Study Title

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

Study Chairs

[redacted]

Clinical Phase:	Phase III
Product:	NiCord®
IND Number:	14459
EudraCT Number:	2016-000704-28

Sponsor

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Director, Medical Affairs:	[redacted]
Protocol No.:	GC P#05.01.020
Amendment #:	VI
Dated:	January 22, 2019

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.

CONFIDENTIAL

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

List of Abbreviations

Ab	Antibody
ABW	Actual Body Weight
AE	Adverse Event
AEP	ANC-Engrafted Population
ALL	Acute Lymphoblastic Leukemia
ALT	Alanine Transaminase
AML	Acute Myelogenous Leukemia
ANC	Absolute Neutrophil Count
AP/PA position	Anteriorposterior/Posterioranterior Position
APL	Acute Promyelocytic Leukemia
ASHI/EFI	American Society for Histocompatibility and Immunogenetics/European Federation for Immunogenetics
AST	Aspartate Transaminase
AT	As Treated
AUC	Area Under the Curve
BAL	Bronchoalveolar Lavage
B CELL	Bone Marrow Lymphocyte Cells (CD19+)
BID	Twice a day
BM	Bone Marrow
BMT	Bone Marrow Transplant
BMTS	Bone Marrow Transplantation Subscale
BSA	Body Surface Area
CB	Cord Blood
CBB	Cord Blood Bank
CBC	Complete Blood Count
CBT	Cord Blood Transplant
CBU	Cord Blood Unit
cDLCO	Corrected Diffusing Capacity of the Lungs for Carbon Monoxide
CF	Cultured Fraction
CFU	Colony-forming Units
CHR	Complete Hematologic Response
CI	Cumulative Incidence
CIBMTR	Center for International Blood and Marrow Transplant Research
CML	Chronic myeloid leukemia
CMR	Complete Molecular Response
CMMoL	Chronic myelomonocytic leukemia
CMV	Cytomegalovirus
CNS	Central Nervous System
COA	Certificate of Analysis
CoNS	Coagulase-Negative Staphylococci
CR	Complete Remission
CRA	Clinical Research Associate
(e-) CRFs	(Electronic) Case Report Forms
CRO	Contract Research Organization
CSA	Cyclosporin A
CSF	Cerebrospinal Fluid
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CY	Cyclophosphamide Administration
(c/p/m) CyR	(Complete/Partial/Minor) Cytogenectic Response
DCC	Data Coordinating Center
DCBT	Double Cord Blood Transplant

DLCO	Diffusing Capacity of the Lungs for Carbon Monoxide
DMC	Data Monitoring Committee
DNA	Desoxyribonucleic Acid
DRI	Disease Risk Index
EBMT	European society for Blood and Marrow Transplantation
EBV	Epstein-Barr Virus
EC	Ethics Committee
EKG	Electrocardiography
EMA	European Medicines Agency
EVCTM	EudraVigilence Clinical Trial Module
FACS	Fluorescence-Activated Cell Sorting
FACT-BMT	Functional Assessment of Cancer Therapy – Bone Marrow Transplant Module
FACT-G	Functional Assessment of Cancer Therapy - General
FBS	Fetal Bovine Serum
FEV1	Forced Expiratory Volume in One Second
FISH	Fluorescent In Situ Hybridization
FLT3	Fms Related Tyrosin Kinase
FLT3-L	Flt3-Ligand
FPQC	Final Process Quality Controls
FVC	Forced Vital Capacity
FWE	Family-wise Error Rate
GC	Gamida Cell
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GFR	Glomerular Filtration Rate
GMF	Grocott Methenamine Silver
GvHD	Graft-versus-host Disease
HCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HBcAb	Hepatitis B core Antibody
HBsAg	Hepatitis B surface Antigen
HHV	Human Herpesvirus
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPC	Hematopoietic Progenitor Cells
HQL	Health-related Quality of Life
HRCT	High-Resolution Computed Tomography
HSC	Hematopoietic Stem Cells
HSCT	Hematopoietic Stem Cell Transplantation
HSPCs	Hematopoietic Stem/Progenitor Cells
HSV	Herpes Simplex Virus
HTLV	Human T-Lymphotropic Virus
IB	Investigator Brochure
IBW	Ideal Body Weight
IC	Informed Consent
ICH	International Conference on Harmonization
ID	Identify Document
Ig	Immunoglobulin
IL6	Interleukin 6
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IPQC	In-process Quality Controls
IPS	Idiopathic Pneumonia Syndrome

IPSS	International Prognostic Scoring System
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent to Treat
IUD	Intrauterine contraceptive Device
IV	Intravenous
LVEF	Left Ventricular Ejection Fraction
MARTs	Mono-ADP-ribosyltransferases
MDS	Myelodysplastic Syndrome
MFI	Mean Fluorescence Intensity
MLL	Myeloid/Lymphoid Leukemia
MM	Medical Monitor
MMF	Mycophenolate Mofetil
MMR	Major Molecular Response
MMUD	Mismatched Unrelated Donor
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
MRU	Medical Resources Utilization
MS	Mass Spectrometry
MS CA	Member States Competent Authority
MUD	Matched Unrelated Donor
MUGA	Multi Gated Acquisition Scan
N/A	Not Applicable
NAD+	Nicotinamide Adenine Dinucleotide
NAM	Nicotinamide
NCI	National Cancer Institute
NF	Non-cultured Fraction
NIH	National Institutes of Health
NK CELL	Natural Killer Cytotoxic Lymphocyte Cells (CD56+/CD16+cells)
NOD/SCID	Non-Obese Diabetic Background, Severe Combined Immunodeficiency
NOS	Not Otherwise Specified
NP	Nurse Practitioner
NRM	Non Relapse Mortality
OOS	Out of Specification
PA	Physician Assistant
PaO2	Partial Pressure of Oxygen
PARPs	Poly-ADP-ribose Polymerases
PB	Peripheral Blood
PBSC	Peripheral Blood Stem Cell
PCP	Pneumocystis Pneumonia
PCR	Polymerase Chain Reaction
PEP	Platelet-Engrafted Population
PI	Principal Investigator
PMN	Polymorphonuclear Leukocytes
PO	By Mouth, or Oral Administration of a Drug
PT	Preferred Term
PTLD	Post-Transplant Lymphoproliferative Disorder
QC	Quality Control
QOL	Quality Of Life
QP	Qualified Person
RBC	Red Blood Cell
Rh	Rhesus
RPR	Rapid Plasma Reagin

RSV	Respiratory Syncytial Virus
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SCD	Sickle Cell Disease
SCF	Stem Cell Factor
SCID	Severe Combined Immunodeficiency
SCT	Stem Cell Transplant
SLM	Study Logistics Manager
SOC	System Organ Class
SOP	Standard Operating Procedures
SP	Safety Population
SPRT	Sequential Probability Ratio Test
SRC	SCID Repopulating Cells
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBI	Total Body Irradiation
T CELL	Thymus derived lymphocytes (CD3+ cells; CD4+/CD8+ cells)
TDM	Therapeutic Drug Monitoring
TID	Three Times a Day Administration of a Drug
TKI	Tyrosine Kinase Inhibitor
TNC	Total Nucleated Cell
TP	Transplanted Population
TPO	Thrombopoietin
TRM	Transplant-related Mortality
UA	Urinalysis
UCB	Umbilical Cord Blood
UCBU	Unmanipulated Cord Blood Unit
UCBT	Umbilical Cord Blood Transplantation
VZV	Varicella-zoster Virus
WBC	White Blood Cell

SPONSOR PROTOCOL APPROVAL PAGE

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Clinical Phase	Phase III
Protocol Number:	GC P#05.01.020
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Approved by:

Director, Medical Affairs

[redacted]

_____ _____

Signature Date

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1. INVESTIGATOR'S AGREEMENT

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 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 subject 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# 05.01.020

Protocol Title
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

Planned Geographical Distribution
Multicenter, multinational

Clinical Phase
Phase III, Registration

Investigational Product
NiCord® is a cryopreserved stem/progenitor cell-based product comprised of:

1) *Ex vivo* expanded, umbilical cord blood-derived hematopoietic $CD34^+$ progenitor cells (NiCord® cultured fraction (CF))

2) The non-cultured cell fraction of the same CBU (NiCord® Non-cultured Fraction (NF)) consisting of mature myeloid and lymphoid cells.

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

Study Duration
The planned total duration for each patient is [redacted] from the signing of informed consent to the last follow-up 15 months following randomization. The trial ends when all patients have completed their last follow-up. Patients who enroll in the optional long-term follow up sub-study will be followed for up to 5 years post-transplantation.

Study Objectives
The overall study objective is to compare the safety and efficacy of NiCord® single *ex vivo* expanded cord blood unit transplantation to unmanipulated cord blood unit transplantation in patients with hematological malignancies following conditioning therapy as follows:

<u>Primary Objective:</u>

Assess the time to neutrophil engraftment following transplantation.

Neutrophil engraftment is defined as achieving an absolute neutrophil count (ANC) ≥ 0.5 x 10^9/L on 3 consecutive measurements on different days with subsequent donor chimerism (≤10% host cells by peripheral blood chimerism or bone marrow chimerism if peripheral blood chimerism is not available) The day of neutrophil engraftment is designated as the first of the 3 consecutive measurements and must occur on or before 42 days post transplant (and also prior to infusion of any additional stem cell product).

Secondary Objective:
Assess the following endpoints.

Secondary Endpoints:

- Incidence of grade 2/3 bacterial or invasive fungal infections by 100 days following transplantation
- Days alive and out of hospital in the first 100 days following transplantation
- Platelet engraftment by 42 days following transplantation

Tertiary Endpoint:

- Non-relapse mortality by 210 days following randomization

Exploratory Endpoints:

- Neutrophil engraftment by 16 days following transplantation
- Time from transplantation to platelet engraftment
- Duration of primary hospitalization
- Non-relapse mortality by 130 days and 15 months following randomization
- Overall survival at 210 days and 15 months following randomization
- Disease-free survival at 15 months following randomization
- Neutrophil engraftment by 42 days following transplantation
- Acute GvHD grade II-IV and III-IV by 100 days following transplantation
- Chronic GvHD (mild/moderate/severe) by 180 days and 1 year following transplantation
- Secondary graft failure by 1 year following transplantation
- Grade 3 viral infections by 180 days and 1 year following transplantation
- Safety and tolerability of NiCord® transplantation
- Relapse by 15 months following randomization
- Relapse mortality by 15 months following randomization
- Immune reconstitution at 28, 70, 100, 180, and 365 days following transplantation
- Supplemental immune reconstitution assessments at a central laboratory (optional)
- Health-related quality of life
- Long-term clinical outcomes up to 5 years following transplantation (optional)

Study Hypothesis
NiCord® as a standalone graft will improve post-transplant outcomes compared to Unmanipulated CBT.

Study Design
This study is an open-label, controlled, multicenter, international, Phase III, randomized study comparing transplantation of NiCord® to transplantation of one or two unmanipulated, unrelated cord blood units in patients with hematological malignancies for whom allogenic SCT is currently a recommended and potentially lifesaving treatment, all with required disease features rendering them eligible for allogeneic transplantation.

Number of Patients
The study will randomize 120 eligible patients [redacted] ratio to receive either NiCord® or unmanipulated cord blood transplantation.

[redacted]

Eligibility Criteria
Patients 12-65 years of age with a diagnosis of hematological malignancy who are candidates for unrelated cord blood transplantation, with qualifying HLA-matched UCB units with sufficient pre-cryopreserved total nucleated cell dose and CD34+ cell dose, as follows:

Treatment CBU #1:

Patients must have a 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 [redacted] as well as a pre-cryopreserved (post processing) total nucleated cell count [redacted] and total nucleated cell dose [redacted]. The CBU will have undergone volume reduction (both plasma and red blood cell depletion) prior to cryopreservation.

- Treatment CBU #1 will be used for the NiCord® arm or for the control arm in case of either single or double CBT.
- Verification typing (confirmatory typing) must be completed before CBU shipment.

Treatment CBU #2 (to be used for the control arm in case of double cord transplantation):

In case treatment CBU #1 is HLA-matched at 5-6/6 and contains a pre-cryopreserved (post processing) total nucleated cell dose of [redacted], OR a pre-cryopreserved (post processing) CD34+ cell dose of [redacted], a second CBU must be added for the control arm, as a double CBT.

In case treatment CBU #1 is HLA-matched at 4/6 and contains a pre-cryopreserved (post processing) total nucleated cell dose of [redacted], OR a pre-cryopreserved (post processing) CD34+ cell dose of [redacted], a second CBU must be added for the control arm, as a double CBT.

The determination of using a single or double cord if randomized to the control arm must be made by the investigator prior to randomization.

- Treatment CBU #2 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. Treatment CBUs #1 and #2 must have a combined pre-cryopreserved (post processing) total nucleated cell dose of [redacted].

Detailed eligibility criteria are provided below; **note that all eligibility testing must be completed and resulted, and entered into [redacted] before randomization:**

Inclusion Criteria

1. Patients must be 12-65 years of age at the time of randomization
2. Patients with one of the following hematological malignancies:
   - Acute lymphoblastic leukemia (ALL) at one of the following stages:

     [redacted]
   - Acute myelogenous leukemia (AML) at one of the following stages:

     [redacted]
   - Chronic myelogenous leukemia (CML) at one of the following phases:

     [redacted]
   - CMMoL or MDS/CMMoL overlap [redacted]
   - Myelodysplastic Syndrome (MDS) with history of one or more of the following:

     [redacted]

     Biphenotypic/undifferentiated/Prolymphocytic/Dendritic Cell Leukemias and Natural Killer Cell Malignancies[redacted], adult T-cell leukemia/lymphoma
   - Lymphoma, meeting one or more of the following criteria:

- Burkitt's lymphoma [redacted],

  OR

- High risk lymphomas [redacted],

  OR

- Chemotherapy-sensitive (defined as at least stable disease) lymphomas [redacted].

