(mg*h)/L = AUC (µM*min)/L* 246 µg/µM * 1 mg/1000µg * 1hr/60 min
- C_{ss} (ng/ml) = AUC (µM*min)/L* 246 µg/µM * 1 hr/60 min * 1000 ng/1 µg * 1 L/1000 mL/(Dosing frequency)

For C_{ss} calculations:

- Dosing frequency for single dose AUC for Q6h dosage regimen = 6
- Dosing frequency for single day AUC for Q6h or Q24h = 24
- Dosing frequency for total exposure (cumulative) for Q6h or Q24h AUC = 96

Dosing of CY:

Route of Administration: The total daily dose will be given as a 1-hour IV infusion in 5% dextrose in normal saline (D5NS). Patients should receive additional hydration with 3000 mL/m^2/day of appropriate maintenance IV fluids starting 10 hours prior to CY and continued until 24 hours after the final dose. Patients will also receive mesna prophylaxis per institutional guidelines.

Dose Adjustment: Adjustment of the dose is required if the actual body weight (ABW) is more than 125% of the IBW for the age and gender. The dose should be calculated using adjusted ideal body weight (AIBW):

IBW Formula:

Less than 60 inches:

- IBW = (ht^2 × 1.65)/1000 where ht = cm, IBW = kg

More than 60 inches

- Males IBW = 39.0 + [2.27 × (ht – 60)] where ht = inches, IBW = kg
- Females IBW = 42.2 + [2.27 × (ht – 60)] where ht = inches, IBW = kg

AIBW Formula:

- AIBW = IBW + [(0.25) × (ABW - IBW)]

Immunosuppression:

All patients will receive the immunosuppression regimen per the study treatment plan as described below:

- **CsA**: Initiate on Day -3. Administer per institutional guidelines with adjustment to maintain target serum trough levels of 200 to 400 ng/ml. Cyclosporine A weaning begins at Day 270 if the patient is stably engrafted and has no active GVHD. The

dose will be tapered to zero by 10% weekly dose reduction over approximately 10 weeks.

- **MMF**: Initiate on Day -3 and continue until Day +45 or 7 days after engraftment, whichever is later if no acute GVHD is seen. Mycophenolate mofetil weaning is per institutional guidelines. Mycophenolate mofetil can be administered IV or orally (PO). For patients <50 kg 15 mg/kg IV/PO three times a day (TID) for patients >50 kg, 1 g IV/PO TID.

5.2 Treatment Arms

This is a single-arm, open-label study and all patients will receive MGTA-456.

5.3 Permitted Dose Adjustments and Interruptions of Study Treatment

MGTA-456 will be administrated only once during the study period. Therefore, dose adjustment of study treatment is not applicable.

5.4 Treatment Assignment

All patients who are consented (including screen failures) will be assigned a patient number. The unique patient identification number will consist of 6 digits (xxx-xxx), the first segment of the number represents the study site and the second segment represents the patient at that site. Any patient identification number that is assigned will not be re-used even if a patient is not treated (see Site Operations Manual for details).

Approximately 6 patients are to be included in each cohort. Up to approximately 15 additional patients may be enrolled in an expansion cohort following dosing of Cohort 2 based on the recommendation of the Data Monitoring Committee (DMC).

5.5 Treatment Blinding

This is a single-arm, open-label study and treatment blinding will not occur.

5.6 Treatment Exposure

MGTA-456 will be administrated only once during the study period. Details of infusion will be captured on the electronic case report form (eCRF).

[redacted]

PK parameters (measures of treatment exposure) will be determined in all patients treated with MGTA-456, as detailed in Section 7.5.

5.7 Recommended Treatment of Adverse Events

Medication used to treat AEs must be recorded on the eCRF. The clinical management of the complications discussed below will be per institutional guidelines. The following text is considered general guidance only.

5.7.1 Slow Engraftment/Graft Failure

The clinical management of slow engraftment/graft failure will be per institutional guidelines. Management of slow engraftment is triggered by the assessment of peripheral blood and bone marrow on Day 21. If at Day 21, the ANC is $\leq 0.5 \times 10^9$/L and bone marrow cellularity is ≤5%, G-CSF dose may be doubled or granulocyte macrophage-colony stimulating factor (GM-CSF) may be added at 250 mcg/m^2/d, the availability of the back-up UCB unit(s) that was put on hold at the time of patient enrolment is confirmed and a Day 28 bone marrow biopsy is scheduled.

If on Day 28 ANC remains $\leq 0.5 \times 10^9$/L and bone marrow cellularity is ≤5%, consideration will be given to performing a second HSC infusion using the previously identified back up source after some form of preconditioning per institutional standard of care. Patients will remain on-study for one-year unless they undergo a second HSC infusion. The patient will come off study at the time of the second HSC infusion and the event will be captured on the eCRF.

Use of medication, including non-drug therapies, for slow engraftment must be recorded on the eCRF.

5.7.2 Anemia

Transfusions of packed red blood cells are indicated for symptomatic management of anemia. An attempt should be made to maintain the hematocrit >24% and hemoglobin >8 g/dL. Irradiated (1500 to 3000 cGy) blood products will be used in accordance with the institutional standard of care and all red blood cell transfusions will be recorded in the eCRF.

5.7.3 Thrombocytopenia

Prophylactic platelet transfusions should be given to maintain the platelet count $>10 \times 10^9$/L or above the level at which signs of bleeding are known to occur, whichever is greater. All aspirin containing drugs are to be avoided. The patients should receive no intramuscular injections while thrombocytopenic. Irradiated (1500 to 3000 cGy) blood products will be used in accordance with the institutional standard of care and all platelet transfusions will be recorded in the eCRF.

5.7.4 Nutrition

All patients will be candidates for total parenteral nutrition; length of use is per institutional guidelines.

5.7.5 Acute Graft Versus Host Disease

Patients will be considered evaluable for aGVHD unless they are known to have autologous recovery or die before Day 28 without GVHD. Organ involvement will be staged using the criteria outlined in the Appendix 2. Biopsy of each organ site at diagnosis or major change in disease activity will be performed unless clinical circumstances make it impossible.

5.7.6 Infusional Reaction

MGTA-456 expanded cell product, like other blood products, may cause infusional reactions, including hemodynamic effects or acute hypersensitivity. Furthermore, the co-infusion of residual components of the expansion culture carries theoretical attendant risks. These time-limited events are expected to occur within the first 24 hours (Regan et al 2010, Kharbanda

et al 2014), and may range from mild to moderate in severity and may include gastrointestinal (nausea, vomiting, diarrhea and abdominal cramps), respiratory (cough, dyspnea), cardiovascular (hypotension, hypertension, bradycardia), neurological, or dermatological (skin flushing, rash) events, infection, and anaphylaxis (Martín-Henao et al 2010).

Emergency drugs such as epinephrine, hydrocortisone, diphenhydramine, and atropine in appropriate dosages and dilutions should be available at the bedside and administered per institutional guidelines. Oxygen with nasal prongs for standby use should be present in the room.

5.7.7 Engraftment Syndrome/Transfusion Related Acute Lung Injury (TRALI)

Engraftment syndrome is a syndrome characterized by fever, fluid retention, rash and pulmonary infiltrates proximal to the time of neutrophil recovery after high dose conditioning and HSCT, likely mediated by activated leukocytes and proinflammatory cytokines. Treatment is supportive, including antipyretics, oxygen and diuretics, and systemic corticosteroids or therapies directed to specific proinflammatory cytokines (e.g., IL6).

TRALI is a rare but serious syndrome characterized by sudden acute respiratory distress following transfusion. It is defined as new, acute lung injury during or within six hours after blood product administration in the absence of other risk factors for acute lung injury. TRALI is thought to be caused by activation of recipient neutrophils by donor-derived antibodies targeting HLA or human neutrophil antigen (HNA), in most cases. Non-antibody-mediated cases occur and may be mediated by biologic response modifiers present in the transfused blood product, along with recipient factors. Treatment is supportive and consists of oxygen, ventilator support and management of fluid balance.

