PROTOCOL

Study Title

An Open Label Expanded Access Study of Omidubicel, for Allogeneic Transplantation in Patients with Hematological Malignancies

Principal Investigator Mitchell Horwitz, MD
Duke University Medical Center

Clinical Phase Phase IIIb

Product: Omidubicel

IND Number: [redacted]

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Protocol No. GC P#07.01.020

Amendment # N/A

Dated January 22, 2020

This clinical study will be conducted in accordance with the Sponsor's Standard Operating Procedures (SOPs), this protocol, current Good Clinical Practice (GCP), the Declaration of Helsinki, the provisions of International Conference on Harmonization (ICH) Guidelines and all local applicable laws and regulations.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Events
ALL	Acute Lymphoblastic Leukemia
ALT	Alanine Transaminase
AML	Acute Myelogenous Leukemia
ANC	Absolute Neutrophil Count
ARDS	Acute Respiratory Destress Syndrome
ASHI/EFI	American Society for Histocompatibility and Immunogenetics/European Federation for Immunogenetics
AST	Aspartate Transaminase
ATG	anti-thymocyte globulin
BID	Twice a day (Bis In Die)
BM	Bone Marrow
BMT	Bone Marrow Transplant
BMT-CTN	Bone Marrow Transplant – Clinical Trials Network
BP	Blood Pressure
BSA	Body Surface Area
CBB	Cord Blood Bank
CBC	Complete Blood Count
CBT	Cord Blood Transplant
CB (U)	Cord Blood (Unit)
CF	Cultured Fraction
CFU	Colony-forming Units
CI	Confidence Interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CML	Chronic myeloid leukemia
CMV	Cytomegalovirus
CNS	Central Nervous System
CoA	Certificate of Analysis
CRA	Clinical Research Associate
CRO	Contract Research Organization
CRFs	Case Report Forms
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DC	Dendritic Cells
DCBT	Double Cord Blood Transplant
DLCO	Diffusing Lung Capacity of Carbon Monoxide
DLI	Donor Lymphocyte Infusion
EBV	Epstein-Barr Virus
EC	Ethics Committee
EDC	Electronic Data Capture
EKG	Electrocardiography

Abbreviation	Definition
EMR	Electronic Medical Records
EVCTM	EudraVigilance Clinical Trial Module
FACS	Fluorescence-Activated Cell Sorting
FBS	Fetal Bovine Serum
FEV1	Forced Expiratory Volume in One Second
FISH	Fluorescent In Situ Hybridization
FLT3-L	Flt3-Ligand
FPQC	Final Process Quality Controls
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GCS	Glasgow Coma Score
G-CSF	Granulocyte Colony-Stimulating Factor
(c)GvHD	(Chronic) Graft-versus-host Disease
HCG	Human Chorionic Gonadotropin
HCT	Hematopoietic Cell Transplantation
HCV	Hepatitis C Virus
HHV	Human Herpesvirus
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPC	Hematopoietic Progenitor Cells
HSCT	Hematopoietic Stem Cell Transplantation
HSPCs	Hematopoietic Stem/Progenitor Cells
HSV	Herpes Simplex Virus
HTLV	Human T-Lymphotropic Virus
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IL6	Interleukin 6
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IPQC	In-process Quality Controls
IRB	Institutional Review Board
IV	Intravenous
LVEF	Left Ventricular Ejection Fraction
mARTs	mono-ADP-ribosyltransferases
MDS	Myelodysplastic Syndrome
MFI	Mean Fluorescence Intensity
MMF	Mycophenolate Mofetil
MRD	minimal residual disease
MUGA	Multi Gated Acquisition Scan
NAD+	Nicotinamide Adenine Dinucleotide
NAM	Nicotinamide

Abbreviation	Definition
NF	Non-cultured Fraction
NK CELL	Natural Killer Cytotoxic Lymphocyte Cells (CD56+/CD16+cells)
NOS	Non Otherwise Specified
NP	Nurse Practitioner
OOS	Out of Specification
PA	Physician Assistant
PARPs	poly-ADP-ribose Polymerases
PB	Peripheral Blood
PCP	Pneumocystis Prophylaxis
PCR	Polymerase Chain Reaction
PET-CT	Positron Emission Tomography - Computerized Tomography
PFT	Pulmonary Function Test
PI	Principal Investigator
PMN	Polymorphonuclear Leukocytes
PO	Per Os (By Mouth, or Oral Administration of a Drug)
PP	Per Protocol
PRES	Posterior Reversible Encephalopathy Syndrome
PTLD	Post-transplantation lymphoproliferative disorders
QC	Quality Control
QP	Qualified Person
RBC	Red Blood Cell
RPR	rapid plasma reagin
SAE	Serious Adverse Event
SC	Subcutaneous
SCF	Stem Cell Factor
SCT	Stem Cell Transplant
SGF	Secondary graft failure
SIRS	Systemic Inflammatory Response Syndrome
SIRT1	sirtuin (silent mating type information regulation 2 homolog) 1
SLM	Study Logistics Manager
SOC	Standard of Care
SOC/PT	System organ class / Preferred Term
SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBI	Total Body Irradiation
TNC	Total Nucleated Cell
TPO	Thrombopoietin
TRM	Transplant-related Mortality
UCB	Umbilical Cord Blood
ULN	Upper Limit Normal
VZV	Varicella-zoster Virus
WBC	White Blood Cell

SPONSOR PROTOCOL APPROVAL PAGE

Protocol Title:

An Open Label Expanded Access Study of Omidubicel, for Allogeneic Transplantation in Patients with Hematological Malignancies

Clinical Phase	Phase IIIb
Protocol Number:	GC P#07.01.020
Amendment Number:	N/A
Dated:	January 22, 2020

Approved by:

Senior Director, Clinical Development

[redacted]

_____ _____

Signature Date

1. INVESTIGATOR'S AGREEMENT

Protocol Title:

An Open Label Expanded Access Study of Omidubicel, for Allogeneic Transplantation in Patients with Hematological Malignancies

Clinical Phase:	Phase IIIb
Protocol Number:	GC P#07.01.020
Amendment Number:	N/A
Dated:	January 22, 2020

I have carefully read the foregoing protocol including all appendices and agree that it contains all the necessary information for conducting the study safely.

I will conduct this study in strict accordance with this protocol and according to the current Good Clinical Practice (GCP) regulations and will attempt to complete the study within the time designated.

I will provide copies of the protocol and all other information relating to pre-clinical and prior clinical experience submitted by the Sponsor to all personnel responsible to me who participate in the study. I will discuss this information with them to ensure that they are adequately informed regarding the drug and conduct of the study.

I agree to keep records on all patient information (CRFs, shipment, and all other information collected during the study) in accordance with the current GCP and local regulations.

_____

Principal Investigator's Name

_____

Signature

_____

Date

_____

Institution

2. STUDY SYNOPSIS

Protocol Number

GC P#07.01.020

Protocol Title

An Open Label Expanded Access Study of Omidubicel, for Allogeneic Transplantation in Patients with Hematological Malignancies

Number of Centers and Planned Geographical Distribution

Multicenter, multinational

Clinical Phase

IIIb

Investigational Product

Omidubicel is a cryopreserved stem/progenitor cell-based product comprised of:

- *Ex vivo* expanded, umbilical cord blood-derived hematopoietic $CD34^+$ progenitor cells (omidubicel cultured fraction (CF))
- The non-cultured cell fraction of the same cord blood unit (CBU) (omidubicel Non-cultured Fraction (NF)) consisting of mature myeloid and lymphoid cells.

Both fractions, i.e., omidubicel CF and omidubicel NF, will be kept frozen until they are thawed and infused on the day of transplantation.

Study Duration

Total study duration per patient is approximately 780 days from the signing of informed consent to the last visit two years following transplantation. The study ends when the last patient completes their last visit.

Study Objectives

The overall study objectives are to provide access to omidubicel for transplantation in patients with hematological malignancies and to collect additional safety and efficacy data.

Primary Endpoint:

Assess the time from transplant to neutrophil engraftment.

Secondary Endpoints:

- Time from transplantation to platelet engraftment
- Non-relapse mortality
- Overall survival
- Disease-free survival

- Donor chimerism at 42, 100 days and 2 years following transplantation
- Secondary graft failure
- Acute Graft versus Host Disease (GvHD) grade II-IV and III-IV
- Chronic GvHD (mild/moderate/severe)
- Relapse
- Safety and tolerability of omidubicel transplantation

Study Hypothesis

The hypothesis is that omidubicel is an acceptable alternative graft source for transplantation.

Study Design

This is an open-label, non-randomized, interventional, single group assignment study of omidubicel in patients with hematological malignancies for whom allogeneic stem cell transplant (SCT) is currently a recommended and potentially lifesaving treatment, all with required disease features rendering them eligible for allogeneic transplantation.

Number of Patients

In consideration of the estimated timelines to licensure, approximately 60 patients are anticipated to be enrolled.

Inclusion Criteria

1. Patients must be at least 12 years of age
2. Patients with one of the following hematological malignancies who are eligible allogeneic transplant candidates according to institutional treatment guidelines:
    - Acute lymphoblastic leukemia (ALL) in complete morphologic remission, defined as no circulating blasts and less than 5% blasts in the bone marrow
    - Acute myelogenous leukemia (AML) in complete morphologic remission, defined as no circulating blasts and less than 5% blasts in the bone marrow
    - Chronic myelogenous leukemia (CML) with no circulating blasts and less than 5% blasts in the bone marrow
    - CLL
    - Myelodysplastic Syndrome (MDS)
    - Biphenotypic/Undifferentiated/Prolymphocytic/Dendritic Cell Leukemias and Natural Killer Cell Malignancies, adult T-cell leukemia/lymphoma in first or subsequent complete morphologic remission
    - Lymphoma with chemosensitive disease at the time of evaluation for transplantation

3. Patients must have a partially HLA-matched CBU:
    a. The unit must be HLA-matched at 4-6/6 HLA class I (HLA-A & HLA-B, low resolution) and II (HLA-DRB1, high resolution) loci with the patient. There must be at least one allele match at DRB1.
    b. The CBU must have a pre-cryopreserved (post processing) total CD34+ cell count of $\geq 8 \times 10^6$ as well as a pre-cryopreserved (post processing) total nucleated cell count of $\geq 1.8 \times 10^9$ and total nucleated cell dose $\geq 1.5 \times 10^7$ TNC/kg.
    c. The CBU will have undergone volume reduction (both plasma and red blood cell depletion) prior to cryopreservation.
    d. Verification typing (confirmatory typing) must be completed before CBU shipment for manufacturing.
4. Patients who will be starting conditioning prior to omidubicel release for infusion (i.e., omidubicel arrival on site in adequate condition) must have an additional partially HLA-matched CBU reserved as a backup to the omidubicel arm in case of production failure.
    a. The backup CBU must be HLA-matched at 4-6/6 HLA class I (HLA-A & HLA-B, low resolution) and II (HLA-DRB1, high resolution) loci with the patient.
5. Patients must be clinically suitable to receive myeloablative conditioning followed by allogeneic hematopoietic stem cell transplantation (HSCT). The patient must meet institutional standards of performance status and physiologic reserves (including cardiac, pulmonary, renal and hepatic functions) to undergo myeloablative conditioning.
6. Females of childbearing potential, defined as any female who has experienced menarche and is not postmenopausal (defined as not having a menstrual period for at least 24 months) or permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy), agree to use an appropriate method of contraception from at least 7 days prior to conditioning regimen therapy until completion of follow-up procedures. An appropriate method of contraception is defined as one that results in a low failure rate (i.e., less than 1 percent per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, intrauterine contraceptive devices (IUDs), true sexual abstinence (when this is in line with the preferred and usual lifestyle of the patient), or a vasectomized partner.
7. Patient (or legal guardian) signs the written informed consent after being aware of the nature of the patient's disease and willingly consents to the treatment program after being informed of alternative treatments, potential risks, benefits, and discomforts.

Exclusion Criteria

1. "Marked", "3+" or "extensive" bone marrow fibrosis
2. Evidence of donor specific anti-HLA antibodies to the selected CBU (MFI>3000 to HLA A, B, C, or DRB1), unless approved by the Sponsor
3. Pregnancy, as indicated by a positive serum or urine human chorionic gonadotrophin (HCG) test, or lactation

4. Clinically significant active malignancy other than that for which the umbilical cord blood (UCB) transplant is being performed within 12 months of enrollment, unless approved by the Sponsor. Fully resected cutaneous squamous cell or basal cell carcinoma or cervical carcinoma in situ within 12 months of enrollment is permitted
5. Evidence of infection or other medical condition which, in the judgment of the investigator, make the patient unsuitable for myeloablative conditioning and hematopoietic cell transplantation (HCT)
6. Availability of a suitable HLA identical sibling or 10/10 matched unrelated donor whose stem cells can be collected in a timely manner without jeopardizing recipient outcome. Patients who have haploidentical related donors or syngeneic donors are not excluded
7. Allergy to bovine products, gentamicin, or to any other product that may interfere with the treatment
8. Psychologically incapable of undergoing HSCT with associated strict isolation or documented history of medical non-compliance and/or psychiatric illness and/or social situations that would limit compliance with study requirements
9. Eligible for enrollment in an ongoing omidubicel investigational study other than this one
10. Enrolled in another interventional clinical study or received an investigational treatment within 30 days prior to the anticipated date of transplantation, unless documented approval obtained from Sponsor prior to CBU shipment for manufacturing.

Treatment Description

Once qualifying CBUs have been identified and the patient (or legal guardian) signs the informed consent form (ICF), the patient undergoes study specific screening. Standard of care workup for transplant may be done prior to patient study consent and results of those tests may be used for the required study assessments, provided they are within the protocol specified timeframes.

The CBU chosen for production will be shipped from the Cord Blood Bank (CBB) to the manufacturing site. Prior to CBU shipment, all screening assessments must be completed and resulted, and patient eligibility must be confirmed as outlined in Section 7.5.

Upon release, omidubicel CF + NF will be shipped to the clinical site before transplantation.

Omidubicel CF will be thawed and infused first, followed by the omidubicel NF.

If omidubicel fails to meet its required release specifications and patient conditioning has already started, the backup CBU/s or a different backup source of stem cells will be transplanted.

Preparative Conditioning Regimens

The preparative conditioning regimen and GvHD prophylaxis regimen may be selected from the list of allowed regimens. Other regimens must be approved by the Sponsor prior to CBU shipment for manufacturing.

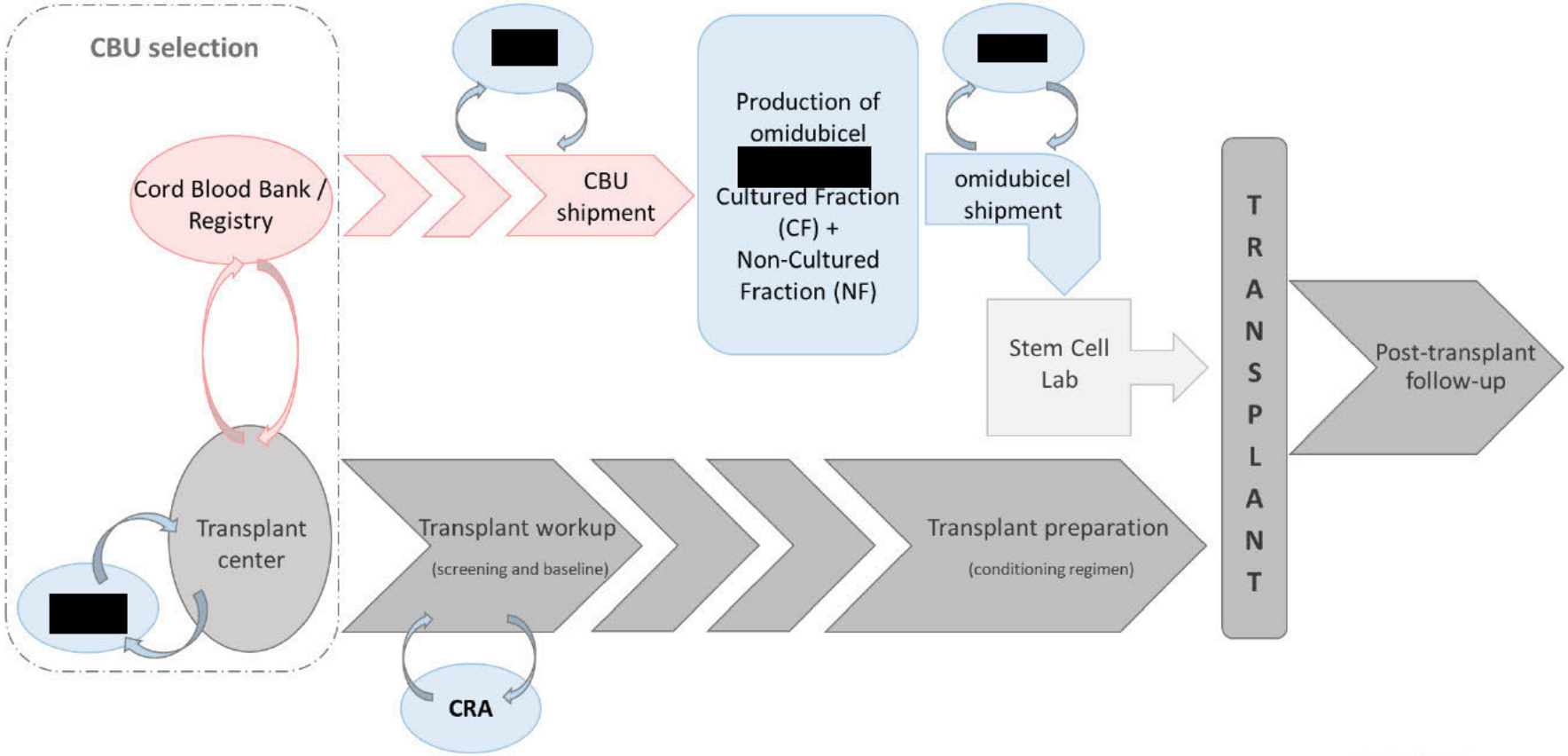
Statistical Considerations

The sample size for the study was not determined by statistical power considerations, [redacted] Statistical analyses will be limited to descriptive statistics and confidence intervals; there will be no hypothesis testing.