  (Patients with CLL are not eligible regardless of disease status)

3. CBU criteria as described above.
4. Patients who will be starting conditioning prior to NiCord release for infusion (i.e., NiCord arrival on site in adequate condition) must have an additional partially HLA-matched CBU reserved as a backup to the NiCord arm in case of production failure. 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. A second back-up CBU is recommended to be added in the below cases:
   - If the back-up CBU is HLA-matched at 5 or 6/6, and contains a pre-cryopreserved (post processing) total nucleated cell dose of [redacted], OR a pre-cryopreserved (post processing) CD34+ cell dose of [redacted],
   - If the back-up CBU is HLA-matched at 4/6, and contains a pre-cryopreserved (post processing) total nucleated cell dose of [redacted], OR a pre-cryopreserved (post processing) CD34+ cell dose of [redacted].

   In case of two back-up CBUs, the second back-up CBU must also 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. The back-up CBUs are recommended to have a combined pre-cryopreserved (post processing) total nucleated cell dose of at least [redacted].
5. Patient's Performance score ≥70% by Karnofsky or Lansky
6. Patient has sufficient physiologic reserves including:
   a. Cardiac: [redacted]
   b. Pulmonary [redacted]
   c. Renal: [redacted]
   d. Hepatic: [redacted]

7. Females of childbearing potential, defined [redacted]
8. 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. MDS or CML with "marked" or "3+" fibrosis
2. CLL
3. Fewer than 21 days have elapsed since initiation of the patient's last chemotherapy cycle and the initiation of the stem cell transplant preparative regimen [redacted]
4. Persistent clinically significant toxicities [redacted]
5. Evidence of donor specific anti-HLA antibodies to the selected treatment CBU #1 (MFI>3000 to HLA A, B, C, or DRB1)
6. Evidence of HIV infection or HIV positive serology
7. Evidence of active Hepatitis B or Hepatitis C as determined by serology or PCR
8. Pregnancy [redacted]
9. Active malignancy other than that for which the UCB transplant is being performed within 12 months of enrollment. Fully resected cutaneous squamous cell or basal cell carcinoma or cervical carcinoma in situ within 12 months of enrollment will be permitted.
10. Evidence of uncontrolled bacterial, fungal or viral infections or severe concomitant diseases, [redacted]
11. Patients with presence of leukemic blasts in the central nervous system (CNS)

12. Patients with an 8/8 allele level HLA-matched and readily available related or 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 will not be excluded
13. Prior allogeneic hematopoietic stem cell transplant
14. Allergy to bovine products, gentamicin, or to any other product that may interfere with the treatment
15. Psychologically incapable [redacted]
16. Enrolled in another interventional clinical trial or received an investigational treatment within 30 days prior to the anticipated date of randomization [redacted]

Treatment Description

Once qualifying CBUs have been identified and the patient (or legal guardian) signs the informed consent form (ICF), the patient will be screened for the study.

Eligibility testing must be completed and resulted, and entered into [redacted] prior to randomization. Eligible patients will be randomized in a [redacted] ratio to receive either NiCord® or unmanipulated cord blood transplantation.

NiCord® transplantation:

The CBU chosen for production (treatment CBU #1) will be shipped from the Cord Blood Bank (CBB) to the manufacturing site.

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

NiCord® CF will be thawed and infused first, followed by the NiCord® NF.

If NiCord® 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.

Unmanipulated cord blood transplantation:

The CBU (treatment CBU #1) or two CBUs (treatment CBU #1 and #2) chosen for transplantation will be shipped from the CBB to the clinical site before transplantation.

Conditioning Regimens

Prior to the start of conditioning the investigator must confirm patient suitability for transplant according to standard site practice.

The conditioning regimen will consist of one of the options below.

[redacted]

Regimen A.1 (Day -11 to -2):

- Total Body irradiation (TBI) [redacted]
- Fludarabine: [redacted]
- Thiotepa [redacted]

Regimen A.2 (Day -8 or -7 to -1):

- Total Body irradiation (TBI) [redacted]
- Fludarabine: [redacted]
- Cyclophosphamide [redacted]

Regimen B (Day -7 to -3):

- Thiotepa [redacted]
- Busulfan [redacted]
- Fludarabine [redacted]

The GvHD prophylaxis regimen will consist of Mycophenolate Mofetil (MMF) and a calcineurin inhibitor (Tacrolimus or Cyclosporine).

[redacted].

Statistical Considerations

Method of primary analysis:

The primary objective is to compare time from transplant to neutrophil engraftment between patients allocated to receive NiCord® transplantation and those allocated to receive unmanipulated cord blood transplantation.

Neutrophil engraftment is defined as achieving an absolute neutrophil count (ANC) ≥ 0.5 x 10^9/L on 3 consecutive measurements on different days with subsequent donor chimerism (≤ 10% host cells by peripheral blood chimerism or bone marrow chimerism if peripheral blood chimerism is not available) any time on or after the day of engraftment up to the earlier of day 100 post-transplant, date of relapse, date of secondary graft failure, or date of death. The day of neutrophil engraftment is designated as the first of

the 3 consecutive measurements and must occur on or before 42 days post transplant (and also prior to infusion of any additional stem cell product).

[redacted]

Thus, the primary analysis, but not all of the secondary analyses, will be conducted on the ITT population, i.e., all patients randomized will be included and their group membership will be the same as the group to which they were randomized, regardless of what treatment they received. Subgroup analyses according to age, disease risk group, disease (ALL, AML, MDS, CML and Lymphoma), gender, race/ethnicity, geographical region, and intention to perform single/double CBT will be performed as supportive analyses for both primary and secondary endpoints.

Method of allocation: Stratification by minimization

Patients will be randomized to treatment by NiCord® or by unmanipulated cord blood (single or double unit).

[redacted]

Interim Analysis and Safety Assessment Guidelines:

The safety data emerging from this study will be reviewed periodically by an independent DMC for safety assessment and to monitor the balance of baseline characteristics between treatment groups. Policies and composition of the DMC are described in the DMC Charter.

In addition to data provided for periodic reviews, the DMC will be provided with information regarding [redacted] mortality on a monthly basis, starting the first month after the first randomization.

Figure 1: Study Scheme

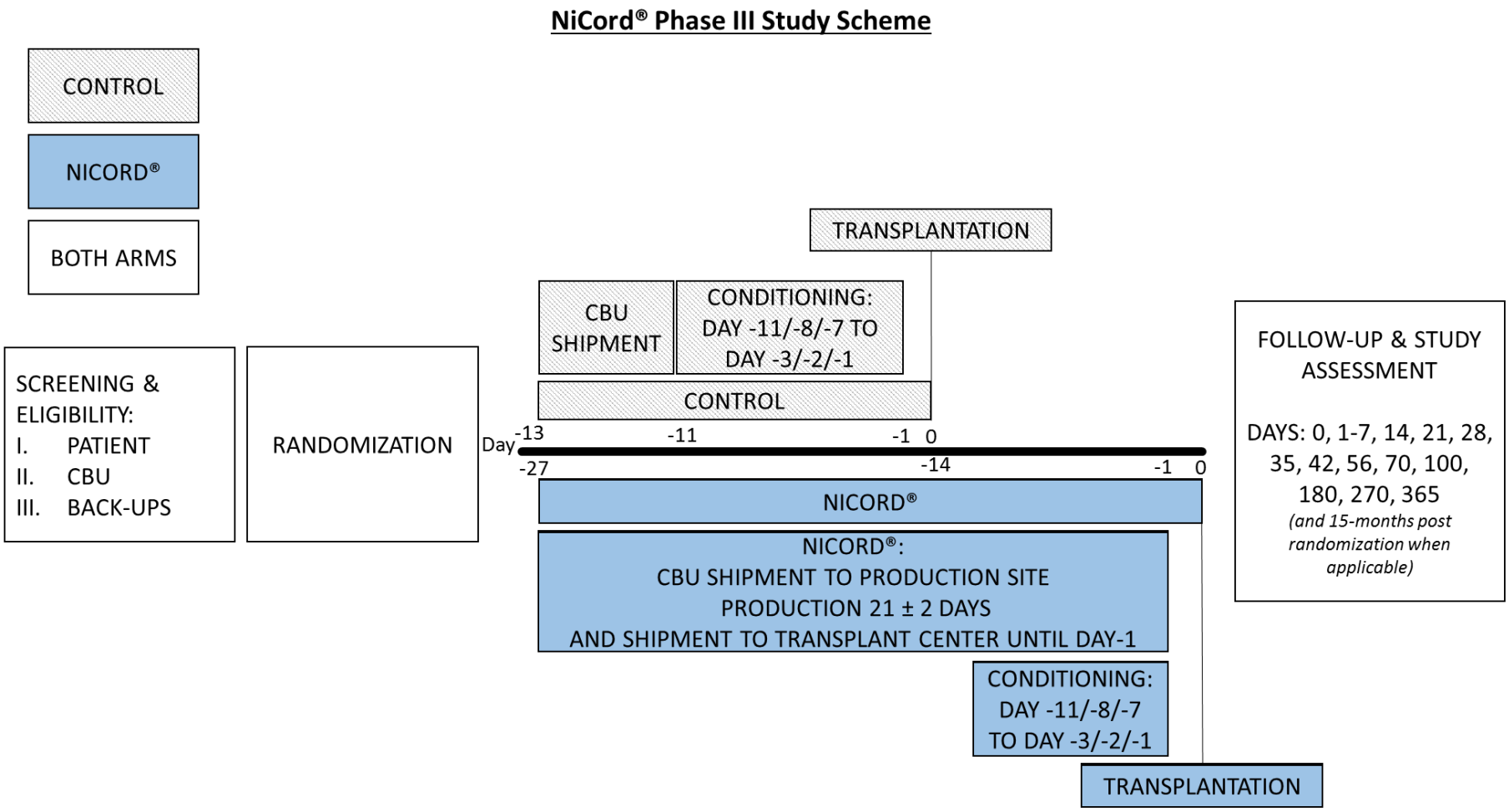


Figure 2: CBU Selection

3. INTRODUCTION

3.1. The unmet need in HSCT

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. In most settings, best results are offered by HLA-identical sibling transplantation; however, more than two-thirds of patients awaiting HSCT lack a suitable matched related donor.[3] When a matched related donor is not available, HSCTs with unrelated donor grafts are the only option. Despite the development of large international volunteer donor registries, fewer than 50% of unrelated donor searches result in identification and availability of a suitably matched donor graft.[2,4,5] Donor searches for recipients of non-Northern-European descent result in even lower success rates. In addition, prolonged searches for suitable donors increase the risk of malignancy recurrence or progression.[6] Three alternative sources for stem cells are offered for patients for whom a suitable matched related donor or matched unrelated donor (MUD) is not available in a timely manner: mismatched unrelated donor (MMUD), haploidentical (haplo)–related donor, and Umbilical Cord Blood (UCB). Currently, no clear advantage has been demonstrated for any of the three alternative stem cell sources. As a result, the same patient evaluated in different transplant centers may be offered MMUD, haplo-HSC, or UCB transplantation, depending on center preference and experience.5,[7]

UCB has been clinically in use over the last 25 years for the treatment of diverse life-threatening diseases, such as hematological malignancies or genetic blood disorders. 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.[8,9] Moreover, the use of 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 the advantages in the use of CBT, its use, especially in adults and adolescents, is limited. The medical need for suitable allogeneic grafts is still insufficiently met because of the delayed hematopoietic recovery in recipients of CBT, with a related increased risk of life-threatening or fatal sequelae.[10,11,12,13] Delayed hematopoietic recovery can result in an increased occurrence or higher severity of infections after transplantation. These infections sometimes lead to substantial organ damage, which may be irreversible, and also death. As a consequence, patients require longer durations of hospitalization, involving more intensive supportive care measures.

A major drawback of UCB is the low stem cell dose available for transplantation, compared to mobilized peripheral blood (PB) or bone marrow.[9] This low stem cell dose can compromise the chances of engraftment and contributes to delayed kinetics of neutrophil and platelet recovery, as well as other transplant outcomes.[14,15,16,17,18]

3.2. The use of DCBT and *ex vivo* expansion to overcome the cell dose limitation in CBT

The transplant community has been actively engaged in developing methods to address the cell dose issue in cord blood transplantation. Several approaches were developed, including dual umbilical cord blood transplantation (DCBT) and *ex vivo* expansion of UCB stem cells. Although to date no prospective clinical trials on the efficacy of single cord versus double cord in adults have been published, the DCBT has become standard practice in CBT for recipients in whom a single CBU of adequate cell dose is unavailable.1,[19,10,20,21]

However, even with use of higher TNC and CD34+, the outcomes of CBT are still not optimal. Engraftment kinetics still parallel those observed with single CBT, despite the use of double amounts of TNC and CD34+ cells. In a recently published pediatric study, patients with hematologic cancer were randomized to receive either a single or dual CBT.[22] Both groups received high doses of TNC and CD34+ cells. Despite this, neutrophil recovery occurred at a median of 21-23 days after transplantation, comparable to neutrophil recovery in adult patients receiving substantially fewer cells.[12,13] This may suggest a selective qualitative and quantitative insufficiency of cells with short-term repopulating activity in UCB grafts.[23]

Short-term repopulating cells are reported to provide early hematopoietic reconstitution after transplantation, but are distinct from HSC that can reconstitute the entire system permanently. Interestingly, while neutrophil and platelet recovery following CBT are often substantially delayed, long-term sustained donor cell chimerism appears to be similarly achieved even in patients receiving a relatively low TNC dose, as long as complications in the initial phase after transplantation are resolved.[24]

Ex vivo expansion is still an experimental approach. 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.[25]

Delaney et al. and De Lima et al. published the results of two clinical studies employing *ex vivo* expanded cord blood grafts in a double cord configuration, i.e., one CBU is used for expansion, while a second CBU is administered unmanipulated.[26,27,28] These studies demonstrated that the expanded cells contributed to initial myeloid engraftment that occurred at a median time of about 15-16 days and platelet engraftment at a median of about 40-42 days. The expanded cells were observed as early as one week post transplantation but for the most part were lost before or after engraftment, while the unmanipulated CBU took over in all of the recipients. A lack of *in vivo* persistence of the expanded graft could be due either to loss of stem cell self-renewal capacity during culture and/or to an immune-mediated rejection of the manipulated graft (which is devoid of T-cells) by the unmanipulated one. It was therefore suggested that combining an

ex vivo expanded CBU for early hematologic recovery with a CBU for long-term sustained haematopoiesis could be an optimal strategy to shorten the neutropenic phase following CBT.