5.7.8 Autoimmune Cytopenia

Autoimmune cytopenia is the single or combination of auto/alloimmune hemolytic anemia, idiopathic thrombocytopenic purpura, and/or autoimmune neutropenia developing after HSCT. The mechanism of AIC development is not clearly understood but is postulated to be from immune dysregulation leading to aberrant antibody production. An increased incidence of AIC has been observed in transplant for non-malignant diseases, in particular for IMDs and Hurler Syndrome with rates between 20 to 56% (Deambrosis et al, 2018; Page et al 2008; Khalil et al 2014). Age at transplant is an independent risk factor for AIC with incidence in infants reported up to 56% (Page et al 2008; Kruizinga et al 2018). Based on an evolving understanding of AIC, if investigation of a cytopenia reveals a single auto-antibody towards one cell line, it is recommended to test for antibodies to all lineages (red cell, platelet, and neutrophil) to guide early treatment. Recommended first line treatment is steroids, intravenous immunoglobulin (IVIg), and rituximab. Initiating plasmapheresis earlier in therapy is suggested to remove the auto-reactive antibody already produced.

5.8 Concomitant Treatment

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the eCRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy. In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient (eg, approved enzyme replacement therapy [ERT]) are allowed.

5.8.1 Pre-medications

Leveteracetam will be administered to all patients in accordance with institutional guidelines as seizure prophylaxis during BU therapy, starting with a loading dose on the day before the first dose of BU and continuing for at least 24 hours after the last dose of BU. The following pre-medications will be administered 30 minutes prior to each dose of ATG including: acetaminophen (10 mg/kg orally; maximum dose 500 mg); diphenhydramine (1 mg/kg IV or PO; maximum dose 50 mg), and methylprednisolone (1 mg/kg IV; maximum dose 125 mg). Mesna will be administered per the institutional guidelines beginning prior to the first infusion of CY and continuing through at least Day -2. Anti-emetics will be administered as needed per institutional guidelines.

Pre-medication for the MGTA-456 infusion will be per institution's standard of care for HSC product infusions.

5.8.2 Stem Cell Engraftment Enhancement

G-CSF will be administered starting on Day +1 (5 mcg/kg IV once daily) and continued until the ANC ≥2,500/µl for 2 consecutive days. G-CSF is used after UCB transplantation to limit the duration of neutropenia (Section 5.1.2.1).

5.8.3 Anti-Oxidants and Anti-Inflammatories

Anti-oxidant and anti-inflammatory drugs should be used for patients with cALD following the institutional guidelines.

6. DISCONTINUATION AND STUDY COMPLETION

6.1 Discontinuation of Study

Patients who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 6.3). Where possible, they should return for the assessments listed for the final visit in Table 5. If they fail to return for these assessments, every effort (e.g., telephone, e-mail, letter) should be made to contact them as specified in Section 6.2.1.

Patients may withdraw from the study at any time. Each patient will be treated only once.

6.2 Study Completion and Post-Study Treatment

Each patient will be encouraged to complete the study in its entirety. Study completion is defined as the patient completing a 1-year end of study visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision. Patients will remain on-study for 1 year unless they undergo a second HSC infusion (see Section 5.7.1).

Following the completion of this study, patients may be eligible to participate in a separate clinical trial for long-term safety monitoring.

The Investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

6.2.1 Lost to Follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the Investigator should show due diligence by documenting in the source documents steps taken to contact the patient (eg, dates of telephone calls, registered letters, etc.). A patient should not be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

6.3 Withdrawal of Consent

A patient may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study anymore, does not want any further visits or assessments and does not want any further study related contact.

If a patient withdraws consent, the Investigator must make every effort to determine the primary reason for this decision and record this information. No further assessments should be conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

6.4 Study Stopping Rules

If there is an indication that the use of MGTA-456 in IMD patients is associated with an unacceptably high rate of graft failure, TRM, or Grade III-IV aGVHD the study will be placed

on hold, available data will be reviewed and a decision on study continuation will be made jointly with the DMC.

The stopping rules described below will be assessed for Cohort 1 and 2 separately:

- Excess graft failure: graft failure will be defined as the absence of ANC recovery >0.5 x 10^9/L for 3 consecutive days or lack of myeloid chimerism (<5%) by Day 42. The expected rate of graft failure is approximately 15% (publication pending). Enrollment will be stopped if 2/2, 2/3, 2/4, 2/5, or 3/6 events are observed.
- Excess TRM by Day 100. The expected mortality rate by Day 100 after transplant is approximately 10% (publication pending). Enrollment will be stopped if 2/2, 2/3, 2/4, 2/5, or 3/6 events are observed.
- Excess Grade III-IV acute GVHD by Day 100. The expected rate of Grade III-IV aGVHD is approximately 15% (Harris et al 2018). Enrollment will be stopped if 2/2, 2/3, 2/4, 2/5, or 3/6 events are observed.
- One death within 30 days of treatment, regardless of cohort.

With 6 patients per cohort, the stopping rules would ensure a reasonable probability (83%) that the cohort would not be stopped if the true event rate was 15% or lower while also ensuring an appropriate probability that the study would be stopped if the true event rate was high (66% probability for true event rates greater than 40%). Enrollment will be allowed to continue while monitoring for safety events that would reach a stopping rule.

Table 4 shows some of the properties of the stopping rule for up to 10 patients (e.g., if after 6 patients it is decided to continue to enroll more patients before moving to the next cohort).

Table 4: Stopping Rule Properties

Cohort Size	Number of events triggering stop	Probability that the true rate is >15% given the data	Probability that the true rate is >10% given the data	Probability of stopping when true rate is 15%	Probability of stopping when true rate is 40%
2	2	>99%	>99%	3%	16%
3	2	98%	>99%	6%	36%
4	2	95%	98%	11%	53%
5	2	92%	97%	16%	67%
6	3	98%	>99%	17%	66%
7	3	96%	99%	17%	71%
8	3	94%	98%	19%	76%
9	3	92%	97%	21%	81%
10	4	97%	>99%	22%	81%

6.5 Early Study Termination

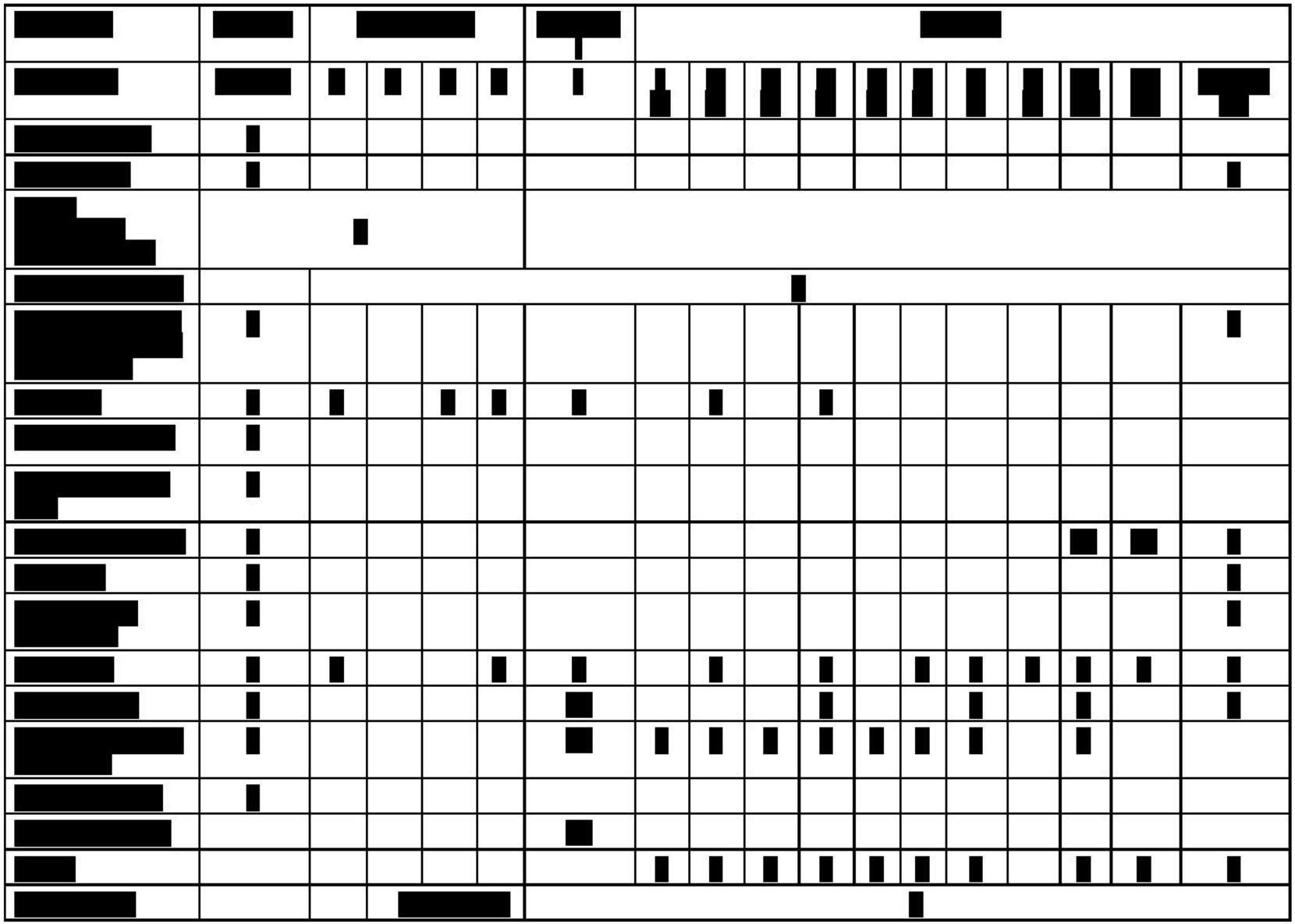
The study may be terminated at any time for any reason by Magenta. Should this occur, patients who are still on study should be seen as soon as possible and treated as a prematurely withdrawn patient. The Investigator may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the patient's interests.