There are no formal stopping rules. Ongoing study safety data will be reviewed by the Medical Monitor in real time and any concerns for patient safety will be promptly communicated to the sponsor with a recommendation to suspend accrual, if applicable.

The primary endpoint is to assess the time from transplant to neutrophil engraftment, as defined in Section 4.2.1.

Figure 1: Study Scheme



3. INTRODUCTION

3.1. Overview

Successful blood and marrow transplantation (BMT) requires the infusion of a sufficient number of hematopoietic stem/progenitor cells (HSPCs), capable of both homing to the bone marrow and regenerating a full array of hematopoietic cell lineages with early and late repopulating ability in a timely fashion.[1]

Several options exist for a stem cell donor for transplantation, but because each option has limitations,[2] these patients still have an unmet medical need. There are numerous advantages to UCB as a transplantable graft source. These include the ease of procurement, the absence of risk to the donor, the reduced risk of transmissible infections, and the availability for immediate use, potentially reducing a long wait and risk of disease progression - particularly important for patients with acute leukemia.[3, 4] Moreover, the use of cord blood transplant (CBT) allows for a higher mismatch with the recipient, without an increased risk of GvHD. Even compared with fully matched donors, UCB is associated with decreased acute and chronic GvHD, allowing for the transplantation of partially HLA-matched CBUs, with the full cellular repertoire, and without the need for T-cell depletion. However, despite these advantages and over 30 years of clinical experience, CBT is still limited in filling the need for suitable allogeneic grafts, due in part to a delayed hematopoietic recovery in recipients of CBT, with a related increased risk of life-threatening or fatal sequelae as well as a finite and limited stem cell dose which may be inadequate.[5-8]

The aim of *ex vivo* expansion of cord blood is to provide a graft with sufficient numbers of cells that have rapid and robust *in vivo* neutrophil and platelet producing potential to enable successful transplantation.[9]

An effective *ex vivo* expansion technology should improve short-term early hematopoietic reconstitution, while preserving the long-term repopulating cells in *ex vivo* cultures.[10-12] The relates not only to the persistence of such unique cells in culture, but also to their potential to differentiate and reconstitute blood cell lineages including myeloid, T, Natural Killer (NK) and B cells, as efficiently as the long-term repopulating cells before expansion.[13]

Omidubicel is a stem/progenitor cell-based product composed of *ex vivo* expanded allogeneic cells from one entire unit of UCB. Omidubicel utilizes the small molecule nicotinamide (NAM), as an epigenetic approach to inhibit differentiation and to increase the migration, bone marrow (BM) homing and engraftment efficiency of hematopoietic progenitor cells (HPC) expanded in *ex vivo* cultures.[14]

[redacted][16] Patients transplanted with omidubicel had a shorter time to neutrophil engraftment compared to historical controls transplanted with standard cord blood. Transplantation with omidubicel was associated with a decrease in the risk of infection and significantly more time out of the hospital in the first

100 days post-transplant compared to a cohort of patients transplanted with standard cord blood.[17] An international, Phase III, randomized study comparing transplantation of omidubicel to transplantation of standard cord blood has completed enrollment. The primary endpoint is time to neutrophil engraftment.

Omidubicel could potentially provide [redacted] donor option in a timely manner, thereby addressing a critical unmet need in the treatment of hematological malignancies.

3.2. [redacted]

Omidubicel is composed of CB-derived allogeneic stem and progenitor cells expanded *ex vivo* from an entire CBU with cytokines and nicotinamide,[redacted]. Omidubicel comprises: 1) *ex vivo* expanded, cord blood-derived, hematopoietic CD34+ progenitor cells (Omidubicel cultured fraction (CF)); and 2) the non-cultured cell fraction of the same CBU (Omidubicel Non-cultured Fraction (NF)) consisting of mature myeloid and lymphoid cells.

The expansion technology is based on the finding that nicotinamide, the active molecule, epigenetically regulates *in vitro* expansion of functional hematopoietic progenitor cells that display increased bone marrow homing and engraftment efficacy.

NAM has been shown to delay differentiation and to increase the engraftment efficacy of cord-blood derived, purified CD133+ cells cultured with a combination of 4-cytokines (FLT3, SCF, TPO and IL6) for 19-23 days. In the presence of NAM, the fraction of CD34+CD38- early progenitor cells increases and the fraction of differentiated myelomonocytic cells (CD14+, CD11b+, CD11c+) decreases as compared with cultures without NAM. CD34+ cells obtained following culturing with NAM displayed increased migration towards SDF-1 and home to the bone marrow with higher efficacy than cells cultured with cytokines alone or non-cultured cells.[14] Negligible amounts of cells displaying T-cell phenotype can be found in the expanded product. Thus, T-cells infused with omidubicel derive entirely from omidubicel NF.

NAM serves as a precursor of nicotinamide adenine dinucleotide (NAD+)[18] and is a potent inhibitor of enzymes that require NAD+ for their activity[19, 20], such as mono-ADP-ribosyltransferases (mARTs), poly-ADP-ribose polymerases (PARPs) and CD38, cADPR/NADase.[21] NAM is implicated in regulation of cell adhesion, polarity, migration, proliferation and differentiation.[22]

NAM has also been demonstrated as a strong noncompetitive inhibitor of sirtuin (silent mating type information regulation 2 homolog) 1 (SIRT1), the NAD-dependent class III histone deacetylase.[23]

3.3. Clinical Experience

The clinical experience with omidubicel includes the following studies:

- GC P#01.01.020 / NCT01221857
  "Allogeneic Stem Cell Transplantation of NiCord®, Umbilical Cord Blood-Derived *Ex Vivo* Expanded Stem and Progenitor Cells, in Combination With a Second, Unmanipulated Cord Blood Unit in Patients With Hematological Malignancies"

- GC P#03.01.020 / NCT01816230
  "A Multi-Center, Multi-National, Allogeneic Stem Cell Transplantation of NiCord, Umbilical Cord Blood-derived Ex Vivo Expanded Stem and Progenitor Cells, in Adolescent and Adult Patients with Hematological Malignancies".
- GC P#05.01.020 / NCT02730299
  "A Multicenter, Randomized, Phase III Registration Trial of Transplantation of NiCord, Ex Vivo Expanded, Umbilical Cord Blood-derived, Stem and Progenitor Cells, versus Unmanipulated Umbilical Cord Blood for Patients with Hematological Malignancies."
- GC P#02.01.020 / NCT01590628
  "Allogeneic Stem Cell Transplantation of NiCord, Umbilical Cord Blood-derived Ex Vivo Expanded Stem and Progenitor Cells, in Patients with Hemoglobinopathies."
- GC P#04.01.020/030 / NCT02039557
  "Long Term Follow Up for patients who have received Allogeneic Stem Cell Transplantation of NiCord/CordIn Umbilical Cord Blood-derived Ex Vivo Expanded Stem and Progenitor Cells."
- GC P#01.01.030 / NCT02504619
  "A Multi-Center, Multi-National, Allogeneic Stem Cell Transplantation of CordIn, Umbilical Cord Blood-Derived *Ex Vivo* Expanded Stem and Progenitor Cells, in Patients with Hemoglobinopathies."

[redacted]

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

[redacted]

551 [redacted]

3.3.1. Study GC P#01.01.020

A pilot clinical study of omidubicel in hematological malignancies in combination with a second, unmanipulated CBU was completed (GC P#01.01.020). This was a single arm pilot study to evaluate the safety of the co-transplantation of omidubicel and an unmanipulated CBU to patients with hematological malignancies following myeloablative therapy.

Patients under the age of 65 years with hematological malignancies and no available matched donor were treated at Duke University School of Medicine or Loyola University Medical Center between December 2010 and August 2012. Eligibility required the availability of 1 cord blood unit containing at least $2.5x10^7$ total nucleated cells per kilogram of the recipient's body weight. This unit was designated as the unmanipulated unit. The second unit, designated for omidubicel expansion, contained at least $1.5x10^7$ total nucleated cells per kilogram of the recipient's body weight. When 2 units with at least $2.5x10^7$ total nucleated cells per kilogram of the recipient's body weight were available, the best-matched unit was assigned as the unmanipulated unit. The cord blood units were required to match the recipient at 4 or more HLA loci by intermediate-resolution typing for HLA class I alleles (A and B) and high-resolution typing for HLA class II DRB1 alleles.

The bone marrow conditioning regimen consisted of 1,350-cGy total body irradiation (TBI) delivered in 9 fractions on days –9 to –5, and fludarabine 40 mg/m^2 was given on days –5 to –2 of the transplantation. An optional infusion of 60 mg/kg cyclophosphamide on days –4 and –3 was given at the discretion of the managing physician. GvHD prophylaxis was provided by tacrolimus and mycophenolate mofetil starting 4 days before transplantation. Mycophenolate mofetil and tacrolimus were continued for a minimum of 60 days and 6 months following transplantation, respectively.

[redacted]

[redacted]

3.3.2. Study GC P#03.01.020

A clinical study of omidubicel in hematological malignancies as a standalone graft source was completed (GC P#03.01.020).[16] This was a single arm study to evaluate the ability of omidubicel to provide durable engraftment as a single graft source in patients with hematological malignancies following conditioning therapy.

Eligible patients were aged 12-65 years old with hematological malignancies and no available matched sibling or matched unrelated adult donor at multiple international centers between August 2013 and June 2018. Eligibility required the availability of a cord blood unit containing at least $8x10^6$ total CD34+ cells as well as a pre-cryopreserved (post-processing) total nucleated cell count of $\geq 1.8x10^9$, and total nucleated cell dose $\geq 1.5x10^7$ TNC/kg. The cord blood unit was

required to match the recipient at 4 or more HLA loci by intermediate-resolution typing for HLA class I alleles (A and B) and high-resolution typing for HLA class II DRB1 alleles.

Multiple conditioning regimens were used, including TBI/Flu/±Cy and Thiotepa/Bu/Flu. GvHD prophylaxis was provided by Tacrolimus or Cyclosporine and mycophenolate Mofetil starting three days before transplantation. Mycophenolate Mofetil and Tacrolimus/Cyclosporine were continued for a minimum of 60 days and 5 months following transplantation, respectively.

43 patients were enrolled and transplanted on the study: 36 received omidubicel alone, 2 received omidubicel with unmanipulated CBU, and 5 received unmanipulated backup CBU alone.

[redacted]

[redacted]

3.3.3. Study GC P#02.01.020

This pilot, multi-center, single arm study was designed to evaluate the safety and efficacy of transplantation of omidubicel in patients with hemoglobinopathies such as sickle cell disease or thalassemia major. The study was conducted at Duke University Medical Center, NC, USA and Cohen Children's Medical Center of New York from May 2012 to October 2019. [redacted]

[redacted]

3.3.4. Study GC P#01.01.030

This multicenter, multi-national, Phase I/II study was designed to evaluate the safety and efficacy of omidubicel transplantation in patients with hemoglobinopathies (sickle cell disease or thalassemia major) following a preparative therapy. One patient was enrolled and transplanted in July 2016, and the study was subsequently closed due to insufficient enrollment.

[redacted]

[redacted]

3.3.5. Study GC P#05.01.020

This study is an open-label, controlled, multicenter, international, Phase III, randomized study comparing transplantation of omidubicel to transplantation of one or two unmanipulated, unrelated cord blood units in patients with hematological malignancies for whom allogenic SCT is currently a recommended treatment. The study was designed to randomize approximately120 patients in a 1:1 ratio using minimization randomization to receive either omidubicel or unmanipulated cord blood transplantation. Patient were to receive one of following conditioning regimens:

- (A.1) TBI, Fludarabine, and Thiotepa; or
- (A.2) TBI, Fludarabine and Cyclophosphamide; or
- (B) Thiotepa, Busulfan and Fludarabine.

The primary endpoint is time to neutrophil engraftment. Secondary endpoints include platelet engraftment, the incidence of infections, hospitalization, treatment-related mortality, disease free survival, and overall survival.

Enrollment to the study was completed in January 2020.

3.3.6. Study GC P#04.01.020/030

Study GC P#04.01.020/030 is an observational study, to collect long-term outcomes data of patients treated with NiCord/CordIn on study protocols GC P#01.01.020, GC P#02.01.020 and GC P#03.01.020. up to 5 years following transplantation.

[redacted]

[redacted]

3.4. Overall Risk Benefit

Omidubicel is an allogeneic graft for HSCT composed of CB-derived stem and progenitor cells expanded *ex vivo* from an entire CBU with cytokines and nicotinamide, as well as non-cultured mature myeloid and lymphoid cells from the same CBU. Omidubicel is intended for the treatment of patients for whom allogeneic hematopoietic stem cell transplantation is indicated, including high risk hematological malignancies. Non-clinical studies have demonstrated that culturing CD133+ cells with NAM delays differentiation and increases engraftment efficacy.

UCB is an easily procured stem cell source for allogeneic HSCT, with high availability for patients of different ethnic backgrounds. However, its use is limited by delayed hematopoietic recovery, leading to increased morbidity and mortality post transplantation.

Clinical data to date suggest that patients treated with omidubicel can rapidly engraft both neutrophils and platelets. Subsequently, patients require a substantially shorter duration of hospitalization after transplantation, which is consistent with more rapid recuperation and a reduced occurrence of post-transplant infections. Available patient follow-up, as long out as 5 years post-transplant, indicates a safe profile in terms of the robustness of engraftment, and the occurrence of GvHD, as compared to unmanipulated CBT despite the use of partially mismatched CBUs. Moreover, the available data show that patients treated with omidubicel are able to develop functional hematopoietic systems, with the development of myeloid and lymphoid cells, supporting immune recovery.

As in all cases of allogeneic HSCT, the overall risks of cord blood administration following a cytotoxic preparative regimen can be serious and fatal. The potential risks associated with cord blood include early death, infusion reactions, GvHD and graft failure. The deaths and other adverse events experienced by omidubicel recipients to date are common effects of allogeneic stem cell transplantation following conditioning regimen therapy.

3.5. Rationale for Study Design & Dosages

3.5.1. Study Population

The study will include patients with hematological malignancies for whom allogeneic SCT is currently a recommended and potentially lifesaving treatment. The study will only enroll patients who do not have a suitably matched and readily available stem cell donor.

Age of adolescents included in the study is based on age ranges set in the previous Phase I/II and Phase III studies. Women, ethnic minorities, and other populations will be included in this study. Demographics of these populations will be reported at the end of the study.

3.5.2. CBU Cell Dose

The CBU intended for expansion is required to contain a pre-cryopreserved (post-processing) total CD34+ cell count of at least $8x10^6$, as well as a pre-cryopreserved (post-processing) total nucleated cell count of at least $1.8x10^9$, and a total nucleated cell dose of at least $1.5x10^7$ TNC/kg body weight, a dose predicted to be sufficient in size to provide robust and sustained engraftment, based on the current clinical experience with omidubicel.

[redacted]

3.5.3. Selection of CBUs

The selection of the optimal CBU is at the investigator's discretion. Decisions on the selection of CBUs are based on specific histocompatibility data, cell dose, availability, and in some cases the source of the CBU. However, there is no clear consensus or evidence-based algorithm as to the hierarchy of these factors. For this reason, the protocol does not specify prioritization rules when more than one eligible CBU is identified.

With regard to HLA matching, all CBUs, whether intended for treatment or as backup CBUs, must be HLA-matched at 4-6/6 HLA class I (HLA-A & HLA-B, low resolution) and II (HLA-DRB1, high resolution) loci with the patient. Low level DNA/molecular matching is sufficient for HLA class I; however, serologic matching may also be used. High resolution matching is required for HLA class II.