3.3. Rationale for the development of NiCord®

Ideally, a successful expansion technology would obviate the need for DCBT, and in most cases would enable the clinician to choose a single CBU for the patient. Most *ex vivo* expansion technologies are successful in expanding a subset of hematopoietic progenitor cells (HPCs), which are expected to improve short-term early hematopoietic reconstitution; the main concern still remains for preservation of long-term repopulating cells in *ex vivo* cultures.[29,30,31] The concern is related 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.[32]

NiCord® is a stem/progenitor cell-based product composed of *ex vivo* expanded allogeneic cells from one entire unit of UCB. NiCord® utilizes the small molecule nicotinamide (NAM), [redacted]

To evaluate the safety and contribution of the expanded graft to short and long-term engraftment, the first-in-human study of NiCord® in hematological malignancies was performed in a double configuration, in combination with a second, unmanipulated CBU (GC P#01.01.020). In this pilot study, the DCBT platform served as a model to evaluate both the safety of use of a manipulated graft and enabled the simultaneous tracking of the contribution of NiCord® to short- and long-term hematopoietic recovery and its relative contribution to the myeloid and lymphoid hematopoietic lineages reconstitution. This study, completed in 2014, demonstrated prompt and durable engraftment of the expanded graft in 8 of the 11 transplanted patients and showed its potential for multi-lineage hematopoiesis.[33] The novel finding of the NiCord® pilot trial was that cord blood-derived hematopoietic stem and progenitor cells that are expanded *ex vivo* for ([redacted]weeks are capable of out-competing an unmanipulated cord blood graft and providing both rapid engraftment and robust, long-term multilineage hematopoiesis. Results of this study justified further evaluation of NiCord® transplanted as a single graft, without the support of a second un-manipulated CBU.

The second study (GC P#03.01.020) evaluated the ability of NiCord® to provide durable engraftment as a single graft source. [redacted]

The chief aim of the proposed study is to compare the safety and efficacy of NiCord® single *ex vivo* expanded cord blood unit transplantation to unmanipulated cord blood unit transplantation in patients with hematological malignancies following conditioning therapy.

NiCord® could potentially provide a superior graft for unrelated donor transplantation in patients who do not have a matched adult donor option in a timely manner, thereby addressing a critical unmet need in the treatment of hematological malignancies.

3.4. Gamida Cell expansion technology

NiCord® is composed of CB-derived allogeneic stem and progenitor cells expanded *ex vivo* from an entire CBU with cytokines and nicotinamide, a form of the vitamin B3. NiCord® comprises: 1) *ex vivo* expanded, cord blood-derived, hematopoietic CD34+ progenitor cells (NiCord® cultured fraction (CF)); and 2) the non-cultured cell fraction of the same CBU (NiCord® Non-cultured Fraction (NF)) consisting of mature myeloid and lymphoid cells.

NiCord® CF was initially developed as a fresh product [redacted]

The cryopreservation of NiCord® allows flexibility in the planning and timing of transplantation, to accommodate the patient's disease status and any changes required, as resulting from the patient's medical condition.

The expansion technology is based on the finding that nicotinamide, the active molecule, [redacted]

The goal of the *ex vivo* expansion of hematopoietic progenitor cells is to increase their numbers while maintaining their self-renewal capacity and their ability to home to the bone marrow (BM) and efficiently reconstitute hematopoiesis. [redacted]34

This discrepancy could be explained, at least in part, by an acquired defect in the BM homing capacity of HPC expanded *ex vivo*,[35] which is primarily attributed to their active cycling[36] accompanied by alterations in adhesion and chemokine receptor expression or functionality.[37] Strategies to augment the BM homing and engraftment efficacy are particularly important to increase clinical applicability of *ex vivo* expanded CD34+ cells.[38]

Gamida Cell's extensive studies discovered that NAM delays differentiation and increases the engraftment efficacy of cord-blood derived, purified CD133+ cells cultured with a combination of 4-cytokines [redacted] for 19-23 days. [redacted]

To study engraftability [redacted]

NAM serves as a precursor of nicotinamide [redacted]

NAM has also been demonstrated [redacted]

3.5. Clinical experience with NiCord® and CordIn™

In addition to NiCord®, Gamida Cell Ltd. has also undertaken to develop CordIn™. CordIn™ CF was initially developed as a fresh product (referred to as fresh NiCord® CF). NiCord® NF was developed as a cryopreserved product. The manufacture of the cryopreserved NiCord® CF and CordIn™ CF are identical until the final DP testing and release. The manufacturing steps of the fresh NiCord® and the cryopreserved NiCord®/CordIn™ CF are exactly the same until [redacted]. The NiCord® NF and CordIn™ NF drug products remain identical. CordIn™ is intended

for the treatment of subjects with non-malignant diseases including hemoglobinopathies, such as SCD and thalassemia, BM failure syndromes and inherited metabolic disorders.

The clinical experience with NiCord® and CordIn™ is summarized in Table 1 below.

Table 1: Overview of ongoing clinical studies of NiCord®

Protocol Number (ClinicalTrials.gov Number)	**Study Title**	**Study Status**	**Institution/Principal Investigator**
GC P#01.01.020 (NCT01221857[a])	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	Complete	Duke University Health System/ [redacted] Cardinal Bernardin Cancer Center, Loyola University/ [redacted]
GC P#02.01.020 (NCT01590628[b])	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 Hemoglobinopathies	Ongoing	Duke University Health System/ [redacted] Cohen Children's Medical Center of New York/ [redacted]

Protocol Number (ClinicalTrials.gov Number)	Study Title	Study Status	Institution/Principal Investigator
GC P#03.01.020 (NCT01816230[c])	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.	Ongoing	Duke University Health System/ [redacted] Hospital Universitario y Politécnico La Fe/ [redacted] Vanderbilt University Medical Center/ [redacted] Hospital Universitari Vall d'Hebrón/ [redacted] AOU San Luigi Gonzaga/ [redacted] Universitair Medisch Centrum Utrecht/ [redacted] Cedars-Sinai Medical Center/ [redacted] Cleveland Clinic/ [redacted] University of Minnesota/ [redacted] Cardinal Bernardin Cancer Center, Loyola University/ [redacted] Oregon Health & Science University/ [redacted] Singapore General Hospital/ [redacted] National University Cancer Institute/ [redacted]

Protocol Number (ClinicalTrials.gov Number)	Study Title	Study Status	Institution/Principal Investigator
GC P#01.01.030 (NCT02504619[d])	Allogeneic Stem Cell Transplantation of CordIn™, Umbilical Cord Blood-Derived Ex Vivo Expanded Stem and Progenitor Cells, in Patients with Hemoglobinopathies	Ongoing	Benioff Medical Center/ [redacted] Children's National Medical Center/ [redacted] Hopital Robert-Debre/ [redacted]
GC P#04.01.020/030 (NCT02039557[e])	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.	Ongoing	Duke University Health System/ [redacted] Hospital Universitario y Politécnico La Fe/ [redacted] Hospital Universitari Vall d'Hebrón/ [redacted]

[a] http://clinicaltrials.gov/ct2/show/NCT01221857
[b] http://clinicaltrials.gov/ct2/show/NCT01590628
[c] https://clinicaltrials.gov/ct2/show/NCT01816230
[d] https://clinicaltrials.gov/ct2/show/NCT02504619
[e] https://clinicaltrials.gov/ct2/show/NCT02039557

The subsequent sections describe the clinical studies mentioned above.

3.5.1. Study GC P#01.01.020

A pilot clinical study of NiCord® in hematological malignancies in combination with a second, unmanipulated CBU was completed (GC P#01.01.020). This is a single arm pilot study to evaluate the safety of the co-transplantation of NiCord® 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 sibling or matched unrelated adult donor were eligible 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 [redacted] of the recipient's body weight. This unit was designated as the unmanipulated unit. The second unit, designated for NiCord® expansion, contained at least [redacted] of the recipient's body weight. When 2 units with at least [redacted] 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 [redacted] TBI delivered in 9 fractions on days –9 to –5, and fludarabine [redacted] was given on days –5 to –2 of the transplantation. An optional infusion of [redacted] 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.

Main results are described below and in the Clinical Study Report available upon request.[33]

Efficacy: Twelve patients were enrolled and transplanted. Eleven of the twelve transplanted patients achieved neutrophil engraftment with full donor chimerism (<10% host chimerism). Eleven of the twelve transplanted patients were evaluable [redacted]. The median days to neutrophil engraftment in NiCord® recipients achieving engraftment was 12.5 days, ranging from 7 days to 26 days.

[redacted]. The median days to neutrophil engraftment in NiCord® recipients achieving engraftment with NiCord® as the predominating donor source was 10.5 days, ranging from 7 days to 18 days. In comparison, historical reports of unmanipulated CB transplants estimate the median days to engraftment at 23-27 days with a range of 13-80 days.[39,40,41,10] In a historical control group of 17 patients who received unmanipulated DCBT with the same conditioning regimen at the same transplant center, median time to engraftment was 25 days (range 13-38).[33]

All engrafted patients maintained full donor chimerism throughout follow-up.

[redacted]

Platelets engraftment was achieved in nine out of eleven patients who received NiCord®. [redacted]. The median time to platelet engraftment to 20,000/mm^3 was 33 days (range 26-49 days) for all patients transplanted with NiCord® and 30 days (range 26-41) for the 7 patients who demonstrated engraftment with NiCord®. The median days for platelet recovery to 50,000/mm^3 in patients achieving engraftment were 36 days.

Immune reconstitution of engrafted patients was robust. Immune reconstitution analysis of the patients last performed at days 100, 180 and 365 post-transplantation also demonstrated the recovery of all blood cell lineages including CD3, CD4 and CD8 (T cells), CD19 (B cells) and CD56 (NK cells). Immune reconstitution was similar for patients engrafting with the NiCord® unit compared to those engrafting with the unmanipulated CBU.

Safety: There was no grade 4 infusion toxicity.

[redacted]

Conclusions: Infusion of NiCord® was well tolerated and provided rapid short-term engraftment as well as stable, long-term multi-lineage hematopoiesis. The results of this study warranted further studies of NiCord® as a solitary graft source.

3.5.2. Study GC P#03.01.020

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

The dataset that served as the basis for this Phase III study design comprised patients aged 12-65 years old with hematological malignancies and no available matched sibling or matched unrelated adult donor that were eligible at multiple international centers between [redacted]. Eligibility required the availability of a cord blood unit containing at least [redacted] cells as well as a pre-cryopreserved (post-processing) total nucleated cell count of [redacted], and total nucleated cell dose [redacted]. 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.

Main results are described below.

Efficacy: [redacted] patients received NiCord® ([redacted] NiCord®-only recipients and [redacted] patients who received both NiCord® and the backup CBU). All [redacted] NiCord®-only recipients achieved neutrophil engraftment by day 42 with full donor chimerism.

The median days to neutrophil engraftment in NiCord®-only recipients was [redacted] days post transplant, ranging from [redacted] days to [redacted] days. All but [redacted] of these patients engrafted prior to day 18 post transplant.

For NiCord®-only recipients, the cumulative incidence of platelet engraftment to 20k/mm^3 and 50k/mm^3 at 100 days post transplant was [redacted]% [redacted] and [redacted]% [redacted] respectively. [redacted] patients died prior to day 100 without 20k/mm^3 platelet engraftment, [redacted] patient failed to engraft platelets at 20k/mm^3 by day 100, [redacted] patients engrafted 20k/mm^3 but not 50k/mm^3 by day 100, and [redacted] patient was pending engraftment at last follow-up of 88 days post transplant. Among the engrafters, the median time to engraftment to 20k/mm^3 and 50k/mm^3 was [redacted] respectively.

The overall survival of NiCord®-only recipients at 180 and 365 days was [redacted]% [redacted] and [redacted]% [redacted] respectively.

Immune reconstitution of CD4+, CD8+, CD19+, CD56+/16+ in NiCord®-only recipients was comparable to unmanipulated cord blood transplantation in historical controls.

Safety: [redacted] experienced secondary graft failure in the year following NiCord® transplant.

For NiCord® alone recipients, the cumulative incidence of non-relapse mortality at day 100 and day 180 post transplant was [redacted]% [redacted] and [redacted]% [redacted] respectively.

The incidence of acute GvHD grade II-IV and III-IV at 100 days post NiCord® only transplant was [redacted]% [redacted] and [redacted]% [redacted] respectively. [redacted] of the [redacted] NiCord®-only recipients experienced chronic GvHD in the year following NiCord® transplant. [redacted] of chronic GvHD was extensive while the other [redacted] were limited.

Among [redacted] patients receiving NiCord® ([redacted] NiCord® only recipients and [redacted] patients who received both NiCord® and the backup CBU), no grade 4 infusion toxicity occurred. [redacted] NiCord® [redacted] had a grade 3 toxicity (atrial fibrillation), [redacted] patients had grade 2 toxicity, [redacted] patients had grade 1 toxicity, and [redacted] patients had no toxicity within 24-hours post infusion. [redacted] infusion toxicities (grade 2 serious infusion related hypersensitivity and grade 2 non-serious hypertension) were reported as related to NiCord®.

[redacted] SAEs were reported in [redacted] of the [redacted] NiCord® recipients. [redacted] of the [redacted] SAEs reported were determined to be related to NiCord®. These [redacted] related SAEs included [redacted] GvHD events and [redacted] grade 2 infusion-related hypersensitivity.

Of the [redacted] NiCord®-only recipients, [redacted] experienced one or more post transplant grade 2 or 3 infections. Of the [redacted] reported post transplant grade 2 or 3 infections, a total of [redacted] grade 3 infections were reported in [redacted] NiCord® only recipients; [redacted] with a Klebsiella infection at day 325 post transplant, [redacted] with an RSV infection at day 5 post transplant, and [redacted] with [redacted] infections (Klebsiella at day 111 post transplant, Aspergillus at day 119 post transplant and Cryptosporidium at day 126 post transplant).

No new malignancies or autoimmune diseases were reported in any of the transplant recipients.

Conclusions: Infusion of NiCord® was well tolerated and provided rapid short term neutrophil engraftment as well as stable, long term multilineage hematopoiesis. Initiation of a phase III trial evaluating the efficacy of NiCord® compared to unmanipulated cord blood is warranted.

The enrollment is complete and the follow-up is ongoing.