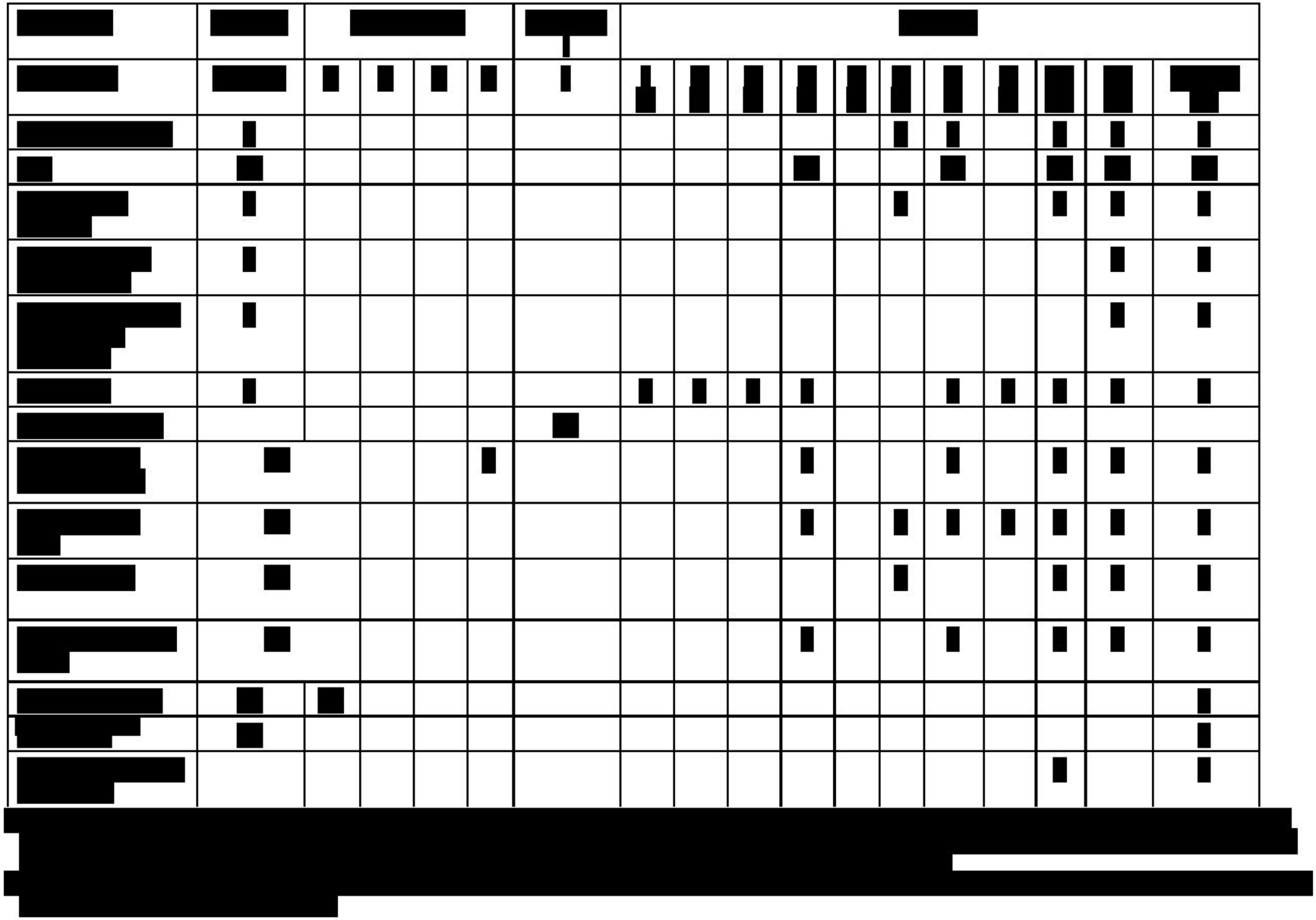
The Investigator will be responsible for informing institutional review boards (IRBs)/independent ethics committees (IECs) of the early termination of the trial.

7. PROCEDURES AND ASSESSMENTS

Patients should be seen for all visits on the designated day, with the assessments performed as per schedule, within the allowed visit/assessment window specified in the Site Operations Manual. However, in the event the patient cannot return to the Transplant Center on the scheduled date, every attempt will be made to obtain the required laboratory tests and shipped to the Transplant Center. Patients who prematurely withdraw from the study for any reason should be scheduled for a visit as soon as possible, at which time all the assessments listed for the final visit will be performed.

Table 5: Schedule of Assessments





7.1 Informed Consent Procedures

Voluntary written informed consent must be obtained before any study-related procedures are performed, in accordance with ICH guidelines and requirements of informed consent (Title 21 Code of Federal Regulations [CFR] Parts 50.20 and 50.25). Consent must be documented by the use of a written consent form approved by Magenta and the site's IRB or IEC in accordance with Title 21 CFR Part 50.27.

For minor patients, the patient's parent/guardian will give consent and the patient should be informed about the study to the extent possible given his/her understanding. Minor patients capable of understanding/reading, will be given a dedicated information form to review.

The process of obtaining informed consent should be documented in the patient source documents. A copy of the signed informed consent will be provided to the person signing the form, and the original will be retained in the source documents of the patient.

Pregnancy outcomes must be collected for the female partners of any males administered study treatment in this study if conception occurred within the first week after MGTA-456 administration. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

In the event that Magenta wants to perform testing on the samples that are not described in this protocol.

A copy of the approved version of all consent forms must be provided to Magenta or designee after IRB/IEC approval.

7.2 Patient Demographics and Other Baseline Characteristics

Patient demographic and baseline characteristic data to be collected on all patients include date of birth, age, sex, race, and predominant ethnicity.

Relevant medical history (including history of disease, enzyme replacement therapy, and response to treatment) and current medical conditions will be recorded until the day of transplantation.

Any event or change in the patient's condition or health status occurring prior to MGTA-456 administration will be reported as medical history, as indicated in the assessment schedule (Table 5).

7.2.1 Lansky Performance Status

Performance status will be recorded as defined by the Lansky Scale for patients less than 16 years of age (Table 6).

Table 6: Lansky Performance Status

Score	Lansky
100	Fully active, normal
90	Minor restrictions in physically strenuous activity
80	Active, but tires more quickly
70	Both greater restriction of, and less time spent in, play activities
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Gets dressed but lies around much of the day, no active play; able to participate in all quiet play and activities
40	Mostly in bed; participates in quiet activities
30	In bed; needs assistance even for quiet play
20	Often sleeping; play entirely limited to very passive activities
10	Unresponsive
0	Dead

7.2.2 Pre-existing Anti-HLA Donor-Specific Antibodies

A single antigen bead (SAB)-based test or an equivalent technology will be utilized to detect pre-existing anti-HLA antibodies for HLA antigens. This assay will aid in selecting appropriate UCB units.

7.2.3 Human Leukocyte Antigen Typing

Human leukocyte antigen typing of the recipient will be done to allow matching of UCB units. The UCB grafts must be at least 6/8 HLA-A, HLA-B, HLA-C, and HLA-DRB1 matched with the recipient (HLA matching at the allele level).

7.2.4 Chest X-ray

Chest X-ray should be performed in all patients at screening, Day 360/EOS, and as clinically indicated during the study.

[redacted]

7.3 Efficacy/Pharmacodynamics

7.3.1 Assessment of Engraftment and Graft Failure

Following HSCT, patients will be monitored for engraftment.