Also, with regards to the use of units not meeting the local applicable regulations, all the patients included in the study may be considered of “urgent medical need” by the nature of their underlying malignancy, and have a high (>50%) likelihood of death without receiving a CBU transplantation. The usage of ineligible units with unusual findings (e.g., "incomplete”) will only be permitted when no comparable eligible CBU is found, and when this is the best CBU found for this patient. The investigator will sign the documentation of urgent medical need; the site will document the signed form, the CBU search results and selection rationale in such cases.

3.5.4. Conditioning Regimens

Over the years, a number of different conditioning regimens have been established as standard of care for unrelated CB transplantation in adults, generally divided into TBI – based versus non-TBI based. In this study, the choice of conditioning regimen and GvHD prophylaxis agents provides the flexibility to choose between TBI-based and non-TBI containing regimens, and to allow for individual country and site accepted practices and experience.

4. STUDY OBJECTIVES, HYPOTHESIS & STUDY ENDPOINTS

4.1. Objectives

The overall study objectives are to provide access to omidubicel for transplantation in patients with hematological malignancies and to collect additional safety and efficacy data.

Study Hypothesis

The hypothesis is that omidubicel is an acceptable alternative graft source for transplantation.

4.2. Definition of Study Endpoints

4.2.1. Neutrophil Engraftment

Neutrophil engraftment is defined as achieving an absolute neutrophil count (ANC) greater than or equal to 0.5 x 10^9/L on 3 consecutive measurements by Day 42 post-transplant inclusive. The first day of the three measurements will be designated the day of neutrophil engraftment.

Primary graft failure is defined as failure to achieve neutrophil engraftment by Day 42 post-transplant as described above. Infusion of a second stem cell product on or prior to Day 42 post-transplant will be considered primary graft failure, with the following exception:

- Infusion of an additional stem cell product after documented neutrophil engraftment will be considered secondary graft failure, even if it occurs on or prior to Day 42 post-transplant.

Secondary graft failure consists of documented neutrophil engraftment, followed by severe neutropenia (<0.5 x 10^9/L for three or more consecutive laboratory values on separate days) with marrow cellularity <5%, without subsequent improvement occurring either spontaneously or after growth factor treatment. Infusion of an additional stem cell product after documented neutrophil engraftment will be considered secondary graft failure.

4.2.2. Platelet Engraftment

4.2.2.1. Platelet Engraftment > 20k

Platelet engraftment >20k is defined as the first day of a minimum of 3 consecutive measurements on different days such that the patient has achieved a platelet count >20x10^9/L with no platelet transfusions in the preceding 7 days (count day of engraftment as one of the preceding 7 days). The first day of the three measurements will be designated the day of platelet engraftment.

4.2.2.2. Platelet Engraftment > 50k

Platelet engraftment >50k is defined as the first day of a minimum of 3 consecutive measurements on different days such that the patient has achieved a platelet count >50x10^9/L with no platelet transfusions in the preceding 7 days (count day of engraftment as one of the preceding 7 days). The first day of the three measurements will be designated the day of platelet engraftment.

4.2.3. Non-Relapse Mortality

Non-Relapse mortality is defined as any death not preceded by relapse.

4.2.4. Overall Survival

Overall survival is defined as the time from the date of transplant to death from any cause.

4.2.5. Disease-Free Survival

Disease-free survival is defined as the time from the date of transplant to the date of disease relapse or death from any cause, whichever comes first

4.2.6. Acute GvHD

Acute GvHD will be staged and graded using the Consensus Conference on Acute GvHD grading (Appendix B) at every protocol-specified scheduled visit up to day 180 post transplant. The date of GvHD, if applicable, will be assigned as the target visit date assigned to the first visit day post transplant on which the maximum symptoms in the assessment period meet the definition of acute GvHD.

4.2.7. Chronic GvHD

Chronic GvHD will be assessed on the day of diagnosis, as well as on day 100, 180, year 1 and year 2 post transplant and classified as mild/moderate/severe according to the 2014 NIH consensus criteria (Appendix B).

4.2.8. Disease Relapse

Relapse of malignancy – recurrence of malignancy after transplantation can be assessed in the blood, marrow or other sites to identify morphological or cytogenetic evidence of disease consistent with pre-transplant features. The below definitions provide general guidelines, however the determination of disease relapse is per Investigator discretion.

Minimal residual disease – minimal residual disease (MRD) is defined by the sole evidence of malignant cells by flow cytometry, or fluorescent in situ hybridization (FISH), or Southern blot or Western blot, or polymerase chain reaction (PCR), or other techniques, in the absence of morphological or cytogenetic evidence of disease in blood or marrow. In some cases, minimal residual disease that progresses can be considered as relapse (in which case the date of relapse will be the date of detection of minimal residual disease). For example, a change in treatment in response to detection of MRD, such as institution of therapy, or withdrawal of immunosuppression can be considered evidence of relapse.

Disease relapse for any malignancy indicated for this study can be defined by the appearance or progression of blasts, dysplastic changes or malignant lesions in the marrow, peripheral blood or other extramedullary tissues, that are not attributable to other causes, or appearance/progression of a previous cytogenetic or molecular marker of malignant disease.

Institution of any therapy to treat persistent, progressive or relapsed disease, including withdrawal of immunosuppressive therapy or donor lymphocyte infusion (DLI), can also be considered evidence of relapse/progression.

In general, the date in which the first evidence of recurrence was found will be considered the date of relapse, unless MRD was previously detected, as mentioned above.

4.2.9. Safety and Tolerability of Omidubicel Transplantation

The safety and tolerability of omidubicel transplantation will be evaluated as described in Section 10.3.2.

It will include the analysis of Adverse Events (AEs) within 24 hours, common events post-transplant (as listed in Appendix A), related events, grade 2-3 infections according to BMT-CTN severity grading (as outlined in Appendix F), Serious Adverse Events (SAEs), deaths and causes of death.

5. STUDY POPULATION

5.1. Number of Patients

Approximately 60 patients will be enrolled. Enrollment is defined as an eligible patient whose CBU has been shipped to the manufacturing facility.

Any patient may be removed from the study at any time if in the judgment of the investigator continuation in the trial is not in the best interests of the patient. Patients may also withdraw themselves from the study at any time and for any reason.

Patients will be defined as screening failures if they are removed from the study before CBU shipment. Screening failures may be replaced.

5.2. Analysis Populations

The analysis population will be all patients who received an omidubicel transplantation.

5.3. Eligibility Criteria

Inclusion Criteria

1. Patients must be at least 12 years of age
2. Patients with one of the following hematological malignancies who are eligible allogeneic transplant candidates according to institutional treatment guidelines:
    - Acute lymphoblastic leukemia (ALL) in complete morphologic remission, defined as no circulating blasts and less than 5% blasts in the bone marrow
    - Acute myelogenous leukemia (AML) in complete morphologic remission, defined as no circulating blasts and less than 5% blasts in the bone marrow
    - Chronic myelogenous leukemia (CML) with no circulating blasts and less than 5% blasts in the bone marrow
    - CLL
    - Myelodysplastic Syndrome (MDS)
    - Biphenotypic/Undifferentiated/Prolymphocytic/Dendritic Cell Leukemias and Natural Killer Cell Malignancies, adult T-cell leukemia/lymphoma in first or subsequent complete morphologic remission
    - Lymphoma with chemosensitive disease at the time of evaluation for transplantation
3. Patients must have a partially HLA-matched CBU:
    a. The unit must be HLA-matched at 4-6/6 HLA class I (HLA-A & HLA-B, low resolution) and II (HLA-DRB1, high resolution) loci with the patient. There must be at least one allele match at DRB1.

b. The CBU must have a pre-cryopreserved (post processing) total CD34+ cell count of ≥8 x10^6 as well as a pre-cryopreserved (post processing) total nucleated cell count of ≥1.8 x10^9 and total nucleated cell dose ≥1.5 x10^7 TNC/kg.

c. The CBU will have undergone volume reduction (both plasma and red blood cell depletion) prior to cryopreservation.

d. Verification typing (confirmatory typing) must be completed before CBU shipment for manufacturing.

4. [redacted]

5. Patients must be clinically suitable to receive myeloablative conditioning followed by allogeneic HSCT. The patient must meet institutional standards of performance status and physiologic reserves (including cardiac, pulmonary, renal and hepatic functions) to undergo myeloablative conditioning.

6. Females of childbearing potential, defined as any female who has experienced menarche and is not postmenopausal (defined as not having a menstrual period for at least 24 months) or permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy), agree to use an appropriate method of contraception from at least 7 days prior to conditioning regimen therapy until completion of follow-up procedures. An appropriate method of contraception is defined as one that results in a low failure rate (i.e., less than 1 percent per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, intrauterine contraceptive devices (IUDs), true sexual abstinence (when this is in line with the preferred and usual lifestyle of the patient), or a vasectomized partner.

7. Patient (or legal guardian) signs the written informed consent after being aware of the nature of the patient's disease and willingly consents to the treatment program after being informed of alternative treatments, potential risks, benefits, and discomforts.

Exclusion Criteria

8. "Marked", "3+" or "extensive" bone marrow fibrosis

9. Evidence of donor specific anti-HLA antibodies to the selected CBU (MFI>3000 to HLA A, B, C, or DRB1), unless approved by the Sponsor

10. Pregnancy, as indicated by a positive serum or urine human chorionic gonadotrophin (HCG) test, or lactation

11. Clinically significant active malignancy other than that for which the UCB transplant is being performed within 12 months of enrollment, unless approved by the Sponsor. Fully resected cutaneous squamous cell or basal cell carcinoma or cervical carcinoma in situ within 12 months of enrollment is permitted

12. Evidence of infection or other medical condition which, in the judgment of the investigator, make the patient unsuitable for myeloablative conditioning and HCT
13. Availability of a suitable HLA identical sibling or 10/10 matched unrelated donor whose stem cells can be collected in a timely manner without jeopardizing recipient outcome. Patients who have haploidentical related donors or syngeneic donors are not excluded
14. Allergy to bovine products, gentamicin, or to any other product that may interfere with the treatment
15. Psychologically incapable of undergoing HSCT with associated strict isolation or documented history of medical non-compliance and/or psychiatric illness and/or social situations that would limit compliance with study requirements
16. Eligible for enrollment in an ongoing omidubicel investigational study other than this one
17. Enrolled in another interventional clinical study or received an investigational treatment within 30 days prior to the anticipated date of transplantation, unless documented approval obtained from Sponsor prior to CBU shipment for manufacturing

6. CONCOMITANT MEDICATIONS & SUPPORTIVE CARE

Required conditioning and supportive care regimens are outlined below.

6.1. Previous Medications

All chemotherapy and radiotherapy courses administered to the patient as prior treatment for the hematological malignancy should be recorded in the Case Report Form (CRF).

6.2. Concomitant Medications

6.2.1. Disallowed Concomitant Medications

The following medications will not be given post-transplant, unless previously approved by Sponsor:

- Any cytokines except G-CSF (including IL-2 or others)
- Investigational agents
- ATG or alemtuzumab from one month prior to transplant

6.2.2. Discouraged Concomitant Medications

- The use of Bactrim (sulfamethoxazole and trimethoprim) or methotrexate is discouraged on or after day -2 until the time of engraftment as it may delay engraftment, and is reserved only for cases where it is assessed to be essential and superior to all alternative medications.
- Prophylaxis with ganciclovir or valganciclovir is strongly discouraged on or after day -2 until engraftment is achieved

6.3. Preparative Conditioning Regimens

All prior chemotherapies or targeted therapies, such as Inotuzumab and Gemtuzumab, should be discontinued in accordance with the prescribing information and institutional treatment guidelines.

Applicable myeloablative conditioning regimens must include at least one of the below:

1) TBI >500 cGy (single) or >800 cGy (fractionated)
2) Busulfan (Bu) >7.2 mg/kg IV (or >9.0 mg/kg PO)
3) Bu >300 mg/m2 IV (or 375 mg/m2 PO)
4) Melphalan > 150 mg/m^2
5) Thiotepa > 10 mg/kg
6) Treosulfan > 30,000 mg/m^2 (or > 30 g/m^2)

Myeloablative conditioning regimens complying with the above definition can be selected from the below combinations. Use of a different conditioning regimen combination must be approved by the Sponsor.

1) Cyclophosphamide (Cy) + TBI
2) Fludarabine (Flu) + TBI
3) Cy + Flu + TBI
4) Thiotepa + Flu + TBI
5) Cy + VP16 (Etoposide) + TBI
6) Bu + Cy
7) Bu + Melphalan
8) Thiotepa + Bu + Flu
9) Clofarabine + Bu + Flu

6.4. GvHD Prophylaxis Medications

The GvHD prophylaxis can be selected from the below combinations. Drug dosing and duration of therapy is per site practice.

- Mycophenolate mofetil (MMF) + Tacrolimus
- MMF + Cyclosporine

6.5. Acute & Chronic GvHD Treatment

Management of acute and chronic GvHD will be at the Investigator's discretion and in accordance with the institution's guidelines.

6.6. Venous Access

Recipients will have appropriate long-term central venous access placed, per institutional standard practice, prior to beginning the conditioning regimen. The placement of a triple lumen tunneled catheter is recommended.

6.7. Infusion Support

The patient will receive premedication 30 to 60 minutes before the administration of omidubicel. Premedication should include any or all of the following: antipyretic, histamine antagonists, and corticosteroids.

Management of infusion reactions during and post-transplant is at the discretion of the managing physician.

6.8. Supportive Cytokine Therapy

G-CSF (e.g., Filgrastim, Neupogen, Granix, Zarxio) therapy will be started on Day +1 at a dose of [redacted] µg/kg/day (rounded to nearest vial size) given IV or SC and continuing at least until the ANC is >1,000/µl x 2 consecutive days. Additional courses of G-CSF may be given per site physician preference/discretion.

6.9. Blood Products

Thrombocytopenia: Platelet counts should be maintained at >10,000/uL after allogeneic transplant by transfusion of platelets. When available, single donor platelets will be used.

Anemia: Transfusions of packed red blood cells (RBC) are indicated for the management of symptomatic anemia per institutional guidelines. In the absence of symptoms, RBC transfusions should be considered to maintain hemoglobin > 7g/dL.

All blood products (except omidubicel or any other stem cell grafts administered) must be irradiated to at least 2500 cGy before administration to transplant recipients to reduce the risk of developing third-party graft-versus-host disease.

6.10. Engraftment Syndrome

Engraftment syndrome is a clinical diagnosis. The most frequently reported manifestations are transient fever, rash, and respiratory symptoms not attributable to infection or GvHD.

The administration of prophylactic methylprednisolone as prophylaxis for engraftment syndrome is not recommended. Therapeutic use of methylprednisolone is permitted.

6.11. Infection Prophylaxis and Surveillance

Institution guidelines will be followed to provide prophylaxis for infections. Strict guidelines for hygiene and care will be applied. Before starting the pre-transplant conditioning there should be no uncontrolled mucosal or cutaneous infections. Oral candida prevention should be vigorously pursued.

All patients must be nursed in a single room during neutropenia and should preferably be nursed in a single room during all admissions. All visitors must be free of active infections. Rigorous hand washing is crucial.

6.11.1. Anti-Viral Prophylaxis

Acyclovir [redacted] mg (or [redacted] mg/m^2) PO BID is recommended for anti-viral prophylaxis with conditioning through the duration of neutropenia and then at [redacted] mg PO BID (or [redacted] mg/kg/day PO divided in 2–3 doses for patients <40kg, up to a maximum of [redacted] mg BID) until 1 year post transplant or until 6 months after immunosuppression is discontinued. If unable to tolerate PO medications, IV prophylaxis will be necessary. Other anti-viral prophylaxis regimens may be administered per institutional guidelines, however, prophylaxis with ganciclovir or valganciclovir is strongly discouraged on or after day -2 until engraftment is achieved.

6.11.2. Anti-Bacterial Prophylaxis

Ciprofloxacin [redacted] mg PO BID day 0-100 is recommended. Other anti-bacterial prophylaxis regimens may be administered per institutional guidelines.

6.11.3. PCP Prophylaxis

Trimethoprim-sulfamethoxazole or an equivalent drug is recommended to be administered after engraftment per institutional guidelines. The use of Bactrim is discouraged on or after day -2 and prior to engraftment as it may delay engraftment, and is reserved only for cases where it is assessed to be essential and superior to all alternative medications.

6.11.4. Fungal Prophylaxis

Anti-fungal prophylaxis is recommended to be given with agents such as fluconazole, itraconazole, voriconazole, or posaconazole per institutional guidelines.