3.5.3. Study GC P#02.01.020

The study GC P#02.01.020 entitled: "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 Hemoglobinopathies" is [redacted] at Duke University Medical Center, NC, USA and Cohen Children's Medical Center of New York. The study is evaluating the transplantation of NiCord® in combination with an unmanipulated CBU, for hematopoietic support of subjects with Sickle Cell Disease (SCD) and Thalassemia major. The study was launched in May 2012.

3.5.4. Study GC P#01.01.030

The study GC P#01.01.030 entitled: "Allogeneic Stem Cell Transplantation of CordIn™, Umbilical Cord Blood-Derived Ex Vivo Expanded Stem and Progenitor Cells, in Patients with Hemoglobinopathies" is [redacted] at Benioff Medical Center and Children's National Medical Center. The study is evaluating the transplantation of CordIn™ as a stand alone graft source, for hematopoietic support of subjects with Sickle Cell Disease (SCD) and Thalassemia major. The study was launched in May 2015.

3.5.5. Study GC P#04.01.020/030

The study GC P#04.01.020/030 entitled: "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." is an ongoing long-term observational study of patients who have received either a NiCord® or CordIn™ transplant. The overall study objective is to describe the clinical outcomes of patients through 5 years post NiCord® or CordIn™ transplantation.

3.6. Overall Risk Benefit

NiCord® 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. NiCord® is intended for the treatment of patients who are medically indicated for allogeneic hematopoietic stem cell transplantation following preparative conditioning, 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. Several technologies are attempting to improve the kinetics of engraftment following CBT, by using dual CBT, whereby one of the CBUs undergoes *ex vivo* manipulation or expansion. Such technologies may shorten the time to neutrophil engraftment; however, the long-term durable hematopoietic recovery is provided by the second, unmanipulated CBU.

The DCBT approach adds a measure of safety to the evaluation of novel approaches to *ex vivo* expansion. However, the use of DCBT has not demonstrated any improvement in the rates or kinetics of engraftment or survival. Unrelated UCBT with NiCord® make it possible to use a single CBT approach.

Clinical data to date suggest that patients treated with NiCord® 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. Available patient follow-up 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 NiCord® 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 NiCord® recipients to date are common effects of allogeneic stem cell transplantation following conditioning regimen therapy.

The chief aim of the proposed study is to compare, in a randomized trial, the safety and efficacy of NiCord® single *ex vivo* expanded cord blood unit transplantation versus unmanipulated cord blood unit transplantation in patients with hematological malignancies following conditioning therapy.

3.7. Rationale for study design and dosages

3.7.1. Study population

As reviewed above, the study will include patients with hematological malignancies for whom allogeneic SCT is currently a recommended and potentially lifesaving treatment. For ethical reasons, the study will only enroll patients who do not have an adequate suitably matched and readily available stem cell donor.

Pediatrics patients aged 12 to < 18 will be enrolled. Inclusion of adolescent patients is justified by the lack of any significant safety or tolerability issues identified to date in completed non-clinical and clinical studies, the strong efficacy profile suggested by the results of the previous clinical studies, and the similarity between adults and adolescents in disease presentation and pathophysiology.

The diseases are considered by transplanters to be biologically similar in adolescent patients of ages 12-18. Adolescent patients usually have a physical mass that is similar to

that of adults, and are thus prone to the same limitations of CBT. Different patients reach this physical mass at different ages, and a clear cut-off cannot be established (as it is more linked to body weight than age). In an effort to allow the inclusion of a broad adolescent population, children above age 12 are included in this clinical study.

3.7.2. CBU cell dose

The CBU intended for expansion is required to contain a pre-cryopreserved (post-processing) total CD34+ cell count of at least [redacted], as well as a pre-cryopreserved (post-processing) total nucleated cell count of at least [redacted], and a total nucleated cell dose of at least [redacted] 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 NiCord®.

This CBU will be used for the NiCord® arm or for the control arm in case of either single or double CBT:

In case this CBU is HLA-matched at 5-6/6 and contains a pre-cryopreserved (post processing) total nucleated cell dose of < [redacted] TNC/kg, OR a pre-cryopreserved (post processing) CD34+ cell dose of < [redacted] CD34+ cells/kg, a second CBU must be added for the control arm, as a double CBT.

In case this CBU is HLA-matched at 4/6 and contains a pre-cryopreserved (post processing) total nucleated cell dose of < [redacted] TNC/kg, OR a pre-cryopreserved (post processing) CD34+ cell dose of < [redacted] CD34+ cells/kg, a second CBU must be added for the control arm, as a double CBT.

This determination must be made by the investigator prior to randomization.

In case of double CBT: The two CBUs must have a combined pre-cryopreserved (post processing) total nucleated cell dose of ≥ [redacted] TNC/kg.

These criteria are intended to assure that CBUs of sufficient cell dose and CD34+ cell dose are used for both the treatment and the control arms, and reflect the published cut-offs for cord blood transplantation, since successful CBT is dependent on sufficient CBU total nucleated cell dose,[42,16,13] and specifically sufficient CD34+ cell dose.[39,14,43] The criteria for CBU selection for the control group are adapted from the formal guidelines for cord blood transplantation.[44]

As a safety precaution in case of production failure, an unmanipulated backup UCB unit or two CBUs are required for patients who will be starting conditioning prior to NiCord release for infusion. It is recommended that these CBU/s comply with the same criteria detailed above for the control group.

In case NiCord® fails to meet its required specifications, and patient conditioning has already started, the backup CBU/s or a different backup source of stem cells will be transplanted as detailed in section 8.3.

As transplantation is considered a life-saving intervention in the study population, the selection of the optimal CBUs is at the investigator's discretion.

3.7.3. Selection of CBUs

Decisions on the selection of CBUs are never arbitrary, but rather 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. Thus, some physicians believe cell dose is of greatest importance, some examine CD34+ dose, and others prioritize HLA matching. 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 one or more 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 one or more 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.

3.7.4. 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. In this study, the choice of conditioning regimen and GvHD prophylaxis agents is kept limited, in order to confirm the use of optimal patient care and to allow for clear interpretation of study results, while still providing the flexibility to choose between TBI-based and non-TBI regimens, and to allow for individual country and site accepted practices and experience.

In general, each transplant center should commit to use the same conditioning regimen and GvHD prophylaxis for all patients transplanted at their center, or according to primary diagnosis/age group. The intended practice must be documented prospectively for the transplant center. In unique cases where the use of a different conditioning regimen is deemed to be in the patient's best interest, approval from the study chairs must be obtained prior to use of the different regimen.

<u>Regimen A.1 (Day -11 to -2):</u>

- Total Body irradiation (TBI) [redacted] cGy total or [redacted] cGy total
- Fludarabine: [redacted] mg/m^2 total
- Thiotepa [redacted] mg/kg total

<u>Regimen A.2 (Day -8 or -7 to -1):</u>

- Total Body irradiation (TBI) [redacted] cGy total or [redacted] cGy total

- Fludarabine: [redacted] mg/m^2 total
- Cyclophosphamide [redacted] mg/kg total

Due to the high reported TRM of myeloablative regimens utilizing TBI/flu/cy,[12] some centers have stopped the use of this regimen and have started to use TBI/flu/Thiotepa instead. Therefore, the study allows the use of Thiotepa instead of cyclophosphamide in Regimen A.1.

Regimen B (Day -7 to -3):

- Thiotepa [redacted] mg/kg total
- Busulfan [redacted] mg/kg total or [redacted] mg/kg total
- Fludarabine [redacted] mg/m^2 total

3.7.5. Study endpoints

The study aims to compare the safety and efficacy of NiCord® transplantation to unmanipulated cord blood unit transplantation in patients with hematological malignancies. The primary endpoint is the time to neutrophil engraftment following transplantation.

This endpoint reflects the importance of early engraftment following CBT and the consideration of the limited patient population which does not allow demonstrating a significant survival benefit of NiCord®. Prompt and robust engraftment of neutrophils is the most notable milestone on the way to hematopoietic recovery following stem cell transplantation. This can be demonstrated by the delay in neutrophil engraftment compared to other stem cell sources.[10,11] Recent multicenter publications from the USA and from Europe continue to report similar hematopoietic recoveries for both double and single UCB, with median 22 and 23 days to neutrophil engraftment in adults.[12,13]

Publications reviewing the differences in outcomes between UCB and other graft sources consistently report higher non-relapse mortality following CBT, generally attributable to inadequate hematopoietic recovery.[10,11] Brunstein et al. emphasized that delayed engraftment is the single greatest barrier to successful CBT and the most important contributor to early NRM. Ruggeri et al. reported the outcomes of 1268 patients with acute leukemia undergoing single CBT in EBMT centers.[13] With the finding that longer time to engraftment was associated with increased transplant-related mortality and lower overall survival, the authors recommended rescue actions for graft failure, such as the search for another graft, starting after day 21 following transplant.

For the secondary endpoints, the trial data may have sufficient power to show an improvement in the NiCord® group compared to the Control group and these endpoints will be subjected to formal statistical significance testing using Hommel's method for multiple comparisons. The tertiary and exploratory endpoints include (i) those where NiCord® is anticipated to be superior to Control, but where there is low statistical power to demonstrate this, and (ii) those where NiCord® is anticipated to be no worse than Control; the p-values for the tertiary and exploratory endpoints will be presented but the family-wise error rate for these endpoints will not be controlled.

Delayed hematopoietic recovery can result in an increased occurrence or higher severity of complications after transplantation, such as infections. These sometimes lead to substantial organ damage, which may be irreversible, and also death. As a consequence, patients require longer durations of hospitalization, involving more intensive supportive care measures. Thus, these events of infections, prolonged hospitalization, and non-relapse mortality are assessed in the secondary and tertiary endpoints.

Platelet engraftment will be assessed by the time from transplantation to platelet engraftment, and by a secondary endpoint of platelet engraftment by 42 days following transplantation. Delayed platelet engraftment is a frequent complication after CBT associated with increased TRM and poorer overall survival. Kim et al.[45] claimed that platelet counts can be used to predict the risk of chronic GvHD development and prognosis after allogeneic PB transplantation - overall survival, and NRM. Ramirez et al. found that delayed platelet recovery was most common after CBT, in comparison to unrelated or sibling BM or PB grafts.[20] Delayed platelet recovery adversely impacted both TRM and overall survival.

Rapid hematopoietic recovery is anticipated to reduce the risk of infections. In particular, bacterial and fungal infections predominate in the early months after transplant and are dependent on rapid and robust neutrophil recovery.[46,47,48,49,50,51,52,53] Therefore, an additional secondary endpoint will be the incidence of bacterial infections (grade 2-3) and invasive fungal infections occurring up to 100 days post transplant.

In line with the incidence of post-transplant complications, recipients of UCB transplants also require longer durations of hospital stay. Ballen et al. compared total hospital length of stay in the first 100 days after HSCT in 1577 patients with acute leukemia in remission receiving UCB, MUD or MMUD HSCT.[54] For adults receiving HSCT using myeloablative conditioning, median days alive and out of hospital in the first 100 days were 52 for single UCB, 55 for double UCB, 69 for MUD BM, 75 for MUD peripheral blood stem cells (PBSC), 63 for MMUD BM and 67 days MMUD PBSC recipients. Multivariate analysis showed that UCB recipients had fewer days alive and out of the hospital compared to other graft sources. The study will assess the number of days each subject is alive and out of hospital in the first 100 days following transplantation as a secondary endpoint.

Such post-transplant complications may result in death, and thus the transplant-related mortality, as reflected by non-relapse mortality at 210 days following randomization (approximately 6 months post transplant), will be assessed as a tertiary endpoint.

Further explanations are provided below for the timing of two of the exploratory endpoints.

Viral infections occur primarily throughout the first year after transplant, in parallel to the recovery of the immune system. Grade 3 viral infections will be assessed in the context of the exploratory endpoints, where NiCord® is anticipated to be no worse than controls, as a safety assessment, and therefore will be assessed at a longer-term timepoint of 180 days and 1 year following transplantation.

NiCord® *ex vivo* expansion is aimed to provide rapid hematopoietic recovery, overcoming the known delay in CBT compared to other graft sources. Thus, neutrophil

engraftment by 16 days following transplantation will be assessed as an additional exploratory endpoint, a cut-off which reflects the usual time of neutrophil engraftment in matched peripheral blood donor transplants.[55,11]

4. STUDY OBJECTIVES, HYPOTHESIS AND STUDY ENDPOINTS

4.1. Objectives

The overall study objective is to compare the safety and efficacy of NiCord® single *ex vivo* expanded cord blood unit transplantation to unmanipulated cord blood unit transplantation in patients with hematological malignancies following conditioning therapy as follows:

Primary Objective:

Assess the time to neutrophil engraftment following transplantation.

Neutrophil engraftment is defined as achieving an absolute neutrophil count (ANC) ≥ 0.5 x 10^9/L on 3 consecutive measurements on different days with subsequent donor chimerism (≤10% host cells by peripheral blood chimerism or bone marrow chimerism if peripheral blood chimerism is not available). The day of neutrophil engraftment is designated as the first of the 3 consecutive measurements and must occur on or before 42 days post transplant (and also prior to infusion of any additional stem cell product).

Secondary Objective

To assess the following:

Secondary Endpoints:

- Incidence of grade 2/3 bacterial or invasive fungal infections by 100 days following transplantation
- Days alive and out of hospital in the first 100 days following transplantation
- Platelet engraftment by 42 days following transplantation

Tertiary Endpoint:

- Non-relapse mortality by 210 days following randomization

Exploratory Endpoints:

- Neutrophil engraftment by 16 days following transplantation
- Time from transplantation to platelet engraftment
- Duration of primary hospitalization
- Non-relapse mortality by 130 days and 15 months following randomization
- Overall survival at 210 days and 15 months following randomization
- Disease-free survival at 15 months following randomization
- Neutrophil engraftment by 42 days following transplantation
- Acute GvHD grade II-IV and III-IV by 100 days following transplantation

- Chronic GvHD (mild/moderate/severe) by 180 days and 1 year following transplantation
- Secondary graft failure by 1 year following transplantation
- Grade 3 viral infections by 180 days and 1 year following transplantation
- Safety and tolerability of NiCord® transplantation
- Relapse by 15 months following randomization
- Relapse mortality by 15 months following randomization
- Immune reconstitution at 28, 70, 100, 180, and 365 days following transplantation
- Supplemental immune reconstitution assessments at a central laboratory (optional)
- Health-related quality of life
- Long-term clinical outcomes up to 5 years following transplantation (optional)

Study Hypothesis

NiCord® as a standalone graft will improve post-transplant outcomes compared to Unmanipulated CBT.