Patients will be routinely monitored for time to neutrophil recovery (first day of 3 consecutive days when ANC $\geq 0.5 \times 10^9$/L) and platelet recovery (as defined in 2 ways: [1] $\geq 20 \times 10^9$/L for 3 consecutive laboratory measurements on different days without transfusion in the prior 7 day [2] $\geq 50 \times 10^9$/L for 3 consecutive laboratory measurements on different days without transfusion in the prior 7 days) as detailed in Table 5.

Patients will also be assessed for neutrophil recovery with MGTA-456 defined as neutrophil recovery by Day 42, as well as days with neutropenia from the day of transplant through Day 42.

Patients diagnosed with graft failure (failure to achieve neutrophil recovery with MGTA-456 by Day 42 or <5% chimerism) or late hematological graft failure (defined as meeting 1 of the following 3 criteria: [1] <5% donor whole blood or myeloid chimerism in peripheral blood or bone marrow beyond Day 42 post-transplant in patients with prior hematopoietic recovery with ≥5% donor cells by Day 42 post-transplant; [2] Sustained decline in the ANC to <500/mm^3 for 3 consecutive measurements on different days, unresponsive to growth factor therapy after initial hematopoietic recovery by Day 42; [3] Subsequent bone marrow aplasia identified after initial hematopoietic recovery by Day 42) must be reported to Magenta (Refer to Section 5.7 for graft failure treatment information).

7.3.2 Chimerism Studies

Chimerism analysis based on microsatellite differences between the transplanted MGTA-456 and the recipient will be conducted as per Table 5. Circulating mononuclear cells will be sorted or separated based on the presence of surface antigens recognized by antibodies or antibody combinations including but not limited to anti-CD3 (pan-T) and, anti-CD33/66 (or CD15) (myeloid) antibodies as well as CD19 and CD56. Deoxyribonucleic acid (DNA) will be prepared from the different samples and the source of the respective subset will be determined based on a method that distinguishes differences between the MGTA-456 and the recipient. Blood volumes required for chimerism assessments are provided in Appendix 1.

[redacted]

7.4 Safety

Safety assessments are specified in the following sections; methods for assessment and recording are specified in the Site Operations Manual, with Table 5 detailing when each assessment is to be performed.

7.4.1 Physical Examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and nervous system. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed.

Information for all physical examinations must be included in the source documentation at the study site and will be recorded on the eCRF. Significant findings that are present prior to MGTA-456 infusion may be recorded as medical history. Significant findings observed after MGTA-456 administration which meet the definition of an AE must be appropriately recorded on the AE eCRF.

7.4.2 Vital Signs

Vitals signs will include body weight, body temperature, systolic and diastolic blood pressure, pulse rate, and pulse oximetry will be obtained at specified times in Table 5.

7.4.3 Height and Head Circumference

Height in centimeters will be measured at Screening and Study Day 360/EOS for all patients. Head circumference will be measured in centimeters at Screening and Study Day 360/EOS for patients with Hurler syndrome only.

7.4.4 Laboratory Evaluations

In the case where a laboratory assessment that is listed in the inclusion/exclusion criteria is outside of a protocol-specified range at screening and/or at the initial baseline, the assessment may be repeated prior to treatment number assignment. If the repeat value(s) remain outside of protocol-specified ranges, the patient will be excluded from the study.

Clinically relevant deviations of laboratory test results should be evaluated for criteria defining an AE and reported as such.

Guidance on maximum blood volume to be collected during the study are based on the recommendations of the USC/LA Children's Hospital (World Health Organization [WHO] – Bulletin of WHO; Howie 2011) on blood volumes in child health research (review of safe limits) and WHO child growth standards. The estimated blood volume for safety and standard of care assessments are based on standard of care laboratory assessments obtained at the site. The recommended maximum daily blood volume is 2 mL/kg/day. Considering the above recommendations, prioritization of sample collection will be needed in the pediatric population based on blood volume. Among protocol mandated research-related blood collections, only PK samples will be required to be collected on Day 0, because they are considered relevant for patient safety. The

remaining study specific samples will be prioritized as follows (highest priority first) and only be collected if considered to be safe by the Investigator: chimerism (CD3 T cell and CD33/66 [or CD15] myeloid chimerism, followed by CD19 and CD56), immune reconstitution, T cell repertoire, PK, and optional plasma biomarkers. Sample must be drawn prior to initiating conditioning regimen Lower priority research-related samples may be collected on a subsequent day as blood volume limitations permit (for details, refer to Appendix 1).

7.4.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelet count, and ANC will be measured.

7.4.4.2 Clinical Chemistry

Sodium, potassium, bicarbonate, phosphate, creatinine, uric acid, chloride, albumin, calcium, alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST), ALT, glucose, and blood urea nitrogen (BUN).

Direct and indirect reacting bilirubin should be differentiated as clinically indicated.

7.4.4.3 Viral Testing/Infection Surveillance

All patients will be screened for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis C virus (HCV), herpes simplex virus (HSV), cytomegalovirus, (CMV), Epstein-Barr virus (EBV), and human T cell lymphotropic virus 1/2 (HTLV1/2) during their pre-transplant evaluation.

Infection Surveillance of viral reactivation by quantitative PCR will be performed as detailed in Table 5. Testing will include CMV, EBV, and human herpesvirus (HHV-6) as deemed appropriate based on the standard of care at the Institution.

7.4.5 Electrocardiogram and Echocardiogram

Electrocardiogram (ECG) and echocardiogram assessments will be conducted as detailed in Table 5 and clinically significant abnormalities should be evaluated for criteria defining an AE and reported as such.

7.4.6 Pregnancy Testing

For all females of child bearing potential, serum pregnancy testing is required at Screening and end of study visit, regardless of reported reproductive status.

7.4.7 Pulmonary Function Tests (PFT)

Pulmonary function tests (PFT) for assessing lung function should be performed in all patients capable of doing so (about age 6 years) at screening and Day 360/End of Study Visit. Otherwise oxygen saturation should be performed at screening and Day 360/End of Study Visit.

7.4.8 Graft Versus Host Disease Assessments

Patients will be assessed for aGVHD and cGVHD based on criteria listed in Appendix 2 and Appendix 3.

7.4.9 Survival Information

Survival outcome will be collected at end of Year 1 for any patient enrolled into the study. Follow-up survival information after 1 year is planned to be collected in a separate long-term follow-up study.

7.4.10 Assessment of Infusional Toxicities

Patients will be investigated for infusional toxicities within 48 hours after MGTA-456 administration. Infusional toxicities coming from MGTA-456 administration may be adverse reactions associated with infusing large numbers of ex vivo expanded HSC that result in hemodynamic effects in the patient or adverse reactions that may come from the combination of components or residual components of the expansion culture or freezing medium, including cytokines, the manufacturing reagent, Dextran 40, HSA and DMSO. Such infusional toxicities may include but are not limited to fever, nausea, vomiting, excessive sweating (diaphoresis), labored breathing (dyspnea), chest discomfort, desaturation (reduced oxygen saturation), hypotension, hypertension, headache, and bradycardia (slow heart rate) (

Scarpa M, Orchard PJ, Schulz A, Dickson PI, Haskins ME, Escolar ML, Giugliani R. Treatment of brain disease in the mucopolysaccharidoses. Mol Genet Metab. 2017 Dec;122S:25-34.

Shu et al 2014, Konuma et al 2008).

7.4.11 Assessment of Infectious Events After Transplantation

After UCBT, patients will be investigated for infectious events including but not limited to bacteremia, documented infections, number of additional antibiotic agents administered on top of prophylactic dosing, number of courses of antibiotics, and measures of infection density.

Infectious testing will be conducted as documented in Table 5.

7.4.12 Transfusion Support

Information on the need for transfusion support will be collected as the number and time point of administered platelet and packed RBC transfusions.

7.5 Pharmacokinetics

[redacted]

[redacted]

7.6 Other Assessments

[redacted]

[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			

[redacted]

[redacted]

[redacted]

8. SAFETY MONITORING

8.1 Adverse Events

An AE is any untoward medical occurrence (ie, any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation patient after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

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

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

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

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

AEs must be recorded on the AE eCRF for patients that meet eligibility and enroll in the study. The AEs should be reported per the signs, symptoms, or diagnosis associated with them, and accompanied by the following information:

1. The Common Toxicity Criteria Adverse Event (CTCAE) grade (version 4.03) If

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

   - 1=mild,
   - 2=moderate,
   - 3=severe,
   - 4=life threatening.