6.11.5. CMV Surveillance

All recipients must be tested for CMV (using the PCR method) at least once during the conditioning period. Testing for CMV using the PCR method is required at weekly study visits after transplantation until Day 28, and recommended to be continued weekly until Day 42 and then as clinically indicated. Antiviral therapy for CMV reactivation is recommended to commence preemptively if CMV testing reveals a high or rising viral load. If CMV reactivation occurs at or before engraftment, foscarnet is recommended to prevent marrow suppression.

6.11.6. HHV6 Surveillance

Quantitative HHV6 DNA assessment by PCR is required to be tested at weekly study visits after transplantation until Day 28. Treatment is recommended if symptomatic or following 2 weeks of rising viral load or an absolute count above 10k copies/ml. Treatment for HHV6 should follow institutional practice. If HHV6 reactivation occurs at or before engraftment, treatment with foscarnet is recommended.

6.11.7. EBV Surveillance

Quantitative EBV viral load assessment by PCR is recommended to be tested at least monthly after the start of the preparative conditioning regimen, or more frequently as clinically indicated, until Day 100 (or longer if on immunosuppression). Patients with a positive result (>1000 copies) should be treated as per institutional guidelines. Rituximab treatment is recommended.

6.11.8. Adenovirus Intervention Guideline

Testing for adenovirus infection in the blood by PCR method is recommended in the event of symptoms suspicious for infection such as diarrhea, hepatic dysfunction or respiratory symptoms. If an active systemic infection is diagnosed, therapy should be instituted per institutional guidelines.

6.11.9. Intravenous Immune Globulin

Intravenous immune globulin may be administered according to institutional practice guidelines.

6.12. Guidelines for Infusing a Second Stem Cell Product

A second transplant may be considered if the patient has impending or actual graft failure, per institutional guidelines.

6.13. Investigational Agents

Unless approved by the Sponsor, investigational agents should not be administered from 30 days prior to transplantation until the 180 days post-transplant for all patients transplanted. Patients who relapsed or had graft failure are allowed to receive investigational agents without sponsor approval.

6.14. Other Medications

Patients should receive full supportive care according to institutions' practice patterns and clinical guidance as described above, including transfusions of blood and platelets, antibiotics, anti-emetics, or any other supportive care according to clinical judgment.

All concomitant medications and blood products administered after the signing of informed consent should be recorded in the source documents.

7. DETAILED STUDY PLAN

Table 2: Transplant Workup and Screening Assessments Flowchart

	Within 3 weeks prior to CBU Shipment to production site *(unless specified differently in the table)*	prior to conditioning
Identify qualifying CBU	Any time before CBU shipment	
CBU Confirmatory HLA typing	Any time before CBU shipment	
CBU review and approval by sponsor	Any time before CBU shipment	
Written Informed Consent	prior to any study specific procedure	
Baseline disease assessment All patients: when clinically indicated, PB and BM morphology (aspiration, and biopsy if applicable) Acute Leukemias: BM FACS analysis (flow cytometry) Lymphoma: CT-scan or PET-CT pelvis, abdomen, chest	Within 6 weeks prior to CBU shipment	
Acute Leukemias: cytogenetics, and molecular markers	From 6 weeks prior to CBU shipment up to start of conditioning	
Anti HLA antibodies	Within 6 weeks prior to CBU shipment	
Complete Blood Count (CBC) with differential	X	
Blood Chemistry *(at a minimum Serum creatinine, ALT, AST, Total bilirubin, Magnesium, Alkaline phosphatase)*	X	
Complete urinalysis	X	
Infectious disease markers *(HIV I/II Ab; HBsAg; HBcAb, EBV Ab, HCV Ab, CMV screen (IgG or Total); optional: HTLV I/II Ab, VZV Ab, Syphilis Ab (such as RPR))*	From 3 weeks prior to CBU shipment up to start of conditioning	
Chest X-ray (not mandatory if chest CT or MRI was performed)	X	
Pulmonary Function Tests (prior to treatment with bronchodilators) with cDLCO, FEV1, FVC, and oxygen saturation	X	
Cardiac: EKG, Echocardiography or MUGA scan with LVEF	X	
Physical Examination	X	
Vital signs: Temperature, BP, pulse, weight, height and BSA	X	
Karnofsky/Lansky performance score	X	
Medical History	X	
Confirm eligibility criteria	X	
Serum or urine β-HCG (for women of childbearing potential)		Within 4 weeks prior to start of conditioning
Peripheral blood sample for Chimerism		X
Historical medications/treatments for primary disease		X

Table 3: Transplant and Follow-Up Assessments Flowchart

	Conditioning	Transplantation and Follow Up (Days Post-transplant)										
		0		7±3	14 ±3	21 ±3	28 ±5	42 ±6	100 ±21	180 ±30	365 ±60	730 ±60
		Pre-Tx	Post-Tx									
CF, NF, and infusion solutions shipped to clinical site before or during conditioning	X											
Conditioning regimen per protocol	X											
Omidubicel CF/NF thawing and infusion		X										
Toxicity assessment from start of infusion through 24 hours post infusion			X									
Vital Signs (Temperature, BP, pulse, weight) *Once between days -3 and -1, and on day 0 pre- and post-transplant*	X	X	X									
Vital signs per SOC - daily until engraftment and then at study visits				X	X	X	X	X	X	X	X	X
CBC (Baseline) *Once between days -3 and -1, and on day 0 prior to transplant*	X	X										
CBC (post-transplant) - daily until engraftment and then at study visits - Differential if WBC≥0.5				X	X	X	X	X	X	X	X	X
Blood Chemistry (baseline) Serum creatinine at minimum *Once between days -3 and -1*	X											
serum creatinine, total bilirubin, alkaline phosphatase, AST, ALT, and magnesium at a minimum *on day 0 prior to transplant*		X										
Blood Chemistry (post-Transplant) per SOC				X	X	X	X	X	X	X	X	X
Physical Examination (baseline) *Once between days -3 and -1, and on day 0 prior to transplant*	X	X										
Physical Examination (post-transplant) per SOC							X		X	X	X	X
Peripheral blood chimerism (Measured by molecular methods, in whole blood or myeloid. Bone marrow chimerism is an acceptable alternative)								X	X			X
Disease assessment per SOC									X	X	X	X
Assess Acute GvHD				X	X	X	X	X	X	X		
Assess Chronic GvHD									X	X	X	X
CMV PCR	X			X	X	X	X					
HHV6 PCR				X	X	X	X					

Adverse events are to be assessed documented in the source documents at each study visit. Safety report in the EDC will be as detailed in section 9.2

7.1. CBU Selection

Potential candidates for CBT for whom a search yielded eligible CBUs, as described below, will be identified as screen candidates for the study. Patients must have one partially HLA-matched CBU. The unit must be HLA-matched at 4-6/6 HLA class I (HLA-A & HLA-B, low resolution) and II (HLA-DRB1, high resolution) loci with the patient. There must be at least one allele match at DRB1.

The CBU must have a pre-cryopreserved (post processing) total CD34+ cell count of $\geq 8x10^6$ as well as a pre-cryopreserved (post processing) total nucleated cell count of $\geq 1.8x10^9$ and total nucleated cell dose $\geq 1.5x10^7$ TNC/kg. The CBU will have undergone volume reduction (both plasma and red blood cell depletion) prior to cryopreservation.

[redacted]

[redacted]

[redacted]

All CBUs should be procured from public banks that meet national applicable regulations. Donors are screened and tested in accordance with the relevant regulatory requirements. The CBU should be tested for the applicable infectious diseases and be eligible. In those instances when the donor of the only appropriately matched unit available was not determined eligible, with unusual findings or doesn't comply with the national regulations of the clinical site, the clinical site must fill out an Urgent Medical Need document signed by the investigator. This document will be sent to the Sponsor's study logistics manager (SLM) and a copy filed in the patient's file.

[redacted]

7.2. Informed Consent and Registration

A conference will be held with the patient and legal guardian as applicable to discuss this study and alternatives available for the treatment of the underlying disease. The conference will be conducted by the principal investigator or other designated qualified person (according to local regulations) who has been delegated to do so.

Standard of care workup for transplant may be done prior to patient study consent and results of those tests may be used for required study assessments, provided they are within the protocol specified timeframes. Prior to performing any study activities/evaluations that are not part of the

site's routine clinical practices, the patient must be thoroughly informed about all aspects of the study, including scheduled study visits and activities, and must sign the written informed consent. In particular, the timelines from consent to transplant should be discussed, taking into account the period of 3 weeks for manufacturing, as compared to standard timelines to transplant. Informed consent from the patient and/or his/her legal guardian will be obtained using a form approved by the Institutional Review Board or Ethics Committee of the institution enrolling the patient. A signed copy of the written informed consent should be given to the patient and/or his/her legal guardian.

Patients will be registered in the EDC system: Within three business days of consent, an authorized user at the transplant center should enter the patient demographics and enrollment information in the EDC system, including a confirmation that the patient (or legal guardian) signed the informed consent. Each patient will be assigned a study number by the EDC system.

7.3. Assessments Prior to CBU shipment

The below assessments must be scheduled and resulted (when applicable) prior to CBU shipment to the production facility, within the given windows below. After consent and before CBU shipment, the CBU documents for the CBU selected for expansion should be redacted and uploaded to EDC system.

- ***CBU requirements (any time before CBU shipment):***
  - The CBU must be typed twice (i.e., initial typing and verification typing). Verification typing (confirmatory typing) should be performed in a lab that is ASHI/EFI accredited and must come from an attached segment; the results must be reported to the center before shipment to the production site
  - The CBU must be fully tested (all tests required for CBU eligibility including verification typing) before shipment to the production site.
  - Patient and CBU ABO and Rh typing
  - Extended typing of patient and CBUs HLA class I (A, B, and C) & II (DRB1) at high resolution. Note that although the matching requirement per protocol only requires low resolution A and B matching, extended high resolution, DNA-based typing is required for loci A, B, and C, as well as DRB1. DQ and DP typing is also recommended.
- ***Patient assessments:***

Patient's eligibility for the study will be assessed. Tests performed during pre-screening period according to the Center's routine evaluation of candidates for stem cell transplantation need not be repeated, provided they were performed recently enough, as detailed below.

Unless otherwise noted, all below mentioned activities must be completed, and should be entered into the EDC system within three weeks prior to CBU shipment. If pre-approved by the Sponsor, the center may proceed with CBU shipment before all required assessments have been completed.

The activities will be performed as detailed in Table 2 and will include:

- **Primary disease characteristics and baseline assessment** including subtype, status, and cytogenetics (within 6 weeks prior to CBU shipment unless otherwise specified)

Note: Peripheral blood and bone marrow morphology - The bone marrow assessment for screening should generally be performed following recovery from prior chemotherapy, reflected by a neutrophil recovery of at least ANC >500.

  - ALL, AML and other acute leukemias
    - **Peripheral blood and bone marrow morphology:** an aspiration is sufficient (a biopsy is not mandatory)
    - **BM FACS analysis (flow cytometry)**
    - **Cytogenetics and molecular markers:** see section 07.5
  - MDS, CML
    - **Peripheral blood and bone marrow morphology:** an aspiration is required. A biopsy will be required if the screening aspiration sample is without evaluable spicules (in order to rule out the possibility of severe fibrosis) or if at any point since diagnosis fibrosis was noted on a prior biopsy
  - Lymphomas
    - **CT Scan or PET-CT of pelvis, abdomen, chest**
    - **Peripheral blood and bone marrow morphology** will be performed if deemed clinically indicated by the investigator. The timing of this assessment will be per standard practice

- **Anti-HLA antibody testing** at HLA A, B, C, and DRB1 must be performed and resulted within 6 weeks prior to CBU Shipment and donor cords with cross-reactive alleles (MFI>3000) at these loci must be avoided. DQ and DP antibody testing is also recommended and donor cords with cross-reactive alleles at these two loci should also be avoided.
- **Lab tests:**
  - CBC with differential
  - Blood chemistry: Serum creatinine, ALT, AST, Total bilirubin, Magnesium, Alkaline phosphatase (at a minimum)
  - Complete urinalysis
- **Organ function assessments**:
  - Chest X-ray (A chest X-ray is not mandatory if a chest CT or MRI was performed).
  - Physiologic reserves assessment:
    - Pulmonary Function Tests (PFT) including
      - Corrected Carbon Monoxide Diffusing Capacity (cDLCO)

- FEV1
- FVC
- oxygen saturation

(If PFT testing included the use of bronchodilators, then the baseline results during testing prior to the administration of any medications should be used when determining eligibility).

- 12 lead EKG
- Echocardiography or MUGA scan with left ventricular ejection fraction (LVEF)

- **Other general assessments**:
  - Physical examination, per standard of care
  - Vital signs including:
    - temperature
    - blood pressure
    - pulse
    - weight
    - height
    - BSA
  - Patients' performance score by Karnofsky/Lansky
- **Medical history** including primary and concomitant diseases.
- **Confirmation of patient eligibility** must be documented by signing off on an eligibility checklist, or documenting eligibility in the patient's medical record.

Note: From time of informed consent signature until the end of the study, all concomitant medications will be recorded in the source documents and the reason for administration should be clearly stated.

7.4. CBU Shipment and Receipt at the Production Site

[redacted]

7.5. Baseline Assessments Prior to Start of Conditioning

- **Acute Leukemias: Cytogenetics and molecular markers** – from 6 weeks prior to CBU shipment up to start of conditioning.
  (It is not mandatory to repeat any molecular marker tests that were negative or not performed at diagnosis)

- **Lab tests:**
  - Serologic infection disease markers for the following (from 3 weeks prior to CBU shipment up to start of conditioning):
    - HIV I/II Ab
    - HBsAg
    - HBcAb
    - EBV Ab
    - HCV Ab
    - CMV screen (IgG or Total)
    - The following are optional: HTLV I/II Ab, VZV Ab, Syphilis Ab (such as rapid plasma reagin (RPR))
  - Serum OR urine β-HCG test for women of childbearing potential (within 4 weeks prior to conditioning)

Peripheral blood sample for post-transplant chimerism

Historical medications/treatments for primary disease

Additional viral screening is suggested prior to administration of the conditioning regimen to confirm absence of infection. At the investigator's discretion, patients with fever or suspected minor infection should await resolution of symptoms before starting the conditioning regimen.

7.6. Omidubicel Release and Shipping to Transplant Center

Upon completion of the manufacturing process, final Quality Control tests of omidubicel CF, NF and infusion solution are initiated (according to the relevant Manufacturer's SOP), and omidubicel is labeled according to the relevant Manufacturer's SOP. The results of the Quality Control tests must meet predefined specifications.

Following product quality control testing, certificate of analysis (CoAs) for the infusion solution and for omidubicel NF are prepared. A preliminary CoA for omidubicel CF is prepared with the quality control results (except the results of CFU, sterility and mycoplasma). The SLM will fax/email these certificates to the clinical site. Qualified Person (QP) appropriate release certificates are sent to the clinical sites depending on the location of the manufacturing site and of the transplant center.

[redacted]

Omidubicel CF and NF will be shipped cryopreserved under quarantine status in a cryoshipper equipped with a calibrated data logger.

The infusion solution, used to thaw and dilute the CF and the NF, will be shipped in a dedicated 2-8°C shipping container equipped with a calibrated data logger in parallel to the shipment of the omidubicel CF and NF.

The shipment of omidubicel will be controlled by the Sponsor in order to assure that shipment conditions were maintained as described in the Sponsor's procedures. The checks performed will be documented in a special form according to the relevant Manufacturer's SOP. When a shipment is received, the consignee will acknowledge receipt.

Upon arrival at clinical sites or local CBBs, omidubicel CF and NF will be kept in a controlled Liquid Nitrogen central storage (≤ -150°C) and the Infusion solution bags will be kept in a 2-8°C refrigerator until transplantation.

7.7. Myeloablative Conditioning

The conditioning regimen will be administered as detailed in Section 6.3. GvHD prophylaxis will be administered as detailed in Section 6.4. Safety monitoring as detailed in Section 9 will be performed. An assessment between days -3 and -1 should be reported in the EDC, to include:

- Physical examination
- Vital signs: weight, temperature, blood pressure and pulse
- CBC
- Blood chemistry (serum creatinine at a minimum)
- All recipients must be tested for CMV (using the PCR method) at least once during the conditioning period (see Section 6.11.5)

7.8. Transplantation Day (Day 0)

7.8.1. Safety Assessments Prior to Transplantation

Prior to the transplantation of omidubicel the patient will be evaluated by the investigator or designee including:

- Physical Examination
- Lab tests (to be resulted before the study product infusion):
  - CBC
  - Blood chemistry (serum creatinine, total bilirubin, alkaline phosphatase, AST, ALT, and magnesium at a minimum)
- Vital Signs: weight, temperature, blood pressure and pulse
- Concomitant medications

7.8.2. Thawing and Infusion of Omidubicel on Day 0

Omidubicel should not be irradiated under any circumstances. To minimize any risk of contamination, no samples should be drawn from omidubicel prior to completion of infusion.