4.2. Definition of study endpoints

4.2.1. Date of randomization

The date of randomization is defined as the date that the patient's treatment assignment is issued.

4.2.2. Date of transplant

The date of transplant is defined as the first date of stem cell infusion following randomization, regardless of stem cell source.

4.2.3. Neutrophil engraftment

Neutrophil engraftment is defined as achieving an absolute neutrophil count (ANC) $\geq 0.5 \times 10^9$/L on 3 consecutive measurements on different days with subsequent donor chimerism ($\leq$ 10% host cells by peripheral blood chimerism or bone marrow chimerism if peripheral blood chimerism is not available) at any time on or after the day of engraftment up to the earlier of day 100 post-transplant, date of relapse, date of secondary graft failure, or date of death. The first day of the three measurements will be designated the day of neutrophil engraftment and must occur on or before 42 days post transplant (and also prior to infusion of any additional stem cell product).

Primary graft failure is defined as failure to achieve neutrophil engraftment by day 42 as described above. Infusion of a second stem cell product on or prior to Day 42 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.

The date of primary graft failure will be designated as day 43 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. The earlier of the first day of severe neutropenia, as defined above, or the date of additional stem cell infusion will be designated the date of secondary graft failure.

4.2.4. Platelet engraftment

Platelet engraftment 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 and must occur prior to any infusion of a second stem cell product.

4.2.5. Grade 2/3 Bacterial Infections and grade 3 Viral infections

See Appendix G for infection grading criteria.

4.2.6. Invasive fungal infection

Invasive fungal infection is defined as any grade 3 fungal infection. See Appendix G for infection grading criteria.

4.2.7. Duration of primary hospitalization

Duration of primary hospitalization is defined as the total number of days from transplant to first discharge from the hospital. [redacted].

4.2.8. Days alive and out of hospital

A day alive and out of hospital is defined as a full day (calendar day) in which the patient was alive and not hospitalized. Partial days alive and out of hospital, such as the day of admission, day of discharge and day of death, do not count as a day alive and out of hospital. The day of transplant will not count as a day alive and out of hospital regardless of whether the patient is treated as an inpatient or outpatient.

4.2.9. Overall survival

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

4.2.10. Disease Relapse

Relapse of malignancy - testing for recurrent malignancy in the blood, marrow or other sites will be used to assess relapse after transplantation. For the purpose of this study, relapse is defined by either morphological or cytogenetic evidence of AML, ALL, CML, or MDS consistent with pre-transplant features.

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. Since the frequency of testing for minimal residual disease is highly variable among centers, and the sensitivity is highly variable among laboratory techniques, evidence of minimal residual disease alone will not be sufficient to meet the definition of relapse in the context of this trial. However, minimal residual disease that progresses can be considered as relapse and the date of relapse will be the date of detection of minimal residual disease, as described below.

Acute Leukemia - Relapse can be defined as any of the following.

[redacted]

- [redacted]

Chronic Myelogenous Leukemia (CML)

[redacted] Hematologic relapse can be diagnosed when:

[redacted]

Cytogenetic relapse can be diagnosed when:

[redacted].

MDS

Relapse can be defined as any of the following.

[redacted]:

- [redacted]

Lymphoma

Relapse can be defined according to the criteria in Table 2 and/or one or more of the following criteria:

[redacted]

4.2.11. Disease-free survival

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

4.2.12. Non-Relapse Mortality

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

4.2.13. Relapse Mortality

Relapse mortality is defined as any death preceded by relapse.

4.2.14. 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.

4.2.15. Chronic GvHD

Chronic GvHD will be assessed on the day of diagnosis, as well as on day 100, 180, 270 and year 1 post transplant and classified as mild/moderate/severe according to the 2014 NIH consensus criteria (Appendix B).

4.2.16. Immune Reconstitution

Immune reconstitution will be assessed on days 28, 70, 100, 180, and 365. Cellular immune recovery will be assessed based on lymphocyte subset analysis to quantify the numbers and proportions of different lymphocyte subpopulations (CD3, CD4, CD8, CD19, CD56/16). Additional assessments requested (but not required) are: CD123+ (dendritic lymphocytes), CD11c+ (dendritic myeloid cells), CD3+CD56+CD16+ (NKT cells), CD45RA+/CD62L+(RTE), CD25+/CD62L+(T-Reg), Total CD25+, CD57+/CD28+(CTL), HLA-DR+(Activated), and quantitative immunoglobulins (and record of IVIG administrations). In patients enrolled in the optional immune reconstitution sub-study, additional exploratory immunologic parameters will be assessed.

4.2.17. Health-Related Quality of Life (HQL)

Patient-reported health-related quality of life (HQL) outcomes will be assessed during the trial using two standardized measures including the Functional Assessment of Cancer Therapy –Bone Marrow Transplant Module (FACT BMT) and the EuroQol EQ-5D, which have been reported in previous trials involving bone marrow transplant patients.[56,57]

4.2.17.1. FACT-BMT

The Functional Assessment of Cancer Therapy –Bone Marrow Transplant (FACT-BMT) Version 4 is a self-administered instrument designed to assess multidimensional aspects of the QOL in BMT patients.

[redacted]

The FACT-BMT is estimated to take approximately 20 minutes to complete.

For patients <18 years old, a validated adapted version has been issued,

[redacted].

4.2.17.2. EQ-5D

The EQ-5D descriptive system of health-related quality of life states consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of three responses.

[redacted]

[redacted]. The EQ-5D is estimated to take approximately 1 minute to complete.

4.2.18. Safety and Tolerability of NiCord® Transplantation

The safety and tolerability of NiCord® transplantation will be evaluated as described in section 10.6.

4.2.19. Other Definitions

4.2.19.1. Response Criteria for Acute Leukemia

- [redacted].

4.2.19.2. Complete Morphologic Remission for CML from Prior Blast Crisis

- [redacted].

4.2.19.3. CML Stages

Chronic phase is defined as:

[redacted]

Accelerated phase is defined as:

- [redacted]

Blasts Crisis is defined as:

- [redacted]

4.2.19.4. Response Criteria for Lymphoma

Response criteria for lymphoma are described in Table 2 below:

Table 2: Response Definitions for Lymphoma[58]

Response Definitions for Clinical Trials				
Response	**Definition**	**Nodal Masses**	**Spleen, Liver**	**Bone Marrow**
CR	**Disappearance of all evidence of disease**	[redacted]		
PR	**Regression of measurable disease and no new sites**			
SD	**Failure to attain CR/PR or PD**			
Relapse disease or PD	**Any new lesion or increase by ≥50% of previously involved sites from nadir**			

Abbreviations: CR, complete remission; FDG [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

5. STUDY POPULATION

5.1. Number of patients

The study will randomize 120 eligible patients in a 1:1 ratio to receive either NiCord® or unmanipulated cord blood transplantation.

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 randomization or as termination/discontinuation if dropout occurs after randomization. Screening failures may be replaced.

For discontinuation patients who do not withdraw consent, the study investigator will make all reasonable efforts to gather information on the clinical outcomes as assessed during the usual clinical management of their disease for the duration of their scheduled follow-up and to capture this information in the CRF.

5.2. Analysis populations

The screened population consists of all subjects who signed informed consent.

Intent-to-Treat (ITT) population includes all patients randomized into the trial, classified in the treatment groups to which they were allocated. Analysis of the ITT population provides the primary analysis of the primary endpoint, and also the primary analyses of the secondary endpoints, tertiary endpoint, and the analyses of the exploratory endpoints unless otherwise stated.

Transplanted (TP) population includes all patients randomized who received a cord blood transplant within 90 days following randomization. Patients are assigned to the treatment groups to which they were allocated. Analysis of the TP population provides the analyses for the exploratory endpoints that depend on transplant, such as graft versus host disease.

As treated (AT) population includes all patients randomized who received a cord blood transplant within 90 days following randomization, grouped by treatment actually performed. Analysis of the AT population is for supportive purposes.

ANC engrafted population (AEP) includes all subjects who received a cord blood transplant within 90 days following randomization and achieved ANC engraftment; analysis is focused on the treatment actually performed. Analysis of the AEP population is for supportive purposes.

Platelets engrafted population (PEP) includes all subjects who received a cord blood transplant within 90 days following randomization and achieved platelet engraftment; analysis is focused on the treatment actually performed. Analysis of the PEP population is for supportive purposes.

Safety population (SP) is identical to the AT population defined above.

5.3. Eligibility criteria

Patients 12-65 years of age with a diagnosis of hematological malignancy who are candidates for unrelated cord blood transplantation, with qualifying HLA-matched UCB units with sufficient pre-cryopreserved total nucleated cell dose and CD34+ cell dose, as follows:

- **Treatment CBU #1:**

Patients must have a 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 ≥[redacted] as well as a pre-cryopreserved (post processing) total nucleated cell count of ≥[redacted] and total nucleated cell dose ≥[redacted] TNC/kg. The CBU will have undergone volume reduction (both plasma and red blood cell depletion) prior to cryopreservation.

  - Treatment CBU #1 will be used for the NiCord® arm or for the control arm in case of either single or double CBT.
  - Verification typing (confirmatory typing) must be completed prior to CBU shipment

- **Treatment CBU #2** (to be used for the control arm in case of double cord transplantation)**:**

In case treatment CBU #1 is HLA-matched at 5-6/6 and contains a pre-cryopreserved (post processing) total nucleated cell dose of <[redacted] TNC/kg, OR a pre-cryopreserved (post processing) CD34+ cell dose of <[redacted] CD34+ cells/kg, a second CBU must be added for the control arm, as a double CBT.

In case treatment CBU #1 is HLA-matched at 4/6 and contains a pre-cryopreserved (post processing), total nucleated cell dose of <[redacted] TNC/kg, OR a pre-cryopreserved (post processing), CD34+ cell dose of <[redacted] CD34+ cells/kg, a second CBU must be added for the control arm, as a double CBT.

The determination of using a single or double cord in the control arm must be made by the investigator prior to randomization.

  - Treatment CBU #2 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. Treatment CBUs #1 and #2 must have a combined pre-cryopreserved (post processing) total nucleated cell dose of ≥[redacted] TNC/kg.

Detailed eligibility criteria are provided below; **note that all eligibility testing must be completed and resulted, and entered into [redacted] before randomization:**

Inclusion Criteria

1. Patients must be 12-65 years of age at the time of randomization
2. Patients with one of the following hematological malignancies:

- Acute lymphoblastic leukemia (ALL) at one of the following stages:

- Acute myelogenous leukemia (AML) at one of the following stages:

- Chronic myelogenous leukemia (CML) at one of the following phases:

- CMMoL or MDS/CMMoL overlap with spleen size <
- Myelodysplastic Syndrome (MDS) with history of one or more of the following:

[redacted]

- Biphenotypic/undifferentiated/Prolymphocytic/Dendritic Cell Leukemias and Natural Killer Cell Malignancies [redacted], adult T-cell leukemia/lymphoma [redacted]
- Lymphoma, meeting one of more of the following criteria: Burkitt's lymphoma [redacted]

  OR

  - High risk lymphomas [redacted], including, enteropathy-associated T cell lymphoma, or hepatosplenic gammadelta T cell lymphoma

  OR

  - Chemotherapy-sensitive (defined as at least stable disease) lymphomas that have failed at least 1 prior regimen of multi-agent chemotherapy and are not candidates for an autologous transplant.

    (Patients with CLL are not eligible regardless of disease status)

3. CBU criteria as described above.
4. Patients who will be starting conditioning prior to NiCord release for infusion (i.e., NiCord arrival on site in adequate condition) must have an additional partially HLA-matched CBU, reserved as a backup to the NiCord arm in case of production failure. 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. A second backup CBU is recommended to be added in the below cases:

   - If the back-up CBU is HLA-matched at 5 or 6/6and contains a pre-cryopreserved (post processing) total nucleated cell dose of < [redacted] TNC/kg, OR a pre-cryopreserved (post processing) CD34+ cell dose of < [redacted] CD34+ cells/kg
   - If the back-up CBU is HLA-matched at 4/6and contains a pre-cryopreserved (post processing) total nucleated cell dose of < [redacted] TNC/kg, OR a pre-cryopreserved (post processing) CD34+ cell dose of < [redacted] CD34+ cells/kg

   In case of two back-up CBUs, the second back-up 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. The back-up CBUs are recommended to have a combined pre-cryopreserved (post processing) total nucleated cell dose of at least [redacted] TNC/kg.
5. Patient's Performance score ≥70% by Karnofsky or Lansky

6. Patient has sufficient physiologic reserves including:
    a. Cardiac:
    b. Pulmonary function tests
    c. Renal:
    d. Hepatic:
7. Females of childbearing potential, defined as
8. 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. MDS or CML with "marked" or "3+" fibrosis
2. CLL
3. Fewer than 21 days have elapsed since initiation of the patient's last chemotherapy cycle and the initiation of the stem cell transplant preparative regimen
4. Persistent clinically significant toxicities that, in the investigator's opinion, make the patient unsuitable for transplant
5. Evidence of donor specific anti-HLA antibodies to the selected treatment CBU #1 (MFI>3000 to HLA A, B, C, or DRB1)
6. Evidence of HIV infection or HIV positive serology
7. Evidence of active Hepatitis B or Hepatitis C as determined by serology or PCR

8. Pregnancy, [redacted]
9. Active malignancy other than that for which the UCB transplant is being performed within 12 months of enrollment. Fully resected cutaneous squamous cell or basal cell carcinoma or cervical carcinoma in situ within 12 months of enrollment will be permitted.
10. Evidence of uncontrolled bacterial, fungal or viral infections or severe concomitant diseases, [redacted]
11. Patients with presence of leukemic blasts in the central nervous system (CNS)
12. Patients with an 8/8 allele level HLA-matched and readily available related or 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 will not be excluded.
13. Prior allogeneic hematopoietic stem cell transplant
14. Allergy to bovine products, gentamicin, or to any other product that may interfere with the treatment
15. Psychologically incapable [redacted]
16. Enrolled in another interventional clinical trial or received an investigational treatment within 30 days prior to the anticipated date of randomization, [redacted]

6. CONCOMITANT MEDICATIONS AND SUPPORTIVE CARE

Required conditioning and supportive care regimens are outlined below. Modifications and dose adjustments based on toxicity risk according to institutional guidelines may be made upon review and approval of a study chairperson.