   CTCAE Grade 5 (death) is not used. Fatal AEs will be collected in other eCRFs as per eCRF completion guidance. There may be cases where an AE with a Grade 4 (life-threatening) may not necessarily be a serious AE (SAE) (e.g., certain lab abnormalities in the absence of meeting other seriousness criteria).

2. Relationship to the study treatment (no/yes).
3. Duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.

4. Whether it constitutes an SAE (see Section 8.2 for definition of SAE).
5. Action taken regarding study treatment.

   All AEs should be treated appropriately. Treatment may include one or more of the following:

   - No action taken (ie, further observation only)
   - Concomitant medication given
   - Non-drug therapy given
   - Patient hospitalized/patient's hospitalization prolonged
6. Outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

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

Information about common side effects already known about the investigational drug can be found in the IB or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

The Investigator should also instruct each patient to report any new AE (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the Investigator's source documents and recorded on the patient eCRF are per the instructions below; however, if the AE meets the criteria of an SAE, it must be reported to Magenta.

8.1.1 Non-Serious AE Documentation

Given the high number of non-serious AEs experienced in the patient population being studied, recording of non-serious AEs will be handled depending on when they occur. Recording of non-serious AEs will start on Day 0, the day of MGTA-456 transplant. All non-serious AEs occurring on Day 0 through 48 hours following infusion of MGTA-456 will be recorded in the clinical database via eCRFs regardless of grade or expectedness. Between 48 hours after the infusion of MGTA-456 and up to Day 100, all non-serious AEs except for frequent and anticipated events related to the HSCT procedure itself, will be recorded in the clinical database. After Day 100, non-serious AEs will be collected as detailed in Table 8.

Table 8: Collection of Non-Serious Adverse Events

Timepoint	Criteria
Day 0 to Hour 48	Record all non-serious AEs on patient eCRF
Hour 48 to Day 100	Record all non-serious AEs on patient eCRF, except for those noted below. These AE are considered anticipated events that are caused by the HSCT procedure, primarily the preparative regimen. They are either anticipated low grade (Grade 1 or 2 per the CTCAE version 4.03) events or they are captured in the database separately (eg, vital sign pages, laboratory pages). The following <u>will not be recorded as an AE</u> in the clinical database: • All non-serious hematologic lab abnormalities AEs anticipated as part of the HSCT procedure, such as out of range absolute neutrophil or absolute lymphocyte counts, thrombocytopenia, anemia • Anticipated Grade 1 and 2 non-serious AEs related to the HSCT procedure including but not limited to: neutropenia, mucositis, gastrointestinal disorders such as vomiting, nausea, diarrhea, anorexia, hypertension, hypotension, electrolyte imbalance, alopecia, fatigue, weight gain or loss The following must be recorded as an AE in the clinical database: • Any other event not meeting the exception criteria above including ▪ All CTCAE Grade 3 or 4 AEs ▪ Any grade CTCAE AE that, in the Investigator's clinical judgment, is not an anticipated result of standard HSCT procedures ▪ Any grade evidence for infection resulting in treatment of the patient ▪ Any grade GVHD ▪ Any evidence for malignancy ▪ Any grade pre-engraftment syndrome ▪ Non-serious AEs that may be anticipated, but continue after Day 100, should be recorded.
Day 100 to end of study (+30d)	All non-SAEs will be available in source documents but only documented infections, cases of GVHD and malignancy will be recorded in the eCRF

8.2 Serious Adverse Event Reporting

8.2.1 Definition of a Serious Adverse Event

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

- Is fatal or life-threatening

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

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

All malignant neoplasms will be assessed as serious under 'medically significant' if other seriousness criteria are not met.

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

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

Serious adverse events are monitored continuously and have also special reporting requirements; see Section 8.2.2.

8.2.2 SAE Reporting

Every SAE, regardless of causality, occurring starting with initiation of the conditioning regimen (ie, Day -9) until 30 days after the last study visit (protocol period +30d) will be collected in the clinical database and must be reported to Magenta within 24 hours of learning of its occurrence as described below. Any SAEs experienced after this should only be reported to Magenta if the Investigator suspects a causal relationship to study treatment.

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

SAEs (initial and follow-up) that are recorded electronically in the electronic data capture system should be entered, saved and e-signed within 24 hours of awareness of the SAE or changes to an existing SAE.

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

Follow-up information provided should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the investigational treatment, Magenta may urgently require further information from the Investigator for Health Authority reporting. Magenta may need to issue an Investigator Notification (IN) to inform all Investigators involved in any study with the same investigational treatment that this SAE has been reported. SUSARs will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

8.3 Pregnancy Reporting

Every pregnancy occurring after the patient was administered MGTA-456 under this protocol and until 30 days after the patient has stopped study participation must be reported to Magenta within 24 hours of learning of its occurrence. The pregnancy should be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. A pregnancy occurring after signing the informed consent and before the patient is enrolled will preclude study participation.

Pregnancy should be recorded on a Pregnancy Report Form and reported by the Investigator to the Magenta Drug Safety Department using the contact information provided in Section 8.2.2.

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

Table 9 indicates the level of contraception (highly effective or effective) which is required during the compound clinical development in males and /or females of child bearing potential. This recommendation is made after consideration of the latest available information on clinical data. Since the immunosuppressive regimen and other frequently used co-medications include medications with teratogenic potential, women who can become pregnant must be made aware of the raised risk of first trimester pregnancy loss and must be counseled about pregnancy prevention and planning.

Table 9: Contraception Requirements

Gender	Study Participation	Need for Contraception	Contraception Level/Method
WOCBP	Yes	Yes	Highly effective
Male	Yes	Yes	Effective

WOCBP=women of child bearing potential

8.4 Prospective Suicidality Assessment

There will be no prospective suicidality assessment. However, all SAEs relating to suicidal behavior will be reviewed by the Safety Management Team.

8.5 Early Phase Safety Monitoring

The Investigator will monitor adverse events in an ongoing manner and inform Magenta of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing Magenta and the Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Magenta and all Investigator(s).

Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When 2 or more clinical site(s) are participating in the clinical study, Magenta will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

9. DATA REVIEW AND DATABASE MANAGEMENT

9.1 Site Monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Magenta representative will review the protocol and eCRFs with the Investigators and their staff. During the study, the Magenta representative or field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study product is being stored, dispensed, and accounted for per specifications. Key study personnel must be available to assist the field monitor during these visits.

The Investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. The Investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Magenta monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the eCRFs are performed per the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

9.2 Data Collection

Designated Investigator staff will enter the data required by the protocol into the eCRFs using fully validated software that conforms to 21 CFR Part 11 requirements. Designated Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to Magenta. The Investigator must certify that the data entered into the eCRFs are complete and accurate. After database lock, the Investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

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

9.3 Database Management and Quality Control

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

Magenta or designee will review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated Investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Magenta or designee who will make the correction to the database.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be made available for data analysis.

9.4 Data Monitoring Committee

An independent and external DMC will be instituted for this study to monitor the safety of patients. The membership of the DMC and the responsibilities of the DMC will be defined in a separate Data Monitoring Committee Charter document. The DMC Charter will include information about data flow, purpose and timing of DMC meetings, communication strategy, procedures for ensuring confidentiality, procedures to address conflicts of interest and statistical monitoring guidelines.

Members of the committee will not otherwise be involved in the conduct of the study. Magenta personnel will support the smooth functioning of the committee.

The DMC will assess the observed safety and clinical outcomes after the first 6 patients have reached Day 42 post-transplant and every approximately 6 months thereafter during the trial and will give a recommendation with respect to trial continuation. DMC members will be responsible for clinical interpretation of the results. At the DMC's discretion, more data and/or meetings may be requested and/or the timing of the meetings may be changed.

10. DATA ANALYSIS

10.1 Analysis Sets

The full analysis set will include all patients that received MGTA-456. This analysis set will be used for all assessments of efficacy and safety.

The PK analysis set will include all patients with available PK data and no major protocol deviations with relevant impact on PK data.

The PD analysis set will include all patients with available PD data and no major protocol deviations with relevant impact on PD data.

In general, data will be presented by cohort (ie, either fresh or cryopreserved HCS835 product) and overall.

10.2 Patient Demographics and Other Baseline Characteristics

All data for background and demographic variables will be listed by patient. Summary statistics will be provided.

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

10.3 Treatments - Study Drug, Rescue Medication, Other Concomitant Therapies, Compliance

MGTA-456 infusions will be summarized as the number of each cell type per kilogram body weight.