In case stored at a local CBB until the transplant day, omidubicel will be shipped on the transplant day to the clinical site in a cryoshipper and the infusion solutions will be shipped in a 2-8°C container, both equipped with a data logger, accompanied by the relevant Manufacturer's Form.

Prior to its infusion, omidubicel must be identified at the Clinical Site according to the relevant Manufacturer's SOP and Form. The Clinical Site should check the product labels as well as the CoAs and QP release certificate for infusion, when applicable, and will make sure that all omidubicel fractions and the Infusion Solutions were shipped in appropriate conditions, their specifications met and are within their shelf life time. The Drug Accountability form must be completed and signed/dated to document this review.

Thawing and dilution of the omidubicel CF and omidubicel NF by the clinical site's personnel will be performed according to the relevant Manufacturer's SOP immediately prior to its infusion.

The final volume of omidubicel CF after thawing and reconstitution is 100 ml.

The final volume of omidubicel NF after thawing and reconstitution is 50 ml.

Pre-medication and hydration prior omidubicel infusion is required. It should include any or all of the following: antipyretic, histamine antagonists, and corticosteroids, and should be administered 30-60 minutes before the administration of omidubicel. The immediate pre-transplant evaluation will be carried out according to section 7.8.1.

Omidubicel CF will be infused first, followed immediately (up to 1 hour) by the infusion of omidubicel NF.

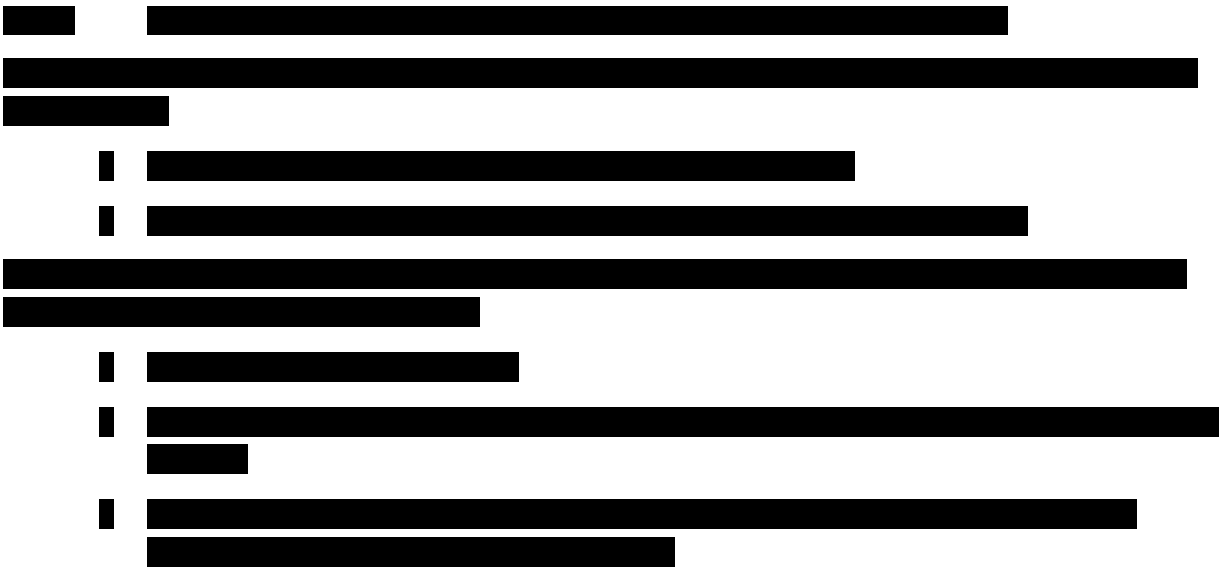
Omidubicel CF and omidubicel NF should be infused via the patient's central venous catheter as per site practice. Omidubicel is intended to be given by gravity without additional support taking into account the overall time of infusion and the minimal infusion time according to the endotoxin limit. Infusion of omidubicel CF and omidubicel NF should target a rate of 5 cc/kg/hr with a maximal rate of 10 cc/kg/hr. Omidubicel CF and omidubicel NF should be infused as soon as possible after thaw.

- Total duration of omidubicel CF infusion will target a maximum of 2 hours from end of thaw to end of infusion, while considering the minimal infusion time specified in the product's CoA.
- Total duration of omidubicel NF infusion will not exceed 1 hour from end of thaw to end of infusion, while considering the minimal infusion time specified in the product's CoA.

The minimal infusion time is calculated based on the actual endotoxin test result and the endotoxin limit of 5 EU/Kg weight/60 minutes. In general, this time is set to a minimal infusion time of 10 minutes.

If the patient develops chest tightness or other symptoms, a brief rest (1-2 minutes) may be required before proceeding with the remainder of the infusion.

A physician or physician extender (NP or PA) must be present on the patient care unit during the infusions and for 1 hour afterwards. Rescue equipment (oxygen) and drugs such as hydrocortisone, epinephrine and diphenhydramine, should be available at the bedside for emergency use if infusion reactions occur. Furosemide (0.5-1.0 mg/kg/dose) may be given if volume overload or decreased urine output occurs.



The transplant site will get a final CoA containing all test results.

7.8.4. Post Transplantation Follow-Up (Day 0 to 1)

The following assessments are mandatory:

- Vital signs: Temperature, BP, pulse, weight
- Toxicity assessment 24 hours post-transplant: from the start of omidubicel CF infusion up to 24 hours after end of omidubicel NF infusion.
- G-CSF administered as specified in Section 6.8.

7.9. Scheduled Treatment Visits Post Transplant

Patients and their treating physicians should be provided clear instructions at discharge that emphasize the importance of continued follow-up as per study protocol, including early reporting of infectious symptoms, medical treatments received and any other medical events to their clinical center.

7.9.1. Scheduled Daily Assessments Post Transplant up to ANC Engraftment or Primary Graft Failure

The following assessments are mandatory:

- AEs and concomitant medications
- Vital Signs (per SOC)
- CBC with WBC differential if WBC≥0.5
- Infection prophylaxis and surveillance as specified in 6.11
- G-CSF administered as specified in Section 6.8
- GvHD prophylaxis as specified in Section 6.4

7.9.2. Scheduled Visits Post Transplant

General notes:

- Disease assessment:
  - Patients should be monitored for objective disease control in accordance with standard of care.
  - Data should be reported into the EDC as applicable at the following visits: 100, 180, 365, 730
- Vital signs, physical examination and blood chemistry assessments:
  - The choice of assessments for vital signs, physical examination and blood chemistry will be left to the investigator's discretion according to the patient's status.
  - Data should be reported into the EDC if available at visits:
    - Vital signs: 7, 14, 21, 28, 42, 100, 180, 365, 730
    - Physical examination: 28, 100, 180, 365, 730
    - Blood chemistry: 7, 14, 21, 28, 42, 100, 180, 365, 730
- Donor/host chimerism:
  - Peripheral blood collection for whole blood or myeloid donor/host chimerism. Bone marrow chimerism is an acceptable alternative to peripheral blood
  - Data will be reported into the EDC at the following visits: 42, 100, 730
- GvHD assessment:
  - Acute GvHD: will be assessed according to the Consensus Conference on Acute GvHD grading (Appendix B).
    - Data will be reported into the EDC at the following visits: 7, 14, 21, 28, 42, 100, 180

- Chronic GvHD: will be assessed and classified mild, moderate, or severe, according to the 2014 National Institute of Health consensus grading criteria (Appendix B).
  - Data will be reported into the EDC at the following visits: 100, 180, 365, 730
- A record of the organ specific scoring must be kept on file at the clinical center.

- GvHD prophylaxis as specified in Section 6.4
- G-CSF administered as specified in Section 6.8
- Information about AEs, infections, and concomitant medications (including RBC and platelet transfusions) will be recorded in the patient's medical record according to Section 9.2 .
- Concomitant medications will also be recorded in the eCRF from the day of transplant through day +30 as detailed in the Data Management Handbook.

7.9.2.1. Day 7 (±3) / Day 14 (±3) / Day 21 (±3)

- Vital signs per SOC
- Lab tests:
  - CBC
    - Daily until engraftment OR at specified visit if engraftment already occurred prior to that visit
    - With differential if WBC ≥0.5
  - Blood Chemistry per SOC
  - CMV PCR
  - HHV6 PCR
- Acute GvHD assessment

7.9.2.2. Day 28 (±5)

- Vital signs per SOC
- Lab tests:
  - CBC
    - Daily until engraftment OR at specified visit if engraftment already occurred prior to that visit
    - With differential if WBC ≥0.5
  - Blood Chemistry per SOC
  - CMV PCR
  - HHV6 PCR
- Physical examination per SOC

- Acute GvHD assessment

7.9.2.3. Day 42 (±6)

- Vital signs per SOC
- Lab tests:
  - CBC with differential if WBC ≥0.5
  - Blood Chemistry per SOC
  - Peripheral blood chimerism
- Acute GvHD assessment

7.9.2.4. Day 100 (±21)

- Vital signs per SOC
- Lab tests:
  - CBC with differential if WBC ≥0.5
  - Blood Chemistry per SOC
  - Peripheral blood chimerism
- Physical examination per SOC
- Disease assessment per SOC
- Acute GvHD assessment
- Chronic GvHD assessment

7.9.2.5. Day 180 (±30)

- Vital signs per SOC
- Lab tests:
  - CBC with differential if WBC ≥0.5
  - Blood Chemistry per SOC
- Physical examination per SOC
- Disease assessment per SOC
- Acute GvHD assessment
- Chronic GvHD assessment

7.9.2.6. Day 365 (±60)

- Vital signs per SOC
- Lab tests:
  - CBC with differential if WBC ≥0.5
  - Blood Chemistry per SOC

- Physical examination per SOC
- Disease assessment per SOC
- Chronic GvHD assessment

7.9.2.7. Day 730 (±60)

- Vital signs per SOC
- Lab tests:
  - CBC with differential if WBC ≥0.5
  - Blood Chemistry per SOC
  - Peripheral blood chimerism
- Physical examination per SOC
- Disease assessment per SOC
- Chronic GvHD assessment

7.9.3. Evaluation and Treatment of Graft Failure

Evaluation of Graft Failure: Should a patient have primary or secondary graft failure; an attempt will be made to determine the cause of failure. Evaluation will include:

- Bone marrow aspiration/biopsy for morphologic analysis as well as cytogenetics;
- Whole blood chimerism studies (bone marrow chimerism is an accepted alternative method);
- Viral/bacterial cultures including serology and PCR analysis for Herpes viruses (including CMV and HHV6); and
- Anti-HLA antibody measurements.

For primary graft failure, the assessments listed above are recommended to be performed around Day 21 if WBC is <= 0.1 $x10^9$/L.

In case of delayed engraftment or impending graft failure, the dose of G-CSF may be increased per investigator discretion.

Treatment of Graft Failure: If the patient has less than 100 neutrophils/µl at Day 28 and most recent BM shows decreased marrow cellularity and paucity of donor cells (less than 20%) by chimerism analysis the patient will be treated at the discretion of the treating physician.

In patients experiencing delayed engraftment, serologic assessment of HHV6 and CMV will be evaluated as a contributing factor.

7.9.4. Early Withdrawal from Follow-up

Reasons for withdrawal of the patient prior to end of study must be stated in the CRF and in the site source documentation for all study patients who were enrolled in the study. This includes patients who were screened and assigned a screening number but were not transplanted. Patients

will be defined as screening failures when withdrawn from the study before CBU shipment. Reason for screening failures will be outlined in the study reports.

In patients who withdraw from study prior to completion of follow-up, SAEs should be reported for at least 30 days after transplant with omidubicel.

7.9.5. Criteria for Early Withdrawal

Patients who are prematurely discontinued or withdrawn from the study should be followed and treated by the investigator according to institutional guidelines. Patients who join the study will be asked for permission that their clinical investigator be allowed to transmit information to the study center on the clinical outcomes as assessed during the usual clinical management of their disease over the study period. A patient may withdraw or be withdrawn from the study for the following reasons:

- Patient withdrew consent
- Sponsor requested patient to be withdrawn
- Request of primary care physician or investigator
- Other (e.g., not transplanted with omidubicel, due to relapse or omidubicel production failure)

7.10. Data Reporting

7.10.1. Criteria for Forms Submission

Criteria for timeliness of submission for all study forms are detailed in the Data Management Handbook and electronic CRF User's Guide. Missing forms will be addressed as described in the handbook.

8. STUDY MEDICATION

8.1. Description

8.1.1. Omidubicel

Omidubicel is a cryopreserved cell-based product of allogeneic, *ex vivo* expanded, umbilical cord blood-derived, hematopoietic CD34+ progenitor cells (omidubicel CF) and the non-expanded cell fraction of the same cord blood unit (omidubicel NF) consisting of mature myeloid and lymphoid cells. See further details on the cell expansion process in Section 3.2.

[redacted]

8.2. CBU Supply

All CBUs should be procured from public banks that meet national applicable regulations. If the optimal unit(s) for the patient was determined ineligible or with unusual findings (e.g., incomplete) as per local regulations, the unit may be used under the urgent medical need provision and in consultation with the Sponsor.

8.3. Manufacturing

Omidubicel CF, NF and infusion solution manufacturing will be performed by central manufacturing sites that have been trained and qualified by the Sponsor according to the Sponsor's SOPs.

Omidubicel is manufactured in a production site, inside a laminar flow hood (class 100, ISO 5) within a room that has been qualified as a Class 10,000 (ISO 7), in compliance with the production instructions and procedures as provided by the Sponsor.

[redacted]

[redacted]

Omidubicel NF will be released with a final CoA specifying quality control test results.

The infusion solutions, used to thaw and dilute the omidubicel CF and NF, will be released with a final CoA specifying quality control test results.

8.3.1. Out of Specification Results

If an Out of Specification (OOS) result is found, a deviation report will be filled out, an investigation will be conducted and completed in a timely manner and any corrective action suggested will be implemented promptly to avoid recurrence of the incident.

The resulting report will be attached to the deviation report and filed in the Batch Record.

If the result is confirmed, the clinical site as well as the site CRA, the QP when applicable and the Sponsor are notified immediately. The Sponsor will report to the local regulatory entity as required.

[redacted]

[redacted]

8.3.1.2. [redacted]

[redacted]

8.4. Handling of Omidubicel

Labeling of omidubicel CF, omidubicel NF and the infusion solutions will be performed according to the relevant Manufacturer's SOP.

Packaging of omidubicel CF, omidubicel NF and the infusion solutions will be performed according to the Sponsor’s procedures.

8.5. Shipment

Omidubicel CF and NF will be shipped to the clinical site/local CBB under quarantine status with all available CBU segments/samples in a cryoshipper equipped with a calibrated data logger and with all necessary documentations. The infusion solutions for omidubicel CF and NF will be shipped to the clinical site/local CBB in parallel in a 2-8°C package equipped with a calibrated data logger.

The shipment of omidubicel will be controlled by the Sponsor in order to assure that shipment conditions were maintained as described in the Sponsor’s procedures. The checks performed will be documented in a special form according to the relevant Manufacturer's SOP. When a shipment is received, the consignee will acknowledge receipt.

9. SAFETY MONITORING

9.1. Definitions

9.1.1. Adverse Event (AE)

Adverse event means any untoward medical occurrence associated with the use of the investigational product, whether or not considered related to the investigational product. Treatment-emergent AEs are any AEs that occur or worsen (i.e., increase in grade) during or after the infusion of the study product.

9.1.2. Infusion Reaction

Any adverse event that begins or worsens (i.e., increases in grade) between the start of omidubicel infusion and 24 hours after the end of omidubicel infusion.

9.1.3. Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction (see Section 9.1.4) is considered “serious” if, in the view of either the investigator or Sponsor, it results in one of the following outcomes:

- Death
- A life-threatening adverse event

NOTE: An event is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. CTCAE grade four events are not automatically defined as life threatening for SAE determination. For example, a grade four increase in ALT/SGPT may or may not be deemed as life threatening by the investigator and/or Sponsor.

- Inpatient hospitalization or prolongation of existing hospitalization

NOTE: Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. Elective or previously scheduled hospitalizations for pre-existing conditions which have not worsened after initiation of treatment should not be classified as SAEs. Any hospitalization regardless of duration will be considered serious unless the hospitalization was for social or convenience reasons during which no untoward medical occurrence occurred.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

NOTE: This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (i.e., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Primary and secondary graft failure events and any suspected or proven transmission of infectious agents (transmissible blood infection) from the donor cells should be reported as SAEs. Relapse and GvHD are not considered a SAE for reporting purposes on this protocol, unless the events are fatal or immediately life-threatening.

Serious adverse events require reporting (see Section 9.2) within 24 business hours of the study team's knowledge of the event. A detailed summary of the events above are required from the investigator within 2 working days of knowledge of the event.

9.1.4. Suspected Adverse Reaction

A suspected adverse reaction is considered as any adverse event for which there is a reasonable possibility that the study product caused the event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the study product and adverse event.