6.1. Previous medications

All medications taken by/given to the patient, as a treatment for the primary and concomitant diseases within 30 days prior to screening, will be recorded in the patient files.

All chemotherapy and radiotherapy courses administered to the patient, as prior treatment for his/her hematological malignancy, will be recorded in the CRF (including treatment regimen, number of cycles, and dates).

6.2. Disallowed concomitant medications

The following medications should not be given post transplant:

- Any cytokines except G-CSF should not be used (including IL-2 or others, [redacted]).
- The use of Bactrim (sulfamethoxazole and trimethoprim) or methotrexate [redacted]
- Maintenance therapies [redacted]
- See section 6.14 for limitations regarding the use of investigational agents

6.3. Conditioning regimen

All patients will receive one of the conditioning regimens shown in Table 3 below. Each transplant center must commit to use the same conditioning regimen for all patients transplanted at their center, or according to primary diagnosis/age group. The intended practice must be documented prospectively for the transplant center. In unique cases where the use of a different conditioning regimen is deemed to be in the patient's best interest, approval from one of the study chairs must be obtained prior to use of the different regimen. Prior to randomization, the investigator will decide and document the conditioning regimen intended to be used for transplantation.

Table 3: Conditioning regimens

Regimen A.1

Study day / Treatment	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0
TBI [redacted] cGy in 8 or 9 fractions[b]			x2 or x1 or x0	x2	x2	x2	x0 or x1 or x2				REST	Infusion of NiCord® or Unmanipulated CBU/s
Fludarabine[a] [redacted] mg/m^2 IV							x	x	x	x		
Thiotepa[a] [redacted] mg/kg IV	x	x										

[a] Adjusted body weight
[b] Or TBI [redacted] cGy, administered as per institutional practice

Regimen A.2

Study day / Treatment	-8	-7	-6	-5	-4	-3	-2	-1	0
TBI [redacted] cGy in 8 fractions[c]				REST[b]	x2	x2	x2	x2	Infusion of NiCord® or Unmanipulated CBU/s
Fludarabine [redacted] mg/m^2 IV	x	x	x						
Cyclophosphamide[a] [redacted] mg/kg IV	x	x							

[a] Adjusted body weight
[b] A day of rest may be included between the last dose of Fludarabine and the start of TBI (as shown above). Alternatively, the day of rest may be moved to day -1 without any rest between Fludarabine and TBI (TBI on day -5, -4, -3, -2) or the day of rest may be omitted altogether (Cyclophosphamide on day -7 and -6 and Fludarabine on day -7, -6 and -5)
[c] Or TBI [redacted] cGy, administered as per institutional practice

Regimen B

Study Day / Treatment	-7	-6	-5	-4	-3	-2	-1	0
Thiotepa[a] [redacted] mg/kg IV	x	x				REST		Infusion of NiCord® or Unmanipulated CBU/s
Busulfan[a] [redacted] mg/kg IV or weight based dosing + TDM[$]		x[b]	x	x	x			

Study Day / Treatment	-7	-6	-5	-4	-3	-2	-1	0
Fludarabine[a] [redacted]mg/m^2 IV			x	x	x			

[a] Adjusted body weight
[b] Can be added as per institutional practice
[$]TDM= therapeutic drug monitoring: aiming for cumulative target AUC (Area Under the Curve) = 75mg*h/L. Bu levels after 1st dose will be measured at 5min, 1h, 2h and 4h after end of Bu infusion and AUC will be calculated based on previously described population PK model.[59]

6.3.1. Radiotherapy (Regimen A)

Patients may be treated either in the AP/PA position and/or in the right and left lateral position. Compensators or blocks may be used to compensate for the thinner parts of the anatomy (head, neck, lower legs and feet).

Regimen A.1: Total dose will be [redacted]cGy in 8 or 9 fractions over 4 or 5 days. Two fractions on the same day will be given at a minimum of 6 hours apart from beam on to beam on. Alternatively, a total dose of [redacted]cGy can be administered, fractionated as per institutional practice.

Regimen A.2: A dose of [redacted]cGy will be administered twice daily on days outlined in Table 3 for a total dose of [redacted]cGy. Alternatively, a total dose of [redacted]cGy can be administered, fractionated as per institutional practice.

Risks and Toxicities:

TBI can cause: nausea and vomiting, diarrhea, parotitis (rapid onset within 24-48 hours, usually self-limited), generalized mild erythema, hyperpigmentation, fever, mucositis and alopecia. Late effects include: possible growth retardation, vertebral deformities, cataracts, probable increased risk of secondary malignant neoplasms, sterility, nephropathy, interstitial pneumonitis and veno-occlusive disease.

6.3.2. Fludarabine Administration (Regimens A and B)

Regimen A.1: Fludarabine [redacted]mg/m^2/day will be administered as an IV infusion on days -5 through -2. For patients weighing more than 125% of their ideal body weight (IBW), Fludarabine will be dosed as per adjusted body weight (see section 6.3.6). For all other patients, dosing is according to the actual body weight.

Regimen A.2: Fludarabine [redacted]mg/m^2/day will be administered as an IV infusion on days outlined in Table 3. The dose is calculated based on actual body weight (ABW). The dose will be adjusted if the GFR or eGFR is $\leq$ 70ml/min/m^2.

Regimen B: Fludarabine [redacted]mg/m^2/day will be administered as an IV infusion on days -5 through -3. For patients weighing more than 125% of their IBW, Fludarabine will be dosed as per adjusted body weight (see section 6.3.6). For patients weighing less than their IBW, dosing is according to the actual body weight. For all other patients, dosing is according to the ideal body weight.

Refer to Appendix F, 'Drug Labels', for risks and toxicities of Fludarabine administration.

6.3.3. Cyclophosphamide (CY) Administration (Regimen A.2)

Refer to Appendix F, 'Drug Labels', for risks and toxicities of cyclophosphamide administration.

Cyclophosphamide [redacted]mg/kg/day will be administered on days outlined in Table 3 as an IV infusion. The dose will be administered after a high volume fluid flush and mesna administration per institutional guidelines.

For patients weighing more than 30kg above their IBW, cyclophosphamide will be dosed based on the adjusted body weight (see section 6.3.6). For all other patients, dosing is according to the actual body weight.

6.3.4. Thiotepa Administration (Regimen A.1 and B)

Regimen A.1: Thiotepa [redacted]mg/kg/day will be administered as an IV infusion on days -11 and -10. For patients weighing more than 125% of their IBW, Thiotepa will be dosed as per adjusted body weight (see section 6.3.6). For all other patients, dosing is according to the actual body weight.

Regimen B: Thiotepa [redacted]mg/kg/day will be administered as an IV infusion on days -7 and -6. For patients weighing more than 125% of their IBW, Thiotepa will be dosed as per adjusted body weight (see section 6.3.6). For patients weighing less than their IBW, dosing is according to the actual body weight. For all other patients, dosing is according to the ideal body weight.

Refer to Appendix F, 'Drug Labels', for risks and toxicities of Thiotepa administration.

6.3.5. Busulfan Administration (Regimen B)

Busulfan [redacted] mg/kg/day will be administered as an IV infusion or in four separate IV infusions every six hours on days -5 (or -6 per institutional practice) through -3. For patients weighing more than 125% of their IBW, Busulfan will be dosed as per adjusted body weight (see section 6.3.6). For patients weighing less than their IBW, dosing is according to the actual body weight. For all other patients, dosing is according to the ideal body weight. Alternatively, Busulfan will be dosed according to previously described weight based dosing[59] + TDM: dose will be adjusted (if necessary) on the second day to achieve a cumulative Busulfan exposure (AUC) after 3 days of 75 mg*h/L.

Doses and schedule for anti-seizure prophylaxis should follow local institutional guidelines.

Refer to Appendix F, 'Drug Labels', for risks and toxicities of Busulfan administration.

6.3.6. Dose adjustment formulas

The following are dose adjustment formulas:

- **Ideal Body Weight (IBW) formulas:**
  - Males IBW = 50 kg+2.3 kg/inch over 5 feet (or 50 kg + 0.91kg/cm over 152.4cm)
  - Females IBW = 45.5 kg+2.3 kg/inch over 5 feet (or 45.5 kg + 0.91kg/cm over 152.4cm)
- **Adjusted Body Weight formula:**
  - **Regimen A.1/A.2:** Adjusted body weight = IBW+[(0.25)x(ABW-IBW)]
  - **Regimen B:** Adjusted body weight = IBW+[(0.4)x(ABW-IBW)]

6.4. GvHD prophylaxis medications

All patients will receive GvHD prophylaxis with two drugs as follows:

Calcineurin inhibitor (Tacrolimus or Cyclosporine)

Each transplant center must commit to use the same calcineurin inhibitor (Tacrolimus or Cyclosporine) for all patients transplanted at their center. In unique cases where the use of a different calcineurin inhibitor is deemed to be in the patient's best interest, approval from the study chairs must be obtained prior to use of the different calcineurin inhibitor Prior to randomization, the investigator will decide and document the GvHD prophylaxis intended to be used for transplantation.

Tacrolimus or Cyclosporine from day -3 to at least day +100.

- Recommended target Tacrolimus trough blood levels of 5-15 ng/ml.
- If administering via continuous IV infusion, it is recommended to target Cyclosporine trough levels of 200-400 ng/mL by TDX method (or equivalent level for other CSA testing methods). For intermittent dosing, it is recommended to target Cyclosporine trough levels of 150-400 ng/mL by TDX method (or equivalent level for other CSA testing methods).

In the event of toxicity, suspected relapse or the development/worsening of GvHD, dosing may be adjusted per institutional standard practice or a different drug may be substituted. In the absence of actual toxicity, calcineurin inhibitor taper can begin at day +100 at the earliest, at the discretion of the managing physician, with the goal for discontinuation at day 180-200. Refer to Appendix F, 'Drug Labels', for risks and toxicities of Tacrolimus and Cyclosporine administration.

Mycophenolate Mofetil (MMF)

Mycophenolate Mofetil (MMF) (or Mycophenolate Sodium) will be given at a dose of [redacted]mg/kg TID (based upon actual body weight) with the maximum total daily dose not to exceed 3 grams (IV or PO rounded to the nearest capsule size) beginning day -3 to at least day +60. In the event of toxicity or suspected relapse, dosing may be adjusted per

institutional standard practice or a different drug may be substituted. Refer to Appendix F, 'Drug Labels', for risks and toxicities of Mycophenolate Mofetil administration.

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

All patients will receive the following medications 30-60 mins prior to NiCord® or unmanipulated CBU infusion.

- Diphenhydramine [redacted]mg IV or PO (or [redacted] mg/kg up to a maximum of [redacted]mg) or Dexchlorpheniramine [redacted]mg IV
- Hydrocortisone [redacted]mg IV (or [redacted] mg/kg up to a maximum of [redacted]mg)
- Acetaminophen/Paracetamol [redacted]mg IV or PO (or [redacted] mg/kg up to a maximum of [redacted]mg)

Changes to the above medications for infusion support can be allowed, but must be approved by the Sponsor prior to transplantation.

Methylprednisolone should not be used in conjunction with standard delivery of NiCord® or unmanipulated CBU to the patient. 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) 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 through the second day of ANC >1,000/µl for 2 consecutive days.

6.9. Blood Products

Thrombocytopenia: Platelet counts should be maintained at >10,000/µL 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 NiCord® 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 pathophysiology is poorly understood, but is thought to be multifactorial mediated by cellular, complement and cytokine components.

Diagnostic criteria include fever (temperature >38.5°C) without an identifiable infectious cause prior to or with neutrophil recovery with or without an erythematous rash or capillary leak (weight gain, edema, ascites, effusions) or respiratory symptoms not attributable to IPS. Mild symptoms may not require therapy due to the self-limiting nature of this syndrome. Methylprednisolone should not be given as prophylaxis for engraftment syndrome prevention. For progressive symptoms, methylprednisolone at 2 mg/kg/day is recommended with tapering once response is achieved. If recurrent or prolonged, investigation for GvHD is recommended.

6.11. Infection Prophylaxis and Surveillance

Unless otherwise specified below, institutional guidelines will be followed to provide prophylaxis for infections. In general, each transplant center should use the same anti-microbial prophylaxis regimens for all patients transplanted at their center, apart from unique cases where the use of a different anti-microbial agent is deemed to be in the patient's best interest. 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

Anti-bacterial prophylaxis is required. 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 will be administered after engraftment. The timing and choice of drug and dosages are at the discretion of the investigator. 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 with agents such as fluconazole, itraconazole, voriconazole, or posaconazole.

6.11.5. Toxoplasmosis Prophylaxis

It is recommended for patients to be screened prior to transplantation for toxoplasmosis exposure. Those who are IgG seropositive for toxoplasmosis are at significant risk for life-threatening infection, and prophylaxis is recommended.

6.11.6. CMV Surveillance

All recipients must be tested for CMV (using the PCR method) at least once during the conditioning period, at the weekly protocol specified visits (see protocol section 7.9.2) up through day 42 and then on day 56, 70 and day 100 or more frequently as clinically indicated. Antiviral therapy for CMV reactivation should 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.

6.11.7. HHV6 Surveillance

Quantitative HHV6 DNA assessment by PCR must be tested at weekly protocol specified visits after transplantation until absolute neutrophil count >500 cells/microliter. Treatment is strongly recommended if symptomatic or following 2 weeks of rising viral load or an absolute count above 10k copies/ml. If HHV6 reactivation occurs at or before engraftment, treatment with foscarnet is recommended.

6.11.8. EBV Surveillance

Quantitative EBV viral load assessment by PCR must be tested at protocol specified visits on days 21, 56, and 100 post transplant, or more frequently as clinically indicated, and at protocol specified visits on days 180, 270, and 365 post transplant if the patient is still on immunosuppression. Patients with a positive result (>1000 copies) should be treated as per institutional guidelines. Rituximab treatment is recommended.

6.11.9. 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.

6.11.10. Intravenous Immune Globulin

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

6.11.11. Identification of Infectious Agents – Recommendations

6.11.11.1. Blood Cultures

Blood cultures should be taken at the presentation of fever prior to initiating antibiotics. In the event of clinical deterioration, suspicion of line infection, or chills following initiation of broad-spectrum antibiotics, additional cultures should be taken. Repeat cultures for subsequent episodes of fever or persistent fever unresponsive to antibiotics.