Concomitant treatments will be listed and summarized by time period to distinguish more easily between those given as part of the conditioning regimen, those given in the first weeks after transplantation, and those used at during other time periods.

10.4 Analysis of the Primary Variable(s)

10.4.1 Endpoints

The primary endpoints are provided in Section 2.

10.4.2 Statistical Model, Hypothesis, and Methods of Analysis

The incidence of each of the primary variables will be determined. The overall incidence will be presented together with the associated 95% confidence interval.

10.4.3 Handling of Missing Values, Censoring, and Discontinuations

All available data will contribute to analyses of primary and secondary variables. Conventions for handling missing values, as applicable, will be further described in the Statistical Analysis Plan.

10.4.4 Supportive Analyses

Not applicable.

10.5 Analysis of Secondary and Exploratory Variables

10.5.1 Secondary and Exploratory Endpoints

The secondary and exploratory endpoints are provided in Section 2.

Time to event variables are measured relative to the time of transplantation with MGTA-456. These variables will be summarized using Kaplan-Meier time to event methods in which patients who discontinue the study or are lost to follow-up are treated as censored observations. The results will be displayed graphically. The number of patients experiencing the events by relevant time windows (including by Day 42 for neutrophil recovery, Day 180 for platelet recovery, Day 100 for aGVHD, and 1 year for cGVHD) will be presented as further detailed in the statistical analysis plan.

In the assessment of acute and chronic GVHD only patients who achieved engraftment will be considered.

[redacted]

Details of the analysis of other exploratory variables will be defined in the Statistical Analysis Plan.

10.5.2 Safety

10.5.2.1 Vital Signs

All vital signs data will be listed by patient and time and abnormalities will be flagged. Summary statistics and graphical displays will be provided by time for the first 48 hours after the transplant.

10.5.2.2 ECG Evaluations

All ECG data will be listed by patient and time and abnormalities will be flagged.

10.5.2.3 Clinical Laboratory Evaluations

All laboratory data will be listed by patient and time, and abnormalities will be flagged.

10.5.2.4 Adverse Events

All information obtained on AEs will be displayed by patient and time period. Adverse events will be split by the time periods of 0 to 48 hours post-transplant and Day 3 to end of study.

The number and percentage of patients with AEs will be tabulated by body system and preferred term. A patient with multiple adverse events within a body system is only counted once towards the total of this body system.

The following AE and SAE summaries will be provided by time period:

- Summary of incidence of all AEs / SAEs
- Summary of incidence of AEs / SAEs by CTCAE grade
- Summary of incidence of AEs / SAEs related to study procedures

10.5.2.5 Concomitant Medications/Significant Non-Drug Therapies

All recorded concomitant medications and therapies will be listed by patient.

10.5.2.6 Other Safety Evaluations

Results of other safety assessments will be listed by patient and summarized by descriptive statistics as appropriate and as defined in the Reporting and Analysis Plan.

[redacted]

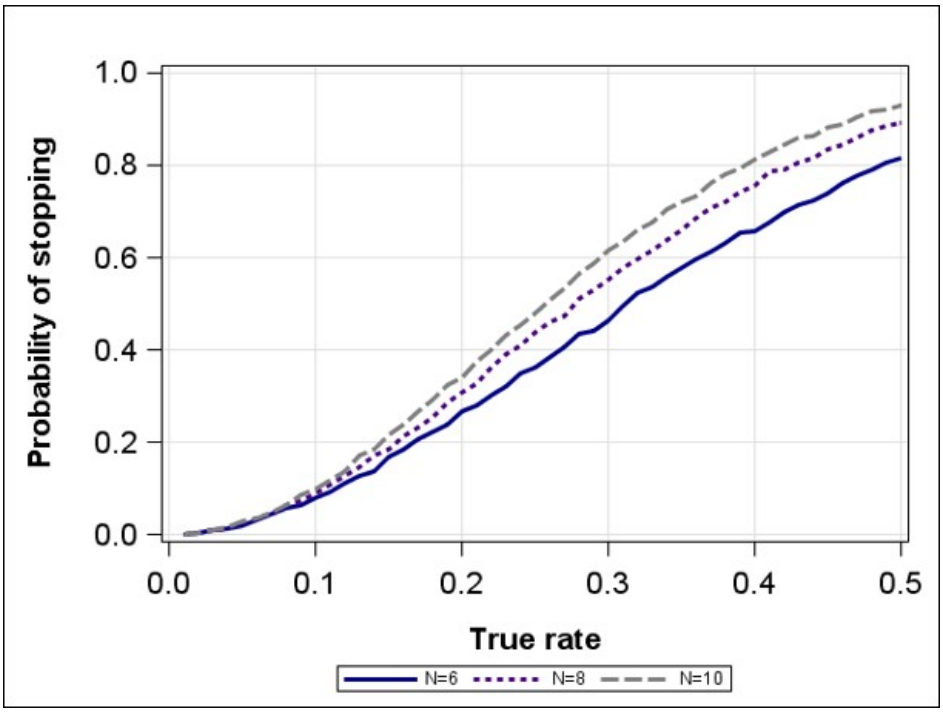
10.6 Sample Size Calculation

The study will consist of 2 cohorts each of approximately 6 patients, leading to a total sample size of 12. The sample size is based on practical considerations considering the orphan patient population and expected rates of events leading to study cessation.

With 6 patients per cohort the stopping rules would ensure a reasonable probability (17%) that the cohort would not be stopped if the true event rate was 15% or lower while also ensuring an appropriate probability that the study would be stopped if the true event rate was high (65% probability for true event rates greater than 40%).

Figure 4 shows the probability of stopping for possible true event rates and for different sample sizes.

Figure 4: Probability of Study Stopping Rules with Various Sample Sizes



11. ETHICAL CONSIDERATIONS

11.1 Regulatory and Ethical Compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the Investigator and IRB/IEC

Before initiating a trial, the Investigator/institution should obtain approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all the instructions and procedures found in this protocol and to give access to all relevant data and records to Magenta monitors, auditors, Magenta Quality Assurance representatives, designated agents of Magenta, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the Investigator must inform Magenta immediately that this request has been made.

For multi-center trials, a Coordinating Investigator will be selected by Magenta around the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

11.3 Publication of Study Protocol and Results

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

12. PROTOCOL ADHERENCE

This protocol defines the study objectives, the study procedures, and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances should an Investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

Investigators must apply due diligence to avoid protocol deviations. If the Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Magenta and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the clinical study report.

12.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Magenta, Health Authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented, provided the Health Authorities and the reviewing IRB/IEC are subsequently notified by protocol amendment.

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the Clinical Leader should be informed and AE/SAE reporting requirements (Section 8) followed as appropriate.

13. REFERENCES

[All references are available upon request]

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APPENDIX 1. PK, BIOMARKER, AND PHARMACODYNAMIC ASSESSMENTS

APPENDIX 2. DIAGNOSIS AND TREATMENT OF ACUTE GRAFT VERSUS HOST DISEASE

Patients will be considered evaluable for aGVHD if they demonstrate donor cell engraftment and survive to Day 28. Organ involvement will be staged using the criteria outlined in Table 10. Biopsy of each organ site at diagnosis or major change in disease activity will be performed unless clinical circumstances make it impossible.

Table 10: Staging and Grading aGVHD

Site	Stage
Skin	0. No rash 1. MaculoPapular rash < 25% of body surface area 2. MaculoPapular rash 25-50% of body surface area 3. Generalized erythroderma 4. Generalized erythroderma with bullous formation or desquamation
Lower GI	0. No diarrhea [peds = <281 mL/m^2] (no change from baseline) 1. 500-1000 cc [peds = 281-555 mL/m^2] (3-4 loose stools/d, not interfering with ADL) 2. 1001-1500 cc [peds = 556-833 mL/m^2] (5-7 loose stools/d, not interfering with ADL, IV fluids <24 hrs) 3. >1500 cc [peds = >833 mL/m^2] (8+ loose stools/d, interfering with ADL, IV fluids >24 hours) 4. Severe abdominal pain, +/- ileus, +/- frank blood
Upper GI	0. No prolonged nausea or vomiting 1. Persistent nausea, vomiting, or anorexia
Liver	0. Bilirubin 2.0 mg/dL or less 1. Bilirubin 2.1 - 3.0 mg/dL 2. Bilirubin 3.1 - 6.0 mg/dL 3. Bilirubin 6.1 - 15.0 mg/dL 4. Bilirubin >15.1 mg/dL

Overall GVHD Grading				
Overall Grade	**Organ Stage**			
	Skin	**Lower GI**	**Upper GI**	**Liver**
I	1-2	0	0	0
II	3	1	1	1
III	-	2-3	-	2-4
IV	4	4	-	-

Treatment

Acute GVHD treatment may be by institutional guidelines. The recommended treatment for patients demonstrating moderate or severe GVHD (Grade II-IV) is methylprednisolone 48 mg/m^2/day or prednisone 60 mg/m^2/day followed by a taper. Patients failing front line therapy

will follow the institutional treatment algorithm. Use of investigational agents will be reviewed with the Sponsor.