The investigator must make the determination of relationship to the study product for each grade 3-5 AE and for any SAE. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study product, will be considered and investigated. The investigator will also consult the Clinical Investigator's Brochure (IB) and/or Product Information for marketed products in the determination of his/her assessment.

9.1.5. Causality

The following question will be used when assessing causality of an adverse event to the study product: Is there a reasonable possibility that the study product caused the event? An affirmative answer designates the event as a suspected adverse reaction.

9.1.6. Expectedness

Unexpected: An event is considered "unexpected" when it is not listed on the specified list of expected events in the IB or it is not listed at the specificity and severity that has been observed. It also refers to adverse events or suspected adverse reactions that are mentioned in the investigator's brochure but are not specifically mentioned as occurring with the particular study product under investigation.

The determination of the expectedness is the Sponsor's responsibility.

9.1.7. Toxicity Grading

GvHD symptoms will be graded according to the Consensus Conference on Acute GvHD grading for acute GvHD[27] and National Institute of Health consensus grading criteria for chronic GvHD[28] (Appendix B).

Infections will be graded according to the BMT CTN Severity Grading table in the BMT CTN MOP (Appendix F).

All other AEs will be graded according to the CTCAE version 4.03. The categories for grade 1 and 2 events will be combined on the Toxicity Form such that events will be assigned a grade of either '1 or 2', '3', '4', or '5'.

An AE that is assessed as CTCAE grade 3 (often described as "severe") should not be confused with an SAE. Severity is a category used for rating the intensity of an event; both AEs and SAEs can be assessed as grades 1-4. An event is described as 'serious' when it fulfils one or more of the criteria described in Section 9.1.3.

9.1.8. Expedited Reporting

The following events meet the criteria for expedited reporting and require reporting by the investigator or delegated study personnel (see Section 9.2) within 24 business hours of knowledge of the event (note that all SAEs require reporting within 24 business hours of knowledge of the event, although not all SAEs will require expedited reporting to regulatory authorities).

- All serious, unexpected, suspected adverse reactions (SUSARs) as defined in 21 CFR 312.32 and Directive 2001/20/EC
- Life threatening or fatal Serious Adverse Reactions will not be considered expected and will be considered a SUSAR for expedited reporting according to the Investigator Brochure for omidubicel

A detailed summary of the events above are required from the investigator within 2 working days of knowledge of the event. The summary will include date of onset, peak grade, potential causes, resolution date (if applicable), past medical history, concomitant medications, an event narrative, and actions taken. A discharge summary or hospital notes with supporting labs and radiologic reports should be attached as well.

Other Adverse Events that do not meet the criteria for expedited reporting should be recorded in the database as outlined in Appendix C. Clinical centers are expected to report AEs to their IRB/EC according to their own institutional guidelines.

An expedited report will also be submitted if an aggregate analysis indicates that serious expected suspected adverse reactions are occurring more frequently or at a higher severity than what was previously expected.

9.2. Observation, Detection and Recording of AEs and SAEs

The investigator and/or study personnel will enquire about the occurrence of AEs at every visit, after the patient has had the opportunity to spontaneously mention any problems. Because of their underlying disease and toxic preparative therapy, a wide range of adverse events is anticipated.

All AEs will be recorded in the source documents with sufficient detail to allow for grading per CTCAE v4.03, and reported on the appropriate CRF page, as applicable.

Infections

Grade 2 or 3 infections will be reported beginning at start of conditioning and continuing through Day 180 post-transplant. Treatments for these infections will be reported through engraftment.

Common Events Post Transplant

Common events post-transplant are summarized in Appendix A and will be reported on the Transplant Toxicity Summary form, with the exception of some GvHD symptoms which will be recorded on the GvHD forms.

For these common events, the highest grade over a given interval will be recorded.

The intervals for reporting common events on the Toxicity form are:

- During conditioning up to omidubicel transplant,
- During and 24 hours post omidubicel transplant,
- From 24 hours post omidubicel transplant to Day 7,
- At periodic intervals between each study visits up to Day 180 post-transplant.

For grade 3-5 events, any suspected relationship of the event to omidubicel will also be collected on the Toxicity form. Beyond 42 days post-transplant, only grade 3-5 common events will be reported on the Toxicity form, with the exception of certain infections and symptoms of GvHD which will continue to be reported on their respective forms irrespective of the grade. Common events that also meet SAE criteria will be reported as described below (See Serious Adverse Events sub-section).

Non-serious Uncommon Events Post Transplant

Non-serious uncommon events occurring or worsening post-transplant through day 42 will be reported. Information to be collected includes the name, dates of onset and resolution (if applicable), intensity, and causality of the event.

After day 42 post-transplant, non-serious uncommon adverse events will not be reported.

Serious Adverse Events

SAEs must be reported to the Sponsor within 24 business hours of learning of their occurrence, until at least 30 days post-transplant and then up until the earlier of end of patient's final study visit, date of relapse, or date of graft failure. Information about all SAEs is collected and recorded on the Serious Adverse Event Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

SAEs to be reported are the following:

– After the patient has provided informed consent until start of conditioning: only life-threatening or fatal SAEs

- From start of conditioning until Day 180 included: All SAEs, regardless of suspected causality
- From Day 181 until end of study, only life-threatening SAEs or death or any other SAE deemed by the investigator to be related to omidubicel (excluding GvHD that is not life threatening or fatal)
- Relapse and GvHD are not considered a SAE for reporting purposes on this protocol, unless the events are fatal or immediately life-threatening.
- Following date of relapse or graft failure only SAEs resulting in death or with suspected causal relationship to the infused product will be reported. However, SAEs must be reported on SAE summary forms set for at least 30 days post-transplant even if relapse or graft failure occur prior to that time point.
- Patients who were enrolled (with enrollment defined as CBU shipment date) but were not transplanted with omidubicel (e.g., due to relapse or omidubicel production failure) will be followed for SAEs until 30 days following enrollment.

The investigator (or designee) must complete the SAE Form directly into the EDC system. If the CRF is completed by a designee, the completed, signed investigator assessment form should be maintained in the sites study files.

Where possible, a diagnosis rather than a list of symptoms should be recorded. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms. If a diagnosis has not been made then each symptom should be listed individually.

When reporting medical records, all patient identifiers (i.e., name, date of birth, medical record number) must be obliterated prior to uploading documents to the EDC system.

9.3. Follow-Up of AEs and SAEs

All reported AEs and SAEs will be followed and recorded until resolution with or without sequelae (the patient's health has returned to baseline status or all variables have returned to normal), until the condition stabilizes (the investigator does not expect any further improvement or worsening of the event), until an outcome is reached or the event is otherwise explained, or until there is agreement between the investigator and Sponsor that additional follow-up is not warranted. Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, stating that this is a follow-up to the previously reported SAE and giving the date of the original report. 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. The follow-up information should describe whether the event has resolved or continues, if and how it was treated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE/SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. Where appropriate, medical tests and examinations will be performed to document resolution of the event(s). Additional follow-up information, if required,

or available, must be reported in the same timelines as initial information. New or updated information will be recorded on the originally completed CRF, with all changes to SAEs signed and dated by the investigator on a source document and maintained in the site's study files.

9.4. Medical Monitor Review

The Sponsor's Medical Monitor will review all reported serious adverse events within one day of notification. If the Sponsor requires additional information, the transplant center should respond to any Sponsor questions regarding adverse events within 2 calendar days.

9.5. Clinical Laboratory Evaluations

All laboratory measurements will be evaluated for abnormalities. An abnormal laboratory value should be interpreted primarily in the context of the disease or the condition leading to it. The latter (instead of the laboratory abnormality itself) should be reported as the adverse event and graded, whenever possible. A laboratory adverse event (i.e., a laboratory abnormality not associated with any particular clinical findings (e.g., symptoms, signs)) will be reported when judged clinically significant by the investigator. An abnormal laboratory finding is not by itself considered to be an AE or SAE unless the investigator considers the abnormal finding to be of clinical significance. The abnormal laboratory finding does not have to be associated with the use of omidubicel to be considered clinically significant. If a laboratory adverse event is reported, it will be graded using the CTCAE toxicity grading scale version 4.03. A laboratory adverse event with a value falling within the specified CTCAE grade 4 boundaries will only be considered life-threatening from a regulatory perspective if it results in a life-threatening consequence i.e., its occurrence places the patient at immediate risk of death. Grade 4 laboratory adverse events that are not life-threatening should not be reported as serious adverse events unless they meet other seriousness regulatory criteria.

9.6. Pregnancy

Pregnancy will not be considered an AE. Any report of pregnancy recorded for any female study patient or a female partner of a male study patient should be reported immediately within 24 hours to the Sponsor

The investigator will follow the pregnant woman until completion of the pregnancy and must notify the Sponsor of the outcome within 24 hours of the investigator's knowledge of the pregnancy outcome. This notification includes pregnancies resulting in live, "normal" births.

If the pregnant patient experiences an SAE during pregnancy, or the outcome of the pregnancy meets the criteria for classification as an SAE, the investigator should follow the procedures for reporting SAEs (i.e., report the event to the Sponsor within 24 hours of the investigator's knowledge of the event).

All neonatal deaths and congenital anomalies that occur within 30 days of birth (regardless of causality) should be reported as SAEs to the Sponsor. In addition, any infant death or congenital anomaly occurring after 8 weeks that the investigator suspects is related to the in utero exposure to the study drug should also be reported to the Sponsor.

9.7. Patient Withdrawal from Study Procedures Due to Adverse Events

Any patient may be removed from the study at any time if in the judgment of the investigator further study procedures are not in the best interests of the patient. Patients may also withdraw themselves from the study at any time and for any reason.

9.8. Regulatory Authorities and IRB/ECs

The Sponsor shall notify the concerned Regulatory Authorities of Suspected Unexpected Serious Adverse Reactions (SUSARs) for the investigational medicinal product (IMP), or other AEs as per local requirements. In accordance with Directive 2001/20/EC and Chapter II of Volume 10 of the Rules Governing Medicinal Products in the European Community, the Sponsor will also report SUSARs to the EudraVigilance Clinical Trial Module (EVCTM).

The Sponsor is responsible for reporting all unexpected fatal or life-threatening suspected adverse reactions to regulatory authorities, as per the concerned authorities' requirements no later than seven calendar days after knowledge of the event. All other serious, unexpected, suspected adverse reactions will be reported to the regulatory authorities by the Sponsor within 15 calendar days of receipt of the information.

The Sponsor or designee shall notify the Ethics Committees (EC) of SUSARs or significant risks to patients, per country requirements.

The Sponsor or designee shall notify the investigator of potential serious risks from clinical studies or any other sources, including the following:

- Suspected adverse reaction that is both serious and unexpected.
- Any findings from other studies that suggest a significant risk in humans exposed to the drug.
- Any finding from animal or in vitro testing that suggest a significant risk to humans exposed to the drug, such as mutagenicity, teratogenicity, or carcinogenicity; or report of significant organ toxicity at or near the expected human exposure.

It is the responsibility of the Principal Investigator (PI) to notify the IRB/EC of all SAEs that occur at his or her site. Each site is also responsible for notifying their IRB/EC of additional safety reports or other safety concerns communicated by the Sponsor. The investigator must keep copies of all AE information, including correspondence with the Sponsor or Local Ethics Committees on file.

10. STATISTICAL METHODOLOGY

10.1. Patients & Analysis Cohorts

The sample size for the study was not determined by statistical power considerations, but by an approximate estimation of the times to product licensure.

The analysis cohort will be comprised of all patients transplanted with omidubicel. For patients consented but not transplanted the reason for non-transplant will be recorded.

Some endpoints may report descriptive statistics among engrafters only, as defined for the particular endpoint.

10.2. Interim Analysis & Early Stopping

No interim analysis is planned. Analyses may be performed if needed to fulfill regulatory requests. Interim analysis for publication purposes may be performed.

There are no formal stopping rules. Ongoing study safety data will be reviewed by the Medical Monitor in real time and any concerns for patient safety will be promptly communicated to the sponsor with a recommendation to suspend accrual, if applicable.

10.3. Statistical Analysis

Demographic, disease characteristics and other baseline data will be summarized descriptively.

Statistical analyses will be limited to descriptive statistics and confidence intervals; there will be no hypothesis testing.

10.3.1. Primary Endpoint: Time to Neutrophil Engraftment Following Transplant

A cumulative incidence curve will be computed along with the cumulative incidence of engraftment and a 95% confidence interval at 42 days post-transplant. Death, relapse, and second transplant prior to neutrophil engraftment will be considered as competing risks. Additionally, the median time to engraftment among engrafters who had neutrophil engraftment by Day 42 (no window) and before competing risks will be estimated.

In consideration of the estimated timelines to licensure, the sample size is estimated to be approximately 60 transplanted patients.

10.3.2. Secondary Endpoints

10.3.2.1. Time to Platelet Engraftment Following Transplant

A cumulative incidence curve for platelet engraftment $>20x10^9$/L will be computed along with an estimates and 95% confidence interval at 42 and 180 days post-transplant. Death, relapse, and second transplant prior to platelet engraftment will be considered as competing risks. The median time to engraftment among all who have had platelet engraftment $>20x10^9$/L by last follow-up and before competing risks will be estimated.

A similar curve and estimates will be provided for platelet engraftment >50x10^9/L. The median time to engraftment among all who have had platelet engraftment >50x10^9/L by last follow-up and before competing risks will be estimated.

10.3.2.2. Non-Relapse Mortality

A cumulative incidence curve will be computed along with an estimate and a 95% confidence interval at 100, 180, and 365 days post-transplant. Relapse will be considered as a competing risk. The event time is time from transplant to any death not preceded by relapse.

10.3.2.3. Overall Survival

A Kaplan-Meier curve will be computed along with an estimate and a 95% confidence interval at 180, 365 and 730 days post-transplant. The event time is time from transplant to death from any cause.

10.3.2.4. Disease-Free Survival

A Kaplan-Meier curve will be computed along with an estimate and a 95% confidence interval at 365, and 730 days post-transplant. The event time is time from transplant to relapse or death, whichever occurs first.

10.3.2.5. Donor Chimerism

The chimerism proportions of the host and/or omidubicel will be measured on visits at Days 42, 100, and 730 post-transplant in patients with neutrophil engraftment. The distribution of these portions (median, quartiles and/or mean and standard deviation) will be estimated at each time point. Patients who relapse, have graft failure, or die before the sample is collected for the Day 42, 100, or 730 visits will be excluded from the analysis for that visit.

10.3.2.6. Secondary Graft Failure

A cumulative incidence curve will be computed along with an estimate and a 95% confidence interval at 365 and 730 days post-transplant. Death, relapse, and primary engraftment failure will be considered competing risks.

10.3.2.7. Acute GvHD

The time to first occurrence of acute GvHD grade II-IV following transplant will be analyzed and the cumulative incidence curve will be computed. Death, failure to achieve neutrophil engraftment, secondary graft failure, and relapse will be considered competing events. An estimate and a 95% confidence interval will be provided at Day 100 post-transplant.

Similar analyses will be provided for first occurrence of a GvHD grade III-IV.

10.3.2.8. Chronic GvHD

The time to first occurrence of chronic GvHD following transplant will be analyzed and the cumulative incidence curve will be computed. An estimate and a 95% confidence interval will be

provided at Day 180 and 730 days post-transplant. Death, failure to achieve neutrophil engraftment, secondary graft failure, and relapse will be considered competing events.

10.3.2.9. Disease Relapse

A cumulative incidence curve will be computed along with an estimate and a 95% confidence interval at 365 and 730 days post-transplant. Death will be considered as a competing risk.

10.3.2.10. Safety and Tolerability

Treatment-emergent infusion reactions will be described by nature and severity. A table will be provided summarizing the maximum severity of treatment-emergent infusion reaction per patient.

The proportion of patients experiencing grade 3-5 events listed in Appendix A will be estimated.

The proportion of grade 2-3 infections, also by subgroups (bacterial, fungal, viral, non-microbiologically defined), and the proportions of patients experiencing these infections will be estimated at 100 and 180 days post transplantation. An overview table of treatment emergent SAEs will be shown, followed by tables summarizing the number and percent of patients with treatment emergent SAEs. In these tables, the number of people reporting an event within each SOC/PT combination will be counted for:

- Treatment emergent SAEs in any SOC/PT combination that are related to study product
- Treatment emergent SAEs in any SOC/PT combination that are related to study product and that are reported as related to study product in at least 3% of the transplanted population
- Treatment emergent events in any SOC/PT combination that are reported in at least 3% of the transplanted population

Primary cause of death will be tabulated.

Descriptive statistics for lab evaluations and vital signs will also be provided.

Additional safety tables or listings describing adverse events, lab evaluations, vital signs, and/or medications may be provided.

Safety events for patients enrolled but not transplanted will be described through 30 days following enrollment.