6.11.11.2. Blood Culture Procedure

It is recommended that blood cultures be sampled twice per procedure. Each sample should be tested for both aerobic and anaerobic organisms. One sample should come from the peripheral blood and one sample from the central line (or a second sample from the peripheral blood if the central line is no longer in use). If a peripheral blood draw is not successful and the patient has a central line with multiple lumens, then draw one sample from each lumen.

6.11.11.3. Additional Identification Procedures

The following procedures are recommended in patients with suspected infection:

- Chest X-ray
- Sinus CT in patients with suspected sinusitis
- Diarrhea: Clostridium difficile toxin PCR to be determined once in patients with clinical suspicion. Viral diagnostics (rotavirus, adenovirus, norovirus, astrovirus) in patients with clinical suspicion of infectious cause.
- Urine culture in patients with suspected infection of indwelling catheter
- CSF culture in patients with suspected meningitis
- Skin lesions: biopsy or aspirate, for culture, Gram stain, GMS and cytology.
- Pulmonary source of infection: sputum culture in patients with productive cough. Consider viral diagnostics using viral throat swab, especially in season: Influenza A and B, RSV, Coronavirus, Rhinovirus, Bocavirus, Para-influenza, Human metapneumovirus and mycoplasm. BAL in patients with chest HRCT abnormalities.

6.11.12. Treatment of Infections

Patients undergoing the conditioning treatment outlined in this study are expected to develop immunodeficiency. Therefore, the approach to the diagnosis and treatment of fever in such patients should be an aggressive one. If any infections occur, they will be treated per institutional practice and will be recorded in the source documents and in the e-CRF. As standard treatment practices differ between institutions, will evolve over time, and vary by patient circumstances, we do not prescribe a specific approach to treatment. Rather, it is the responsibility of the treating physician to manage infections according to their institutional best practices.

6.11.13. Discharge Instructions and Follow-up

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. The transplant center should attempt weekly contact with patients through day 70 to ask about infectious symptoms and any other medical events or treatments. Transplant centers will continue with monthly contact from day 70 to the completion of follow-up (day 365).

6.12. Nutrition

All patients will be candidates for total parenteral nutrition; length of use is at the attending physician's discretion.

6.13. Guidelines for Infusing a Second Stem Cell Product

A second transplant should not be considered unless the patient has impending or actual graft failure. In the event of impending or actual graft failure then the patient may be treated per institutional guidelines. As standard treatment practices differ between institutions, will evolve over time, and vary by patient circumstances, we do not prescribe a specific approach to treatment. Rather, it is the responsibility of the treating physician to manage graft failure according to their institutional best practices.

6.14. Investigational Agents

Unless approved by the Sponsor, investigational agents should not be administered from 30 days prior to randomization until the end of study follow-up for all patients randomized.

For patients enrolled in the post-randomization follow-up segment (see section 7.5) the Sponsor approval is not required.

6.15. 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, from time of signature on the IC until the end of the study, will be recorded in the source documents. The reason for administration should be clearly stated and, as applicable, also documented as contributing to an SAE. Concomitant medication reporting on the eCRF will follow the guidelines detailed in the Data Management Handbook.

Rescue equipment (oxygen) and drugs such as hydrocortisone, epinephrine (other inotropic agents), and antihistamines should be available at the transplantation unit and will be administered at the investigator's discretion.

Table 4: Evaluations and examinations flow sheet

Schedule of Assessments Summary
[redacted]

Schedule of Assessments Summary

[redacted]

Schedule of Assessments Summary

[redacted]

[1] [redacted]

[2] Before signing informed consent and according to CBUs matching criteria as detailed in section 5.3 of the protocol. After consent, the CBU documents for the CBU selected for expansion (treatment CBU #1) must be redacted and uploaded to [redacted] prior to randomization.

[3] Signed consent is required prior to performing any protocol specific tests or procedures that are not part of the standard site practice. The ICF signature can be obtained earlier than [redacted] weeks prior to randomization.

[4] All eligibility criteria must be met prior to randomization. Unless otherwise indicated, screening and eligibility testing must be performed and resulted within [redacted] weeks prior to randomization.

[5] Infectious disease markers must include: HIV I/II Ab, HTLV I/II Ab, HBsAg, HBcAb, HCV Ab, VZV Ab, syphilis Ab (such as RPR), EBV Ab, and CMV screen (IgG or Total).

[6] Tests performed within 4 weeks prior to randomization are acceptable.

[7] Test results from within 9 weeks prior to randomization are acceptable. Chest X-ray is not mandatory if a chest CT or MRI was performed

[8] Verification typing (confirmatory typing) must be performed and resulted prior to CBU shipment to the Production site. Extended high resolution typing at HLA -A, -B, -C, -DRB1 is also required for the patient and CBU#1 but (with the exception of -DRB1) can be performed after randomization unless anti-HLA antibody testing reveals a positive result (MFI>3000) at HLA A, B, C, or DRB1. If assigned to the control arm and treatment CBU #2 is selected, then HLA -A, -B, -C, -DRB1 high resolution typing is also required for treatment CBU #2; ABO and Rh typing is also required for the patient, CBU#1 and CBU#2 (if applicable)

[9] Baseline disease assessment should be as close as possible to randomization to minimize findings of relapse during CBU expansion. Specific requirements for the timing of this assessment are provided in section 7.2.2 . [redacted]

[10] Temperature, blood pressure and pulse at all visits; Weight through day 100 visit Respiratory rate through day 1 post-transplant.

[11] Including height, weight, and BSA.

[12] CBC performed at screening, daily from Day 0 until neutrophil engraftment, and at all study visits post transplant. Starting on transplant day, differentials required if WBC ≥0.5. Blood chemistries must include (at a minimum): serum creatinine, total bilirubin, alkaline phosphatase, AST, ALT, and magnesium (at screening, day -1 (creatinine only), day 0 and then at least twice weekly until Day 28, and weekly after Day 28 until 10 weeks post-transplant; at 100 days, 6 months, 9 months, and 1 year post-transplant).

[13] All concomitant medications and blood products administered, including total number of RBC and platelet units transfused, from time of signature on the IC until the end of the study, will be recorded in the source documents and the reason for administration should be clearly stated. Concomitant medications will also be recorded in the e-CRF as detailed in the Data Management Handbook.

[14] Including standard of care cardiac and pulmonary monitoring

[15] On days 28, 70, 100, 180, and 365, site will perform a basic lymphocyte subset analysis (CD3, CD4, CD8, CD19, CD56/16) locally. Additional assessments requested (but not required) are: CD123+ (dendritic lymphocytes), CD11c+ (dendritic myeloid cells), CD3+CD56+CD16+ (NKT cells), CD45RA+/CD62L+(RTE), CD25+/CD62L+(T-Reg), Total CD25+, CD57+/CD28+(CTL), HLA-DR+(Activated), and quantitative immunoglobulins (In case quantitative immunoglobulins are assessed, a record of the most recent IVIG administrations is required).

[16] [redacted]

[17] Measured by molecular methods, in whole blood or myeloid at day 21 or day 28 and at days 42, 100, 180, and 365. Bone marrow chimerism is an acceptable alternative.

[18] Day 7 GvHD assessment must be done on day 7 post transplant. All the other Day 7 assessments can be done until day 10 post-transplant included

[19] All recipients must be tested for CMV (using the PCR method) at least once during the conditioning period (see section 6.11.6).

[20] Not required if patient no longer on immunosuppression

[21] Beginning after the Day 100 visit, the site will continue at least monthly contact with the subject until day 365 visit. If there is no hospital or clinic visit scheduled at the transplant center for more than 30 days, then a member of the study team will contact the subject via phone or email within 35 days from the last contact to inquire about adverse events, hospitalizations, infections, and medication changes (including transfusions). This contact will be documented in the subject's medical or research record.

[22] The patient survival and relapse status should be assessed at 15 months or later post-randomization

[23] Samples to be shipped to a central laboratory for analysis. See details in section 7.9.2

[24] Serum or urine beta HCG can be collected up to 4 weeks before randomization

[25] HRQoL not required if a survey is not available in the patient's primary language. Refer to protocol section 7.9.3 for details on HRQoL administration.

[26] Flow cytometry on BM or PB sample if judged necessary by the treating physician

[27] It is not mandatory to repeat molecular markers tests that were negative at diagnosis

[28] If positive: BM aspirate with morphology, cytogenetics and quantitative RT-PCR BCR/ABL

[29] Serum or urine beta HCG can be collected up to 2 weeks before randomization

Table 5: Follow-Up Assessments for Patients Who Do Not Receive a Transplant within 90 Days of Randomization

Post Randomization Follow Up Forms Submission Schedule

Forms	Visit Days post Randomization				
	090	130	210	365	457[#]
[redacted]					

[#] 15-month assessment of survival and relapse must be on or after 15 months post randomization

* HRQoL Questionnaires are requested if possible, but not mandatory

7. DETAILED STUDY PLAN

7.1. Pre-screening activities search for matching CBUs

Potential candidates for CBT for whom a search yielded eligible CBUs, as described below, will be identified as screen candidates for the study.

Treatment CBU#1

Patients must have a 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 [redacted] as well as a pre-cryopreserved (post processing) total nucleated cell count of [redacted] and total nucleated cell dose [redacted] TNC/kg. The CBU will have undergone volume reduction (both plasma and red blood cell depletion) prior to cryopreservation.

Treatment CBU #2 (to be used for the control arm in case of double cord transplantation)

- In case treatment CBU #1 is HLA-matched at 5-6/6 and contains a pre-cryopreserved (post processing) total nucleated cell dose of [redacted] TNC/kg, OR a pre-cryopreserved (post processing) CD34+ cell dose of [redacted] CD34+ cells/kg, a second CBU must be added for the control arm, as a double CBT.
- In case treatment CBU #1 is HLA-matched at 4/6 and contains a pre-cryopreserved (post processing) total nucleated cell dose of [redacted] TNC/kg, OR a pre-cryopreserved (post processing) CD34+ cell dose of [redacted] CD34+ cells/kg, a second CBU must be added for the control arm, as a double CBT.

The determination of using a single or double cord in the control arm must be made by the investigator prior to randomization.

Treatment CBU #2, if selected, 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. Treatment CBUs #1 and #2 must have a combined pre-cryopreserved (post processing) total nucleated cell dose of ≥[redacted] TNC/kg.

Backup CBUs

Patients who will be starting conditioning prior to NiCord release for infusion must have an additional partially HLA-matched CBU reserved as a backup to the NiCord arm (in case of NiCord production failure). 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. A second back-up CBU is recommended to be added in the below cases:

- If the back-up CBU is HLA-matched at 5 or 6/6 and contains a pre-cryopreserved (post processing) total nucleated cell dose of <[redacted] TNC/kg, OR a pre-cryopreserved (post processing) CD34+ cell dose of <[redacted] CD34+ cells/kg.

- If the back-up CBU is HLA-matched at 4/6 and contains a pre-cryopreserved (post processing) total nucleated cell dose of < [redacted] TNC/kg, OR a pre-cryopreserved (post processing) CD34+ cell dose of < [redacted] CD34+ cells/kg.

In case of two back-up CBUs, the second back-up CBU must also 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. The back-up CBUs are recommended to have a combined pre-cryopreserved (post processing) total nucleated cell dose of at least [redacted] TNC/kg.

Treatment CBU #2 (to be used for the control arm in case of double cord transplantation) can be used also as a backup CBU for the NiCord arm, if it meets the above requirements.

In case NiCord® fails to meet its required specifications, and patient conditioning has already started, the backup CBU/s or a different backup source of stem cells will be transplanted as detailed in section 8.3.

It is strongly recommended to consider all necessary backup graft options for the patient in case of any other problems that may occur during graft procurement or preparation, taking into account the required urgency, as deemed necessary by the patient's condition.

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 case the CBU is ineligible, 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 filed in the patient's file.

Once matching CBUs have been found, the patient will be required to sign a written informed consent for cord blood access as per Institutional and National requirements.

The CBU documents of the CBU selected for expansion (treatment CBU #1) must be redacted and uploaded to [redacted] prior to randomization. If the search results contain more than one unit that meets the minimum cell dose and HLA match requirements for treatment CBU #1, it is recommended that all CBU documents for expansion eligible units be sent to the SLM – designating the investigator's primary and secondary choices. At the request of the investigator, the SLM can send the CBU documents to the study chairs for further discussion on the best available unit.

7.2. Screening Assessments

7.2.1. Informed Consent and Registration

A conference will be held with the patient and family to discuss this study and alternative treatments 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. 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 randomization to transplant should be discussed, taking into account the period of 3 weeks for manufacturing on the research arm, 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 using the [redacted] system: Within three business days of consent, an authorized user at the transplant center enters the patient demographics and enrollment information in [redacted]. The Screening Enrollment Form includes a question confirming the patient (or legal guardian) signed the informed consent. Each patient will be assigned a study number by the [redacted] system.

Since the study is an open label study, Gamida Cell (GC) took upon themselves a level of blinding as appropriate measures to minimize bias. Therefore, the sites should not contact GC with any patient specific questions other than to the SLM concerning HLA typing and CBU selection.

7.2.2. Eligibility and Baseline Assessments ([redacted] weeks prior to randomization)

Unless otherwise specified, eligibility and baseline assessments must be scheduled within ([redacted] weeks prior to randomization. Tests performed during the pre-screening period according to the Centers' routine evaluation of candidates for stem cell transplantation need not be repeated, provided they were performed recently enough, as detailed below.