APPENDIX 3. NIH CONSENSUS CRITERIA FOR DIAGNOSIS AND GRADING OF SEVERITY OF CHRONIC GVHD

Signs and symptoms of cGVHD are presented in Table 11.

Table 11: Signs and Symptoms of Chronic GVHD

Organ or site	Diagnostic (Sufficient to establish the diagnosis of cGVHD)	Distinctive (Seen in cGVHD, but insufficient alone to establish a diagnosis of cGVHD)	Other features	Common (Seen with both aGVHD and cGVHD)
Skin	Poikiloderma	Depigmentation	Sweat impairment	Erythema
	Lichen planus-like features		Ichthyosis	Maculopapular rash
	Sclerotic features		Keratosis pilaris	Pruritus
	Morphea-like features		Hypopigmentation	
	Lichen sclerosus-like features		Hyperpigmentation	
Nails		Dystrophy		
		Longitudinal ridging, splitting, or brittle features		
		Onycholysis		
		Pterygium unguis		
		Nail loss (usually symmetric; affects most nails)†		
Scalp and body hair		New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) Scaling, papulosquamous lesions	Thinning scalp hair, typically patchy, coarse, or dull (not explained by endocrine or other causes)	
			Premature gray hair	

Organ or site	Diagnostic (Sufficient to establish the diagnosis of cGVHD)	Distinctive (Seen in cGVHD, but insufficient alone to establish a diagnosis of cGVHD)	Other features	Common (Seen with both aGVHD and cGVHD)
Mouth	Lichen-type features	Xerostomia		Gingivitis
	Hyperkeratotic plaques	Mucocele		Mucositis
	Restriction of mouth opening from sclerosis	Mucosal atrophy Pseudomembranes † Ulcers †		Erythema Pain
Eyes		New onset dry, gritty, or painful eyes‡	Photophobia	
		Cicatricial conjunctivitis Keratoconjunctivitis sicca ‡ Confluent areas of punctate keratopathy	Periorbital hyperpigmentation	
			Blepharitis (erythema of the eyelids with edema)	
Genitalia	Lichen planus-like features	Erosions†		
	Vaginal scarring or stenosis	Fissures†		
		Ulcers†		
GI tract	Esophageal web Strictures or stenosis in the upper to mid third of the esophagus †		Exocrine pancreatic insufficiency	Anorexia Nausea Vomiting Diarrhea
				Weight loss
				Failure to thrive (infants and children)

Organ or site	Diagnostic (Sufficient to establish the diagnosis of cGVHD)	Distinctive (Seen in cGVHD, but insufficient alone to establish a diagnosis of cGVHD)	Other features	Common (Seen with both aGVHD and cGVHD)
Liver				Total bilirubin, alkaline phosphatase >2×ULN†
				ALT or AST >2×ULN
Lung	Bronchiolitis obliterans diagnosed with lung biopsy	Bronchiolitis obliterans diagnosed with PFTs and radiology‡		BOOP
Muscles, fascia, joints	Fasciitis Joint stiffness or contractures secondary to sclerosis	Myositis or Polymositis	Edema Muscle cramps Arthralgia or arthritis	
Hematopoietic and immune			Thrombocytopenia	
			Eosinophilia	
			Lymphopenia	
			Hypo- or hypergammaglobulinemia	
			Autoantibodies (AIHA and ITP)	
Other			Pericardial or pleural effusions	
			Ascites	
			Peripheral neuropathy	
			Nephrotic syndrome	
			Myasthenia gravis	
			Cardiac conduction abnormality or cardiomyopathy	

aGVHD=acute graft versus host disease; ALT=alanine aminotransferase; AST=aspartate aminotransferase; cGVHD=chronic graft versus host disease; PFT=pulmonary function test; ULN=upper limit of normal

Can be acknowledged as part of the cGVHD symptomatology if the diagnosis is confirmed.

† In all cases, infection, drug effects, malignancy, or other causes must be excluded.

‡ Diagnosis of cGVHD requires biopsy or radiology confirmation (or Schirmer test for eyes).

The Working Group recommends that the diagnosis of cGVHD require at least 1 diagnostic manifestation of cGVHD or at least 1 distinctive manifestation, with the diagnosis confirmed by pertinent biopsy, laboratory tests, or radiology in the same or another organ. As in aGVHD, infection and other causes may confound or complicate the differential diagnosis of cGVHD (eg, nail dystrophies associated with onychomycosis, herpes simplex, or *Candida albicans* infections of the oral cavity; drug toxicity) and must be excluded. Diagnostic and distinctive manifestations of cGVHD can be found in the skin and appendages, mouth, eyes, female genitalia, esophagus, lungs, and connective tissues. Biopsy or other testing is always encouraged and often valuable to confirm the presence of cGVHD, but it is not always feasible and is not mandatory if the patient has at least 1 of the diagnostic findings of cGVHD (Table 11). Please note that an in-depth discussion of recommended terminology for histopathologic interpretation may be found in a forthcoming histopathology working group report. A biopsy read as "consistent with" or "unequivocal" cGVHD will be considered sufficient to establish the diagnosis of cGVHD if accompanied by at least 1 distinctive clinical manifestation.

Characteristics that establish the diagnosis of cGVHD might not serve as the most appropriate parameters for assessing the severity of cGVHD. Valid and reliable diagnostic criteria might not be sufficiently sensitive to change to be useful as treatment-response criteria. Conversely, a sensitive measure of cGVHD response might not necessarily serve as an appropriate diagnostic and scoring tool.

Organ-specific Manifestations of Chronic GVHD

In all cases, drug reaction, infection, recurrent or new malignancy, and other causes must be excluded. Diagnostic clinical or laboratory features sufficient for the diagnosis of cGVHD are italicized in the sections below.

Skin

Diagnostic manifestations include *poikiloderma* (eg, atrophic and pigmentary changes), *lichen planus-like eruption* (eg, erythematous/violaceous flat-topped papules or plaques with or without surface reticulations or a silvery or shiny appearance on direct light), *deep sclerotic features* (eg, smooth, waxy, indurated skin "thickened or tight skin," caused by deep and diffuse sclerosis over a wide area), *morphea-like* superficial sclerotic features (eg, localized patchy areas of moveable smooth or shiny skin with a leathery-like consistency, often with dyspigmentation), or *lichen sclerosus-like lesions* (eg, discrete to coalescent gray to white moveable papules or plaques, often with follicular plugs, with a shiny appearance and leathery consistency). Severe sclerotic features characterized by thickened, tight, and fragile skin are often associated with poor wound healing, inadequate lymphatic drainage, and skin ulcers from minor trauma.

A distinctive feature for cGVHD (not seen in aGVHD, but not sufficiently unique to be considered diagnostic of cGVHD) is depigmentation. However, depigmentation would contribute to the diagnosis of cGVHD in combination with biopsy or laboratory confirmation of GVHD in skin or another organ. Sweat impairment and intolerance to temperature change from loss of sweat glands are seen in cGVHD. Other common, nondistinctive skin manifestations found with both aGVHD and cGVHD include erythema, maculopapular rash, and pruritus.

Nails

Dystrophy consisting of longitudinal ridging, nail splitting or brittleness, onycholysis, pterygium unguis, and nail loss (usually symmetric and affecting most nails) are distinctive signs of cGVHD, but are not sufficient for diagnosis.

Hair

Distinctive features of cGVHD include new scarring and nonscarring scalp alopecia (after recovery from chemotherapy or radiotherapy) and loss of body hair. Other characteristics seen with cGVHD include premature graying, thinning, or brittleness, but these findings are not diagnostic.

Mouth

Diagnostic features of oral cGVHD include *lichen planus-like changes* (white lines and lacy-appearing lesions of the buccal mucosa, tongue, palate, or lips), *hyperkeratotic plaques* (leukoplakia), or *decreased oral range of motion in patients with sclerotic features of skin GVHD*. Distinctive features of cGVHD include xerostomia (dryness), mucoceles, mucosal atrophy, pseudomembranes, and ulcers (infectious pathogens such as yeast or herpes virus; secondary malignancy must be excluded). Manifestations common to both aGVHD and cGVHD include gingivitis, mucositis, erythema, and pain.