10.4. Missing Data

Patients who are lost to follow-up before an event or an event's competing risk will be censored in the time-to-event analyses. In the descriptive statistics for non time-to-event analyses, the number evaluated for the endpoint will be provided.

10.5. Analysis Plan Deviations

Deviations from the original statistical analysis plan will be reported in the final study report.

10.6. Statistical Software

SAS® version 9.4 or higher software or R version 2.10.0 or higher will be used for statistical analysis and data presentation of the information collected in this study.

11. CLINICAL DATA MANAGEMENT

11.1. Data Quality Assurance

This study will be organized, performed, and reported in compliance with the Sponsor/CRO's SOPs, protocols and working practice documents, and the requirements of the Declaration of Helsinki and ICH/GCP guidelines. Compliance will be achieved through a combination of study specific audits of investigative sites and audits at regular intervals of the Sponsor/CRO's systems for data handling, analysis, and reporting.

A quality assurance audit of this study may be conducted by the Sponsor or Sponsor's designees. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation that is relevant to this clinical study.

11.2. Data Collection

Patients will be registered in the EDC system. Investigators or designees will enter the information required by the protocol onto the electronic CRFs. Each investigative site will be visited as frequently as documented in the monitoring plan by the CRO on behalf of the Sponsor to review the CRFs for completeness and accuracy. The CRO representative will highlight any discrepancies found between source documents and the completed CRFs, and will ensure that appropriate site personnel address the discrepancies. When a discrepancy results in corrected CRF data, the correction will be reviewed again against the correct source documentation. Uniform procedures will be discussed at the Site Initiation Visit.

Confidentiality will be maintained by individual names being masked and assigned a patient identifier code. The code linking the patient's identity with the ID code will be kept separately at the center. The ID code will be entered in the EDC system. Additionally, patient's full date of birth will not be collected and only year of birth will be recorded in the database.

11.3. Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. All clinical data entered onto the CRF must be supported by source documentation maintained at the clinical site. Data entered in the CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records; also, current medical records must be available.

Direct access to source data - documents

- The investigator / institution will permit study-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents.
- CRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the Sponsor's clinical study monitor and inspection by health authorities (e.g., MS CA/EMA). The

Clinical Research Associate (CRA) / on site monitor may review all CRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents.

11.4. Staff Training

Prior to enrollment, all clinical study personnel will be trained to ensure adherence to the protocol and assure the highest possible data quality. Training will be led by CRO and the Sponsor at a central location. Training presentations will address informed consent procedures, study operations and protocol requirements, data collection procedures, maintenance of source documentation, CRF completion and review, routine reporting requirements, data entry and management, and policies and procedures. Additional training may be provided via teleconferences as needed.

11.5. Data Monitoring

CRAs will be responsible for monitoring CRFs and source documents for accuracy, protocol compliance, patient safety, and adherence to guidelines in the Site Operations Manuals.

At each site visit, the CRA will review recruitment guidelines and study eligibility criteria. As the study progresses, completed data forms may be reviewed during site visits and compared to source documentation (medical or site records) to confirm accuracy.

APPENDIX A. COMMON ADVERSE EVENTS

Note: This list does not include all events considered common for analytical purposes (e.g., GvHD, infection). Rather it is a minimal list of common events that are collected on the Toxicity Form in the database.

Cardiac
Cardiac Arrhythmias

Gastrointestinal
Abdominal distension
Nausea/Anorexia
Vomiting
Constipation
Diarrhea
Dyspepsia
Dysphagia
Mucositis

General Disorders
Allergic reaction
Chills
Edema
Fatigue/Malaise/Lethargy
Fever
Pain

Injury/Poisoning/Procedural Complications
Bruising
Hemorrhage
Vascular access complications

Investigations
Elevated alkaline phosphatase
Elevated creatinine
Elevated liver transaminases (ALT, AST)
Elevated triglycerides
Weight loss

Metabolism and Nutrition
Abnormal sodium
Dehydration
Hyperglycemia
Hypocalcemia
Hypokalemia
Hypomagnesemia
Hypophosphatemia
Hypoalbuminemia

Musculoskeletal
Generalized muscle weakness

Neurologic
Dizziness
Dysgeusia
Somnolence
Syncope
Tremors

Ocular
Dry eyes
Blurry vision

Psychiatric
Anxiety
Depression
Insomnia

Renal
Non-infectious cystitis

Respiratory
Cough
Dyspnea
Epistaxis
Hypoxia

Skin
Dry skin
Pruritis
Skin hyperpigmentation
Skin ulceration

Vascular
Hypertension
Hypotension

APPENDIX B. GVHD CLASSIFICATION

Acute GvHD Definition

Acute GvHD will be assessed at every visit from transplantation until Day 180 post-transplant or more frequently as clinically indicated. GvHD will be classified according to the Consensus Conference on Acute GvHD grading.[27]

Table 4: GvHD classification

Overall Grade	Skin	Liver	Gut
I	Stage 1-2	None	None
II	Stage 3 or	Stage 1 or	Stage 1
III		Stage 2-3 or	Stage 2-4
IV	Stage 4 or	Stage 4	

*See following table for individual organ staging. The overall grade of GvHD, however, reflects the actual extent of disease. For each overall grade, an assessment of skin disease plus liver and/or gut involvement is required.

Acute GvHD may be documented after Day 99 ("late acute") if according to clinical judgment the investigator feels it should be classified as acute rather than chronic.

Table 5: Clinical manifestations and staging of acute graft versus host disease

Organ	Clinical Manifestations	Staging[e]
Skin[a]	Erythematous, maculopapular rash involving palms and soles; may become confluent Severe disease: bullae.	Stage 1: <25% rash Stage 2: 25-50% rash Stage 3: generalized erythroderma Stage 4: bullae
Liver[b]	Painless jaundice with conjugated hyperbilirubinemia and increased alkaline phosphatase.	Stage 1: bilirubin 2-3 mg/dL Stage 2: bilirubin 3.1-6 mg/dL Stage 3: bilirubin 6.1-15 mg/dL Stage 4: bilirubin >15 mg/dL
Gastrointestinal tract[c]	Upper: nausea, vomiting, anorexia. Lower: diarrhea, abdominal cramps, distention, ileus, bleeding.	Stage 1: diarrhea >500 ml/day or persistent nausea, vomiting, or anorexia [d] Stage 2: diarrhea >1000 ml/day Stage 3: diarrhea >1500 ml/day Stage 4: large volume diarrhea and severe abdominal pain +/- ileus

[a] Use 'Rule of Nines' or burn chart to determine extent of rash
[b] Range given as total bilirubin. Downgrade one stage if a cause of elevated bilirubin other than GvHD has been documented.
[c] Downgrade one stage if a cause of diarrhea other than GvHD has been documented.

[d] Downgrade upper GI one stage if biopsy result is negative, or if no biopsy done and GvHD is not an etiology, or if the biopsy is equivocal and GvHD is not an etiology.
[e] Although GvHD will be assessed at every protocol-specified visit, GvHD will only be analyzed if it occurs after primary neutrophil engraftment. If GvHD is not an etiology for any organ, then GvHD is downgraded to stage 0.

Chronic GvHD Definition

Chronic GvHD will be assessed at the time of diagnosis and at every visit from day 100 until day 730 or more frequently as clinically indicated.

Chronic GvHD will be classified as mild, moderate, or severe, according to the National Institute of Health consensus grading criteria[28] summarized below:

Table 6: NIH Global Severity of chronic GvHD

Global Severity	Criteria
Mild	1-2 organs involved with a max organ severity score of 1 AND Lung score=0
Moderate	≥3 organs involved with a max organ severity score of 1 OR Any organ (except lung) with a severity score of 2 OR Lung score=1
Severe	Any organ with a severity score of 3 OR Lung score ≥2

Notes for global severity scoring:

Clinical centers must reference the 2014 consensus criteria for organ specific severity grading.[28] A record of the organ specific scoring must be kept on file at the clinical center. See cGvHD scoring worksheet in the Data Management Handbook; either the provided worksheet or an equivalent EMR adaptation of the form (approved by the sponsor) must be used to document chronic GvHD.

In skin: higher of the 2 scores to be used for calculating global severity.

In lung: FEV1 is used instead of clinical score for calculating global severity.

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).

[redacted]

[redacted]

APPENDIX D. COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V4.03 (CTCAE)[29]

Document available upon request (for site personnel, document available on the Gamida Cell Studies Coordinating Center website https://gamidadcc.com/)

APPENDIX E. DRUG LABELS

Documents available upon request (for site personnel, documents available on the Gamida Cell Studies Coordinating Center website https://gamidadcc.com/)

APPENDIX F. INFECTION GRADING

Type of infection/ severity grade	Grade 1	Grade 2	Grade 3
Bacterial infections	Bacterial focus NOS requiring no more than 14 days of therapy for treatment (e.g., urinary tract infection)	Bacteremia (except CoNS) without severe sepsis	Bacteremia with deep organ involvement (e.g., with new or worsening pulmonary infiltrates; endocarditis)
	Coag Neg Staph (S. epi), Corynebacterium, or Proprioniobacterium bacteremia	Bacterial focus with persistent signs, symptoms or persistent positive cultures requiring greater than 14 days of therapy	Severe sepsis with bacteremia
	Cellulitis responding to initial therapy within 14 days	Cellulitis requiring a change in therapy d/t progression Localized or diffuse infections requiring incision with or without drain placement	Fasciitis requiring debridement
		Any pneumonia documented or presumed to be bacterial	Pneumonia requiring intubation
			Brain abscess or meningitis without bacteremia
	C. Difficile toxin positive stool with diarrhea < 1L without abdominal pain (child < 20 mL/kg)	C. Difficile toxin positive stool with diarrhea ≥ 1L (child ≥ 20 mL/kg) or with abdominal pain	C. Difficile toxin positive stool with toxic dilatation or renal insufficiency with/without diarrhea
Fungal infections	Superficial candida infection (e.g., oral thrush, vaginal candidiasis)	Candida esophagitis (biopsy proven).	Fungemia including Candidemia
		Proven or probable fungal sinusitis confirmed radiologically without orbital, brain or bone involvement	Proven or probable invasive fungal infections (e.g., Aspergillus, Mucor, Fusarium, Scedosporium).
			Disseminated infections (defined as multifocal pneumonia, presence of urinary or blood antigen, and/or CNS involvement) with Histoplasmosis, Blastomycosis, Coccidiomycosis, or Cryptococcus.
			Pneumocystis jiroveci pneumonia (regardless of PaO2 level)
Viral infections	Mucous HSV infection		
	Dermatomal Zoster with 2 or fewer dermatomes	VZV infection with 3 or more dermatomes	Severe VZV infection (coagulopathy or organ involvement)

Type of infection/ severity grade	Grade 1	Grade 2	Grade 3
	Asymptomatic CMV viremia untreated OR a CMV viremia with viral load decline by at least 2/3 of the baseline value after 2 weeks of therapy	Clinically active CMV infection (e.g., symptoms, cytopenias) OR CMV Viremia not decreasing by at least 2/3 of the baseline value after 2 weeks of therapy	CMV end-organ involvement (pneumonitis, enteritis, retinitis)
	EBV reactivation not treated with rituximab	EBV reactivation requiring institution of therapy with rituximab	EBV PTLD
	Adenoviral conjunctivitis asymptomatic viruria, asymptomatic stool shedding and viremia not requiring treatment	Adenoviral upper respiratory infection, or symptomatic viruria requiring treatment	Adenovirus with end-organ involvement (except conjunctivitis and upper respiratory tract)
	Asymptomatic HHV-6 viremia untreated OR an HHV-6 viremia with a viral load decline by at least 0.5 log after 2 weeks of therapy	HHV-6 viremia without viral load decline 0.5 log after 2 weeks of therapy	Clinically active HHV-6 infection (e.g., symptoms, cytopenias)
	BK viremia or viruria with cystitis not requiring intervention	BK viremia or viruria with clinical consequence requiring prolonged therapy and/or surgical intervention	
		Enterocolitis with enteric viruses	
		Symptomatic upper tract respiratory virus	Lower tract respiratory viruses
	Viremia (virus not otherwise specified) not requiring therapy	Any viremia (virus not otherwise specified) requiring therapy	Any viral encephalitis or meningitis
Protozoal/ Parasitic infections	Infection (not including toxoplasmosis or strongyloides) not requiring therapy	Infection (not including toxoplasmosis or strongyloides) requiring therapy	Infection causing severe sepsis
			CNS or other organ toxoplasmosis
			Strongyloides hyperinfection
Non-microbiologically defined infections	Uncomplicated fever with negative cultures responding within 14 days		
	Clinically documented infection not requiring inpatient management	Pneumonia or bronchopneumonia not requiring mechanical ventilation	Any acute pneumonia requiring mechanical ventilation
		Typhlitis	Severe sepsis without an identified organism
*Concomitant or multimicrobial infections are graded according to the grade of the infection with the higher grade of severity. **Therapy includes both PO and IV formulations			

Definition of Severe Sepsis

Adults:

Hypotension

- A systolic blood pressure of <90 mm Hg or a reduction of >40 mm hg from baseline in the absence of other causes for hypotension

Multiple Organ Dysfunction Syndrome

- 2 or more of the following: Renal failure requiring dialysis, respiratory failure requiring bipap or intubation, heart failure requiring pressors, liver failure

Pediatrics:

Pediatric SIRS definition and suspected or proven infection and cardiovascular dysfunction or ARDS or TWO or MORE other organ dysfunctions.

Pediatric SIRS definition:

Two or more of the following, *one of which must be abnormal temperature or leukocyte count*

1) Core temperature >38.5°C ***or*** < 36°C
2) Tachycardia, otherwise unexplained persistent in absence of external stimulus, chronic drugs or painful stimuli. ***or*** bradycardia, in < 1 year old, otherwise unexplained persistent.
3) Tachypnea or mechanical ventilation for an acute process not related to underlying neuromuscular disease or general anesthesia
4) Leukocytosis or leukopenia for age (not secondary to chemotherapy) or >10% bands

Pediatric Organ dysfunction criteria:

Cardiovascular: despite administration of fluid bolus ≥40 ml/kg in 1 hour:

- Hypotension <5th percentile for age (***or*** per Table 1)
- Pressors at any dose
- Two of the following:
  - Capillary refill > 5 secs
  - Core to peripheral temperature gap > 3°C
  - Urine output < 0.5 mL/kg/hr
  - Unexplained metabolic acidosis (Base deficit > 5.0 mEq/L)
  - Blood lactate > 2 x ULN

Respiratory:

- ARDS ***or***
- Intubated ***or***
- >50% FiO2 to maintain SaO2 > 92%

Neurological:

- Glasgow Coma Score (GCS) ≤ 11 ***or***
- Acute change in mental status with a decrease in GSC ≥3 pts from abnormal baseline

Renal:

- Serum creatinine ≥ 2 x ULN for age ***or*** 2-fold increase in baseline creatinine

Hepatic:

- Total bilirubin ≥4 mg/dL ***or***
- ALT ≥2 x ULN for age

Table F-1: Four age groups relevant to HCT:

Age	Tachycardia (bpm)	Bradycardia (bpm)	Tachypnea (breaths/min)	Leukocytosis / Leukopenia (WBC)	Hypotension Systolic BP mmHg
1 mo to 1 yr	>180	<90	>34	>17.5 to <5.0	<100
2 yr to 5 yr	>140	NA	>22	>15.5 to <6.0	<94
6 yr to 12 yr	>130	NA	>18	>13.5 to <4.5	<105
13 yr to < 18 yr	>110	NA	>14	>11 to <4.5	<117

Disseminated Infections:

- Two or more non-contiguous sites with the SAME organism
- A disseminated infection can occur at any level of severity, but most will be grade 2 or 3.

Recurrence Intervals to Determine Whether an Infection is the Same or New:

- CMV, HSV, EBV, HHV6: 2 months (≤ 60 days)
- VZV, HZV: 2 weeks (≤ 14 days)
- Bacterial, non-C. difficile: 1 week (≤ 7 days)
- Bacterial, C. difficile: 1 month (≤ 30 days)
- Yeast: 2 weeks (≤ 14 days)
- Molds: 3 months (≤ 90 days)
- Helicobacter: 1 year (≤ 365 days)
- Adenovirus, Enterovirus, Influenza, RSV, Parainfluenza, Rhinovirus: 2 weeks (≤ 14 days)
- Polyomavirus (BK virus): 2 months (≤ 60 days)

For infections coded as “Disseminated” per the *Infection Form*, any previous infection with the same organism but different site within the recurrence interval for that organism will be counted as part of the disseminated infection.