Eyes

Distinctive manifestations of cGVHD include new onset of dry, gritty, or painful eyes; cicatricial conjunctivitis; keratoconjunctivitis sicca; and confluent areas of punctate keratopathy. Other features include photophobia, periorbital hyperpigmentation, difficulty in opening the eyes in the morning because of mucoid secretions, and blepharitis (erythema of the eye lids with edema). New ocular sicca documented by low Schirmer test values with a mean value of both eyes ≤5 mm at 5 minutes or a new onset of keratoconjunctivitis sicca by slit-lamp examination with mean values of 6 to 10 mm on the Schirmer test is sufficient for the diagnosis of cGVHD if accompanied by distinctive manifestations in at least 1 other organ.

Genitalia

Diagnostic features for the genitalia include *lichen planus-like features* and *vaginal scarring or stenosis* (often associated with oral GVHD).

Gastrointestinal Tract

Diagnostic features for the GI tract include *esophageal web*, *stricture*, or *concentric rings* documented by endoscopy or barium contrast radiograph. Chronic GVHD may be associated with pancreatic exocrine insufficiency, which often improves with enzyme supplementation. Manifestations common to both aGVHD and cGVHD (as well as other causes, such as drug side effects, motility disorders, infections, or malabsorption) include anorexia, nausea, vomiting, diarrhea, weight loss, and failure to thrive. Wasting syndrome may be a manifestation of cGVHD, but is often multifactorial (eg, decreased caloric intake, poor absorption, increased resting energy expenditures, and hypercatabolism). Endoscopic findings of mucosal edema and erythema or focal erosions with histologic changes of apoptotic epithelial cells and crypt cell dropout may be seen but are not considered diagnostic of cGVHD unless the patient also has

distinctive features in a non-GI system. Patients with unresolved aGVHD may have more severe intestinal mucosal lesions, including ulcers and mucosal sloughing.

Liver

Hepatic aGVHD and cGVHD typically presents as cholestasis, with increased bilirubin or alkaline phosphatase, but it may also present as acute hepatitis. Because of many possible alternative diagnoses, a liver biopsy is required to confirm GVHD involvement of the liver. Note that because of the histologic similarity between acute and chronic liver GVHD, the diagnosis of cGVHD cannot be made on the basis of liver biopsy alone, but requires a distinctive manifestation in at least 1 other organ system.

Lungs

The only diagnostic manifestation of cGVHD is biopsy-proven *BO*. BO diagnosed via pulmonary function and radiologic testing requires at least 1 other distinctive manifestation in a separate organ system to establish the diagnosis of cGVHD. BO is characterized by the new onset of an obstructive lung defect. Clinical manifestations may include dyspnea on exertion, cough, or wheezing. Some patients may be asymptomatic early in the disease process. Pneumothorax, pneumomediastinum, and subcutaneous emphysema are rare and often represent advanced disease. Restrictive pulmonary function abnormalities secondary to advanced sclerosis of the chest wall are attributable to skin GVHD. BO is clinically diagnosed when all of the following criteria are met:

1. Forced expiratory volume in 1 second/forced vital capacity ratio <0.7 and forced expiratory volume in 1 second <75% of predicted.

1. Evidence of air trapping or small airway thickening or bronchiectasis on high-resolution chest CT (with inspiratory and expiratory cuts), residual volume >120%, or pathologic confirmation of constrictive bronchiolitis.
2. Absence of infection in the respiratory tract, documented with investigations directed by clinical symptoms, such as radiologic studies (radiographs or CT scans) or microbiologic cultures (sinus aspiration, upper respiratory tract viral screen, sputum culture, or bronchoalveolar lavage).
3. BO-organizing pneumonia not due to infections may represent a manifestation of either aGVHD or cGVHD and is considered a common feature.

Musculoskeletal System

Diagnostic features include *fascial involvement* often affecting the forearms or legs and often associated with sclerosis of the overlying skin and subcutaneous tissue. Fascial involvement may develop without overlying sclerotic changes of the skin and can result in *joint stiffness or contractures* when present near joints. *Fasciitis* is detected on examination by stiffness, a restricted range of motion (eg, often decreased dorsal wrist flexion or inability to assume a Buddha prayer posture), edema of the extremities with or without erythema (early sign), peau d'orange (edematous skin with prominent pores resembling the surface of an orange), or *joint contractures* (late complications). Clinical myositis with tender muscles and increased muscle enzymes is a distinctive but nondiagnostic manifestation of cGVHD. Myositis may present as proximal myopathy, but this complication is rare and does not explain the frequent complaints of severe cramps. Evaluation of myositis involves electromyography and measurement of creatine

phosphokinase or aldolase. Arthralgia and arthritis are uncommon and are occasionally associated with the presence of autoantibodies.

Hematopoietic and Immune Systems

Abnormalities are common in cGVHD, but cannot be used to establish the diagnosis of cGVHD. Cytopenias may result from stromal damage or autoimmune processes. Lymphopenia (≤500/μL), eosinophilia (≥500/μL), hypogammaglobulinemia, or hypergammaglobulinemia may be present. Autoantibodies may develop with autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura. Thrombocytopenia (<100,000/μL) at the time of cGVHD diagnosis has been associated with a poor prognosis.

Other Findings

Serositis (pericardial or pleural effusions or ascites), peripheral neuropathy, myasthenia gravis, nephrotic syndrome, and cardiac involvement have been attributed to cGVHD, but these manifestations are rare. For these manifestations, cGVHD is often a diagnosis of exclusion.

Differential diagnosis between acute and chronic GVHD

The Working Group recognized 2 main categories of GVHD, each with 2 subcategories (Table 12). The broad category of aGVHD includes:

(1) classic aGVHD (maculopapular rash, nausea, vomiting, anorexia, profuse diarrhea, ileus, or cholestatic hepatitis) occurring within 100 days after transplantation or donor lymphocyte infusion (DLI; without diagnostic or distinctive signs of cGVHD); and

(2) persistent, recurrent, or late aGVHD: features of classic aGVHD without diagnostic or distinctive manifestations of cGVHD occurring beyond 100 days of transplantation or DLI (often seen after withdrawal of immune suppression).

The broad category of cGVHD includes:

(1) classic cGVHD without features characteristic of aGVHD; and

(2) an overlap syndrome in which features of cGVHD and aGVHD appear together. In the absence of histologic or clinical signs or symptoms of cGVHD, the persistence, recurrence, or new onset of characteristic skin, GI tract, or liver abnormalities should be classified as aGVHD regardless of the time after transplantation.

With appropriate stratification, patients with persistent, recurrent, or late aGVHD or overlap syndrome can be included in clinical trials with patients who have cGVHD.

Table 12: Categories of Acute and Chronic GVHD

Category	Time of Symptoms after HCT or DLI	Presence of Acute GVHD Features	Presence of Chronic GVHD Features
Acute GVHD			
Classic aGVHD	≤100 days	Yes	No
Persistent, recurrent, or late-onset aGVHD	>100 days	Yes	No
Chronic GVHD			
Classic cGVHD	No time limit	No	Yes
Overlap syndrome	No time limit	Yes	Yes

DLI=Donor lymphocyte infusion; GVHD=graft versus host disease; HCT=hematopoietic cell transplantation

Table 13 presents calculations of mild, moderate, and severe global severity, with examples. If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity. If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

Table 13: Calculation of Mild, Moderate, and Severe Global Severity of Chronic GVHD

Severity	Calculation (with Examples)
Mild	• 1 or 2 organs or sites (except lung) with score 1 – Mild oral symptoms, no decrease in oral intake – Mild dry eyes, lubricant eye drops ≤3x/day
Moderate	• 3 or more organs with score 1 • At least 1 organ or site with score 2 – 19% to 50% body surface area involved or superficial sclerosis – Moderate dry eyes, eye drops >3x/day or punctal plugs • Lung score 1 (FEV_1 60% to 79% or dyspnea with stairs)
Severe	• A least 1 organ or site with score 3 – >50% body surface area involved – Deep sclerosis, impaired mobility, or ulceration – Severe oral symptoms with major limitation in oral intake – Severe dry eyes affecting ADL • Lung score 2 (FEV_1 40% to 59% or dyspnea walking on flat ground)

FEV_1=forced expiratory volume in 1 second; GVHD=graft versus host disease

APPENDIX 4. [redacted]

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