Definitions of Invasive Fungal Infections in Patients with Cancer and Recipients of Hematopoietic Stem Cell Transplants

Category, Type of Infection	Description
Proven invasive fungal infections	
Deep Tissue Infections	
Moulds[a]	Histopathologic or cytopathologic examination showing hyphae from needle aspiration or biopsy specimen with evidence of associated tissue damage (either microscopically or unequivocally by imaging); or positive culture result for a sample obtained by sterile procedure from normally sterile and clinically or radiologically abnormal site consistent with infection, excluding urine and mucous membranes
Yeasts[a]	Histopathologic or cytopathologic examination showing yeast cells (Candida species may also show pseudohyphae or true hyphae) from specimens of needle aspiration or biopsy excluding mucous membranes; or positive culture result on sample obtained by sterile procedure from normally sterile and clinically or radiologically abnormal site consistent with infection, excluding urine, sinuses, and mucous membranes; or microscopy (India ink, mucicarmine stain) or antigen positivity[b] for *Cryptococcus* species in CSF
Fungemia	
Moulds[a]	Blood culture that yields fungi, excluding aspergillus species and *Penicillium* species other than *Penicillium marneffei*, accompanied by temporally related clinical signs and symptoms compatible with relevant organism
Yeasts[a]	Blood culture that yields *Candida* species and other yeasts in patients with temporally related clinical signs and symptoms compatible with relevant organism
Endemic fungal infections[c]	
Systemic or confined to lungs	Must be proven by culture from site affected, in host with symptoms attributed to fungal infection; if culture results are negative or unattainable, histopathologic or direct microscopic demonstration of appropriate morphological forms is considered adequate for dimorphic fungi (*Blastomyces*, *Coccidioides* and *Paracoccidiodes* species) having truly distinctive appearance; *Histoplasma capsulatum* variant capsulatum may resemble *Candida glabrata*
Disseminated	May be established by positive blood culture result or positive for urine or serum antigen by means of RIA
Probable invasive fungal infections	At least 1 host factor criterion; and 1 microbiological criterion; and either a) 1 major (or 2 minor) clinical criteria from abnormal site consistent with infection for sites other than lower respiratory tract, or b) one of the clinical criteria for lower respiratory tract site

Category, Type of Infection	Description
Presumptive invasive fungal infection	• At least 1 host factor criterion and 1 clinical criterion for lower respiratory tract infection as listed below. A microbiological criterion is NOT required. The clinical criterion for lower respiratory tract infection must be consistent with the microbiological findings, if any, temporally related to current episode and other potential causes must have been eliminated, along with: – The presence of one of the following "specific" imaging signs on CT: (1) Halo sign, (2) wedge-shaped infiltrate, (3) air crescent sign, OR – The presence of a new non-specific focal infiltrate, PLUS at least one of the following: pleural rub, pleural pain, or haemoptysis, AND no evidence of other etiology demonstrated by bronchoscopic examination • Or if lacking a host criterion, but otherwise meets the microbiological and clinical criteria for a presumptive, probable or proven invasive fungal infection. The clinical criterion for lower respiratory tract infection must be consistent with the microbiological findings, if any, temporally related to current episode and other potential causes must have been eliminated, along with: – The presence of one of the following "specific" imaging signs on CT: (1) well-defined nodule with or without a halo sign, (2) halo sign, (3) wedge-shaped infiltrate, (4) air crescent sign, (5) cavity within area of consolidation OR – The presence of a new non-specific focal infiltrate, PLUS at least one of the following: pleural rub, pleural pain, or haemoptysis AND no evidence of other etiology demonstrated by bronchoscopic examination
Possible[d] invasive fungal infections	At least 1 host factor criterion; and 1 microbiological criterion; or either a) 1 major (or 2 minor) clinical criteria from abnormal site consistent with infection for sites other than lower respiratory tract, or b) one of the clinical criteria for lower respiratory tract site

[a] Append identification at genus or species level from culture, if available.
[b] False-positive cryptococcal antigen reactions due to infection with *Trichosporan beigelli* (1), infection with *Stomatococcus mucilaginosis* (2), circulating rheumatoid factor (3), and concomitant malignancy (4) may occur and should be eliminated if positive antigen test is only positive result in this category.
[c] Histoplasmosis, blastomycosis, coccidioidomycosis, and paracoccidioidomycosis.
[d] This category is not recommended for use in clinical trials of antifungal agents but might be considered for studies of empirical treatment, epidemiological studies, and studies of health economics

Host Factor, Microbiological, and Clinical Criteria for Invasive Fungal Infections in Patients with Cancer and Recipients of Hematopoietic Stem Cell Transplants

Type of Criteria	Criteria
Host factors	• Neutropenia (<500 neutrophils/mm^3 for > 10 days) • Persistent fever (≥ 38°C) for > 96 h refractory to appropriate broad-spectrum antibacterial treatment in high-risk patients • Body temperature either > 38°C or < 36°C and any of the following predisposing conditions: prolonged neutropenia (> 10 days) in previous 60 days, recent or current use of significant immunosuppressive agents in previous 30 days, proven or probable invasive fungal infection during previous episode of neutropenia, or coexistence of symptomatic AIDS • Signs and symptoms indicating graft-versus-host disease, particularly severe (Grade ≥2) or extensive chronic disease • Prolonged (>3 weeks) use of corticosteroids in previous 60 days
Microbiological	• Positive result of culture for mould (including aspergillus, *Fusaruim*, or *Scedosporium* species or Zygomycetes) or *Cryptococcus neoformans* or an endemic fungal pathogen[a] from sputum or bronchoalveolar lavage fluid samples • Positive result of culture or findings of cytologic/direct microscopic evaluation for mould from sinus aspirate specimen • Positive findings of cytologic/direct microscopic evaluation for mould or Cryptococcus species from sputum or bronchoalveolar lavage fluid samples • Positive result for aspergillus antigen in blood samples[b] • Positive result for aspergillus antigen in specimens of bronchoalveolar lavage fluid or CSF • Positive result for cryptococcal antigen in blood sample[c] • Positive findings of cytologic or direct microscopic examination for fungal elements in sterile body fluid samples (e.g., *Cryptococcus* species in CSF) • Positive result for *Histoplasma capsulatum* antigen in blood, urine, or CSF specimens • Two positive results of culture of urine samples for yeasts in absence of urinary catheter • *Candida* casts in urine in absence of urinary catheter • Positive result of blood culture for *Candida* species
Clinical	Must be related to site of microbiological criteria and temporally related to current episode
Lower respiratory tract infection	• The presence of one of the following "specific" imaging signs on CT: (1) well defined nodule(s) of at least 1 cm in diameter with or without a halo sign, (2) wedge-shaped infiltrate, (3) air crescent sign, or (4) cavity within area of consolidation[d], OR • The presence of a new non-specific focal infiltrate, PLUS at least one of the following: pleural rub, pleural pain or hemoptysis

Type of Criteria	Criteria
Sinonasal infection *Major*	Suggestive radiological evidence of invasive infection in sinuses (i.e., erosion of sinus walls or extension of infection to neighboring structures, extensive skull base destruction)
Minor	Upper respiratory symptoms (e.g., nasal discharge, stuffiness); nose ulceration or eschar of nasal mucosa or epistaxis; periorbital swelling; maxillary tenderness; black necrotic lesions or perforation of hard palate
CNS infection *Major*	Radiological evidence suggesting CNS infection (e.g., mastoiditis or other parameningeal foci, extradural empyema, intraparenchymal brain or spinal cord mass lesion)
Minor	Focal neurological symptoms and signs (including focal seizures, hemiparesis, and cranial nerve palsies); mental changes; meningeal irritation findings; abnormalities in CSF biochemistry and cell count (provided that CSF is negative for other pathogens by culture or microscopy and negative for malignant cells)
Disseminated fungal infection	Papular or nodular skin lesions without any other explanation; intraocular findings suggestive of hematogenous fungal chorioretinitis or endophthalmitis
Chronic disseminated candidiasis	Small, peripheral, target-like abscesses (bull's-eye lesions) in liver and/or spleen demonstrated by CT, MRI, or ultrasound, as well as elevated serum alkaline phosphatase level; supporting microbiological criteria are not required for probable category
Candidemia	Clinical criteria are not required for probable candidemia; there is no definition for possible candidemia

[a] *H. capsulatum* variant *capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis*, or *Paracoccidioides brasiliensis*.
[b] Galactomannan Positivity: A positive galactomannan assay is defined as two positives on the same specimen or two consecutive positives on different specimens, i.e., a repeat test on the first specimen was not performed. Sera with an index less than 0.5 are considered to be negative. Sera with an index greater than or equal to 0.5 are considered to be initially positive.
Whenever a sample has an index ≥ 0.5, positivity must be confirmed by re-testing the sample, including repeating the heat treatment on a new aliquot, and by testing another sample obtained from the patient. This confirmation is necessary in order to eliminate any false-positive results due to contamination of the sample after collection.
[c] False-positive cryptococcal antigen reactions due to infection with *Trichosporan beigelli* (1), infection with *Stomatococcus mucilaginosis* (2), circulating rheumatoid factor (3), and concomitant malignancy (4) may occur and should be eliminated if positive antigen test is only positive result in this category.
[d] In absence of infection by organisms that may lead to similar radiological findings including cavitation, such as *Mycobacterium*, *Legionella*, and *Nocardia* species.

REFERENCES

1. Cottler-Fox, M.H., Lapidot, T., Petit, I., Kollet, O., DiPersio, J. F., Link, D., Devine, S., *Stem cell mobilization.* Hematology Am Soc Hematol Educ Program, 2003: p. 419-37.
2. Grewal, S.S., Barker, J. N., Davies, S. M., Wagner, J. E., *Unrelated donor hematopoietic cell transplantation: marrow or umbilical cord blood?* Blood, 2003.
3. Aljitawi, O.S., *Ex vivo expansion of umbilical cord blood: where are we?* Int J Hematol, 2012. **95**(4): p. 371-9.
4. Wagner, J.E., *Should double cord blood transplants be the preferred choice when a sibling donor is unavailable?* Best Pract Res Clin Haematol, 2009. **22**(4): p. 551-5.
5. Barker, J.N., Fei, M., Karanes, C., Horwitz, M., Devine, S., Kindwall-Keller, T. L., Holter, J., Adams, A., Logan, B., Navarro, W. H., Riches, M., *Results of a prospective multicentre myeloablative double-unit cord blood transplantation trial in adult patients with acute leukaemia and myelodysplasia.* Br J Haematol, 2014.
6. Brunstein, C.G., Gutman, J. A., Weisdorf, D. J., Woolfrey, A. E., Defor, T. E., Gooley, T. A., Verneris, M. R., Appelbaum, F. R., Wagner, J. E., Delaney, C., *Allogeneic hematopoietic cell transplantation for hematological malignancy: relative risks and benefits of double umbilical cord blood.* Blood, 2010.
7. Eapen, M., et al., *Effect of graft source on unrelated donor haemopoietic stem-cell transplantation in adults with acute leukaemia: a retrospective analysis.* Lancet Oncol, 2010.
8. Ruggeri, A., Labopin, M., Sormani, M. P., Sanz, G., Sanz, J., Volt, F., Michel, G., Locatelli, F., Diaz De Heredia, C., O'Brien, T., Arcese, W., Iori, A. P., Querol, S., Kogler, G., Lecchi, L., Pouthier, F., Garnier, F., Navarrete, C., Baudoux, E., Fernandes, J., Kenzey, C., Eapen, M., Gluckman, E., Rocha, V., Saccardi, R., *Engraftment kinetics and graft failure after single umbilical cord blood transplantation using a myeloablative conditioning regimen.* Haematologica, 2014. **99**(9): p. 1509-15.
9. Cheung, A.M., et al., *Distinct but phenotypically heterogeneous human cell populations produce rapid recovery of platelets and neutrophils after transplantation.* Blood, 2012. **119**(15): p. 3431-9.
10. Ando, K., Yahata, T., Sato, T., Miyatake, H., Matsuzawa, H., Oki, M., Miyoshi, H., Tsuji, T., Kato, S., Hotta, T., *Direct evidence for ex vivo expansion of human hematopoietic stem cells.* Blood, 2006. **107**(8): p. 3371-7.
11. Drake, A.C., Khoury, M., Leskov, I., Iliopoulou, B. P., Fragoso, M., Lodish, H., Chen, J., *Human CD34+ CD133+ hematopoietic stem cells cultured with growth factors including Angptl5 efficiently engraft adult NOD-SCID Il2rgamma-/- (NSG) mice.* PLoS ONE, 2011. **6**(4): p. e18382.
12. Srour, E.F., Abonour, R., Cornetta, K., Traycoff, C. M., *Ex vivo expansion of hematopoietic stem and progenitor cells: are we there yet?* J Hematother, 1999. **8**(2): p. 93-102.
13. Holmes, T., et al., *Ex vivo expansion of cord blood progenitors impairs their short-term and long-term repopulating activity associated with transcriptional dysregulation of signalling networks.* Cell Prolif, 2012. **45**(3): p. 266-78.
14. Peled, T., Shoham, H., Aschengrau, D., Yackoubov, D., Frei, G., Rosenheimer, G. N., Lerrer, B., Cohen, H. Y., Nagler, A., Fibach, E., Peled, A., *Nicotinamide, a SIRT1*

inhibitor, inhibits differentiation and facilitates expansion of hematopoietic progenitor cells with enhanced bone marrow homing and engraftment. Exp Hematol, 2012.
15. Horwitz, M.E., Chao, N. J., Rizzieri, D. A., Long, G. D., Sullivan, K. M., Gasparetto, C., Chute, J. P., Morris, A., McDonald, C., Waters-Pick, B., Stiff, P., Wease, S., Peled, A., Snyder, D., Cohen, E. G., Shoham, H., Landau, E., Friend, E., Peleg, I., Aschengrau, D., Yackoubov, D., Kurtzberg, J., Peled, T., *Umbilical cord blood expansion with nicotinamide provides long-term multilineage engraftment.* J Clin Invest, 2014. **124**(7): p. 3121-8.
16. Horwitz, M.E., et al., *Phase I/II Study of Stem-Cell Transplantation Using a Single Cord Blood Unit Expanded Ex Vivo With Nicotinamide.* J Clin Oncol, 2018: p. JCO1800053.
17. Anand, S., et al., *Transplantation of Ex Vivo Expanded Umbilical Cord Blood (NiCord) Decreases Early Infection and Hospitalization.* Biol Blood Marrow Transplant, 2017.
18. Berger, F., M.H. Ramirez-Hernandez, and M. Ziegler, *The new life of a centenarian: signalling functions of NAD(P).* Trends Biochem Sci, 2004. **29**(3): p. 111-8.
19. Banasik, M., et al., *Specific inhibitors of poly(ADP-ribose) synthetase and mono(ADP-ribosyl)transferase.* J Biol Chem, 1992. **267**(3): p. 1569-75.
20. Corda, D. and M. Di Girolamo, *Functional aspects of protein mono-ADP-ribosylation.* Embo J, 2003. **22**(9): p. 1953-8.
21. Krebs, C., et al., *CD38 controls ADP-ribosyltransferase-2-catalyzed ADP-ribosylation of T cell surface proteins.* J Immunol, 2005. **174**(6): p. 3298-305.
22. Glowacki, G., et al., *The family of toxin-related ecto-ADP-ribosyltransferases in humans and the mouse.* Protein Sci, 2002. **11**(7): p. 1657-70.
23. Denu, J.M., *The Sir2 family of protein deacetylases.* Curr Opin in chemical biology, 2005: p. 431-440.
24. Laughlin, M.J., Barker, J., Bambach, B., Koc, O. N., Rizzieri, D. A., Wagner, J. E., Gerson, S. L., Lazarus, H. M., Cairo, M., Stevens, C. E., Rubinstein, P., Kurtzberg, J., *Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donors.* N Engl J Med, 2001. **344**(24): p. 1815-22.
25. Rocha, V., Labopin, M., Sanz, G., Arcese, W., Schwerdtfeger, R., Bosi, A., Jacobsen, N., Ruutu, T., de Lima, M., Finke, J., Frassoni, F., Gluckman, E., *Transplants of Umbilical-Cord Blood or Bone Marrow from Unrelated Donors in Adults with Acute Leukemia.* N Engl J Med, 2004. **351**(22): p. 2276-2285.
26. Barker, J.N., Weisdorf, D. J., Defor, T. E., Blazar, B. R., McGlave, P. B., Miller, J. S., Verfaillie, C. M., Wagner, J. E., *Transplantation of 2 partially HLA-matched umbilical cord blood units to enhance engraftment in adults with hematologic malignancy.* Blood, 2005. **105**(3): p. 1343-7.
27. Przepiorka, D., et al., *1994 Consensus Conference on Acute GVHD Grading.* Bone Marrow Transplant, 1995. **15**(6): p. 825-8.
28. Jagasia, M.H., et al., *National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report.* Biol Blood Marrow Transplant, 2015. **21**(3): p. 389-401 e1.
29. U.S.DEPARTMENT_OF_HEALTH_AND_HUMAN_SERVICES, *Common Terminology Criteria for Adverse Events v4.0 (CTCAE).* 2009.