Patient's eligibility for the study will be assessed. The activities will be performed as detailed in Table 4 and will include:

- Baseline evaluation:
  - Medical history including primary and concomitant diseases.
  - Primary disease characteristics including subtype, status, and cytogenetics
  - Concomitant medications will be recorded in the patient's medical record.
  - Patients' performance score by Karnofsky or Lansky scale
  - Health-Related Quality of Life patient self-report questionnaires (See section 7.9.3 for further details)
  - Physical examination and vital signs (including height, weight and BSA)
  - Laboratory: CBC
  - Blood chemistry (serum creatinine, total bilirubin, alkaline phosphatase, AST, ALT, and magnesium *at a minimum*)

- Serum or urine beta HCG (females) (tests from within 2 weeks prior to randomization are acceptable)
- Complete urinalysis including microscopic examination
- Anti-HLA antibody testing at HLA A, B, C, and DRB1 must be performed (tests from 4 weeks prior to randomization are acceptable) 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.
- Chest X-ray (results from within 9 weeks prior to randomization are acceptable; A chest X-ray is not mandatory if a chest CT or MRI was performed).
- Disease Assessment
  - Prior to Randomization:
    - For Lymphoma patients: CT scan or PET-CT chest, abdomen, pelvis (tests from within 9 weeks prior to randomization are acceptable)
    - 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.
      - For MDS and CML patients, aspiration is required. If the screening aspiration sample from a patient with MDS or CML is without evaluable spicules, then a bone marrow assessment must be performed with a biopsy to rule out the possibility of severe fibrosis Biopsy is also required at screening if at any point since diagnosis fibrosis was noted on a prior biopsy
      - For ALL, AML and other leukemia (not including MDS and CML) patients, an aspiration is sufficient (a biopsy is not mandatory).
      - For Lymphoma - when clinically indicated: aspiration and/or biopsy
    - To minimize findings of relapse during CBU expansion, bone marrow must be assessed within the following timelines (excursions up to seven days from the required window are acceptable in cases where randomization is delayed):
      - For the following patients, bone marrow morphology must be assessed within [redacted] weeks prior to randomization:
        - MDS patients [redacted],

- CML patients [redacted]
- For all other MDS and leukemia patients, bone marrow morphology must be assessed within ([redacted] weeks prior to randomization

BM FACS analysis/flow cytometry for AML, ALL, and other leukemia (not including MDS and CML) patients.

- Assessment of CNS disease is per institutional practice. [redacted]

- Prior to Conditioning:
  - BM FACS analysis/flow cytometry for MDS and CML patients if sample available; - no need to repeat BM procedure.
  - Cytogenetics and molecular markers for MDS/Leukemia patients (it is not mandatory to repeat any molecular markers tests that were negative at diagnosis).

– Serologic infectious disease markers for HIV I/II Ab, HTLV I/II Ab, HBsAg, HBcAb, HCV Ab, VZV Ab, Syphilis Ab (such as RPR), EBV Ab, and CMV Screen (IgG or Total)

– Physiologic reserves assessment:
  - Pulmonary Function Tests [redacted]
  - 12 lead EKG [redacted]
  - Echocardiography or MUGA [redacted]

– (optional for patients who consented to the Immune reconstitution sub-study: collect blood samples for T-cell receptor analysis see separate paragraph under section 7.9.2)

- CBU requirements:
  – Treatment CBU #1 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

- Treatment CBU #1 must be reserved by the site prior to randomization and 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. High resolution typing (with the exception of DRB1) does not need to be completed prior to randomization unless anti-HLA antibody testing reveals a potential donor-specific positive result (MFI>3000) at HLA A, B, C, or DRB1.
- Peripheral blood baseline sample for chimerism (anytime during the screening period or post randomization prior to conditioning)

Once all eligibility testing has been completed, an authorized user at the transplant center enters the patient eligibility information in [redacted].

The investigator (or designee) must document in the source documents and in [redacted] the following information:

- Disease characteristics including subtype, status, and cytogenetics
- Screening results from flow cytometry test for minimal residual disease (ALL, AML, and other leukemia (not including MDS and CML) patients only)
- The primary unit to be used for either expansion or as the unmanipulated CBU.
- Intended use of single or double cord in the event the patient is randomized to the unmanipulated CBU arm
  - If the investigator chooses to perform a double cord transplant in the event of randomization to the unmanipulated CBU arm, then the additional unit should also be identified and CBU documents uploaded to [redacted].
- Confirmation of back-up CBU(s) reservation, if applicable
- Intended conditioning regimen (regimen A1, regimen A2, or regimen B) and GvHD prophylaxis (cyclosporine or tacrolimus).

The decisions to use single or double cord for the unmanipulated CBU arm, the conditioning regimen and the GvHD prophylaxis are binding and cannot be modified according to the treatment allocation.

Unless otherwise noted, all above mentioned activities must be completed, and entered into [redacted] prior to randomization.

7.3. Randomization

Before randomization, the PI or physician designee must confirm that the patient is eligible to randomize per protocol requirements, by signing off the eligibility checklist or documenting the patient eligibility in the patient's medical records.

When all eligibility information is entered, the PI (or designee) signs the confirmation of eligibility in [redacted], which confirms that all eligibility information entered is accurate and complete, and the patient is eligible to randomize per protocol requirements. Then, the system generates the treatment assignment for the registered patient and an email confirmation is sent; **this assignment page or email confirmation must be printed and saved in the Patient Study Binder**. The treatment assignment is immediately displayed to the individual entering the information and an email is immediately sent to the site, the Sponsor and Emmes.

7.4. CBU shipment and receipt

7.4.1. NiCord® arm – CBU shipment and receipt at the production site

Following randomization to the NiCord® arm, SLM review of all CBU documentation uploaded into [redacted] and SLM approval of the Treatment CBU#1 for production, the clinical site will immediately discuss shipment and production timelines with the SLM, and alert the CBB/Registry to immediately send the selected CBU for NiCord® expansion to the production site. The limit for CBU arrival to the production site is two working days before the start of production. Qualified personnel at the production site will ensure that this is the requested CBU to be manipulated for the patient according to communication with the SLM and based on the CBU accompanying documentation (according to the relevant Manufacturer's SOP).

7.4.2. NiCord® arm – post production release and shipping

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

[redacted]

NiCord® CF, NiCord® NF with all available CBU segments/samples, and the infusion solution are either shipped immediately following manufacturing or stored at the manufacturing facility until they are shipped to the clinical site.

NiCord® 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 NiCord® CF and NF.

The shipment of NiCord® 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, NiCord® CF and NF should be kept in a controlled Liquid Nitrogen central storage (≤ -150°C) and the Infusion solution bags should be kept in a 2-8°C refrigerator until transplantation.

7.4.3. Unmanipulated CBU arm – CBU shipment and receipt at the clinical site

Following randomization to the Unmanipulated CBU arm, the clinical site will alert the CBB(s) to send the selected CBU(s) to their site. Receipt and storage of the CBU(s) will be according to site standard practice.

7.5. Post Randomization Follow-Up

In the event of a failure to transplant the patient (with any stem cell source) within 90 days post randomization, the following assessments are required at (±21) 90, 130, 210, and 365 days post randomization:

- Survival status
- Infection history (Grade 2 & 3 infections through Day 130 and Grade 3 viral infections through Day 365)
- Relapse history
- Optional (whenever possible): Health-Related QoL patient self-report questionnaires (See section 7.9.3 for further details)
- Disease assessment for patients who did not relapse after randomization, including the following as clinically indicated.

[redacted]

CML patients:

[redacted]

[redacted]

Lymphoma patients:

[redacted]

In addition, the patient survival and relapse status should be assessed at 15 months or later post-randomization.

7.6. Transplant Suitability Confirmation: (within 24 hours prior to start of conditioning)

Confirm that the patient is still suitable for transplant according to standard site practice. The primary investigator, or designee, must sign a statement within 24 hours prior to the start of conditioning indicating that the patient remains suitable for transplant. Patients no longer suitable for transplant will be treated according to investigator's discretion and will be followed for one year post randomization, as per section 7.5.

History of grade 2/3 infections from randomization to the start of conditioning will be assessed and recorded in the study CRF.

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.

7.7. 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. Patient monitoring during the conditioning phase will be conducted per site practice with a mandatory assessment at day -1 (assessments from as early as day -3 are acceptable) to include:

- Physical examination
- Vital signs
- CBC and 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 6.11.6)
- Documentation of historical and concomitant medications

7.8. Transplantation Day (Day 0)

Safety Assessment

Prior to the transplantation of NiCord® or the unmanipulated CBU(s), the patient will be evaluated by the investigator or designee including:

- Physical Examination
- CBC with WBC differential (differential not required if WBC<0.5) and blood chemistry (serum creatinine, total bilirubin, alkaline phosphatase, AST, ALT and magnesium, at a minimum). These lab tests should be resulted before the study product infusion.
- Vital Signs: weight, temperature, blood pressure, pulse, and respiratory rate
- Concomitant medication including RBC and platelet transfusions

7.8.1. Preparation and Infusion of NiCord® or the Unmanipulated CBU(s)

7.8.1.1. Preparation and Infusion of the Unmanipulated CBU(s)

Patients assigned to the Unmanipulated CBU arm will receive a transplant of treatment CBU#1 (and treatment CBU #2 if applicable) according to institutional best practice. The unmanipulated CBU(s) should be thawed and diluted by trained personnel using institutional procedures.

Post-thawing data:

If the Unmanipulated CBU(s) has/have been tested for TNC count, Percent viability, Total CD34+ cell count, Total CD3+ cell count and Total number of colonies in product (CFU-GM + CFU-GEMM + BFU-E), this should be reported into [redacted] .

The unmanipulated CBU(s) should not be irradiated under any circumstances.

Pre-medication prior to cord blood infusion should be administered according to section 6.7 (hydration should be administered per institutional procedure). The immediate pre-transplant evaluation will be carried out according to the operating procedures of the participating institutions and should be in keeping with the data reporting requirements of this study.

The unmanipulated CBU(s) should be infused via the patient's central venous catheter as per site practice. It is recommended that the infusion should target a rate of 5 cc/kg/hr with a maximal rate of 10 cc/kg/hr. The unmanipulated CBU(s) should be infused as soon as possible after thaw. 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.

7.8.1.2. Thawing and Infusion of NiCord® on Day 0

NiCord® should not be irradiated under any circumstances.

In case stored at a local CBB until the transplant day, NiCord® 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, NiCord® 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 NiCord® 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 NiCord® CF and NiCord® 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 NiCord® CF after thawing and reconstitution is [redacted]ml.

The final volume of NiCord® NF after thawing and reconstitution is [redacted]ml.

Pre-medication prior to cord blood infusion should be administered according to section 6.7 (hydration should be administered per institutional procedure). The immediate pre-transplant evaluation will be carried out according to the operating procedures of the participating institutions and should be in keeping with the data reporting requirements of this study.

NiCord® CF will be infused first, followed immediately [redacted] by the infusion of NiCord® NF.

NiCord® CF and NiCord® NF should be infused via the patient's central venous catheter as per site practice. NiCord 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 NiCord® CF and NiCord® NF should target a rate of 5 cc/kg/hr with a maximal rate of 10 cc/kg/hr. NiCord® CF and NiCord® NF should be infused as soon as possible after thaw.

- Total duration of NiCord® CF infusion will target [redacted] from end of thaw to end of infusion, while considering the minimal infusion time specified in the product's CoA.
- Total duration of NiCord® NF infusion will not exceed [redacted] 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.

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.

7.8.2. Evaluation and Treatment of IPQC/FPQC Safety Tests Failure

The following safety quality control test results may not be available at the time the patient is transplanted:

[redacted]

In the event that one of these tests proves positive, the transplant site will be notified and the following steps will be implemented:

1. Blood cultures will be drawn
2. Antibiotic coverage will be modified such that the known isolate will be adequately covered
3. Antibiotic coverage will be discontinued if blood cultures prove negative and antibiotic cessation is clinically indicated

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

7.8.3. Post Transplantation Follow-Up ([redacted])

The following assessments are mandatory:

- Vital signs: weight, temperature, blood pressure, pulse, and respiratory rate
- Toxicity assessment 24 hours post transplant.
  - For the NiCord® arm: from the start of NiCord® CF infusion up to 24 hours after end of NiCord® NF infusion.
  - For the Control arm: from the start of the unmanipulated CBU infusion up to 24 hours after the end of the infusion (or end of CBU#2 infusion, if applicable)
- G-CSF administered as specified in section 6.8

7.9. Scheduled treatment visits Post Transplant (as detailed in Table 4: Evaluations and examinations flow sheet)

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 including RBC and platelet transfusions
- Vital Signs – Weight, temperature, blood pressure and pulse; additional measurements per institutional practice
- CBC with WBC differential (differential not required if WBC<0.5)
- Infection prophylaxis and surveillance as specified in section 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 on days [redacted]

[redacted] visit: All the assessments can be done until Day [redacted] post-transplant included, except for the acute GvHD assessment that must be performed at Day [redacted])

The following assessments are mandatory:

- Information about AEs, hospitalizations, infections, and concomitant medications (including RBC and platelet transfusions) will be recorded in the patient's medical record. Concomitant medications will also be recorded in the eCRF as detailed in the Data Management Handbook.
- Health-Related Quality of Life self-report questionnaires (days [redacted]) (See section 7.9.3 for further details)
- Vital signs:
    - Temperature, blood pressure and pulse at each scheduled post-transplant visit
    - Weight at each scheduled post transplant visit through day 100

  (Additional measurements per institutional practice)
- Physical examination: days [redacted] including standard of care cardiac and pulmonary monitoring
- Patients' performance score by Karnofsky or Lansky scale: [redacted]

- CBC with WBC differential (differential not required if WBC<0.5)
- Blood chemistry (serum creatinine, total bilirubin, alkaline phosphatase, AST, ALT and magnesium, at a minimum) - at least twice weekly until Day [redacted], and weekly after Day [redacted] until 10 weeks post-transplant; at days [redacted] post-transplant
- Disease assessment:

  Disease assessment must be done on days [redacted] post transplant as follows. Further tests as clinically indicated should be performed to assess for disease relapse on days [redacted]. Additional assessments may be performed according to the treating physician's best judgment.

  - Leukemia and MDS patients:
    - Clinical evaluation for relapse per physician's judgement (Days [redacted])
    - CBC with differential (Days [redacted])
    - Bone marrow morphology (Days [redacted])
    - Flow cytometry on BM or PB sample if judged necessary by the treating physician (Days [redacted])
    - Cytogenetics and molecular markers as appropriate; It is not mandatory to repeat molecular makers tests that were negative at diagnosis (Days [redacted])
  - CML patients:
    - Clinical evaluation for relapse per physician's judgement (Days [redacted])
    - Quantitative RT-PCR BCR/ABL in peripheral blood. If positive, BM morphology, cytogenetics, and quantitative RT-PCR BCR/ABL (Days [redacted])
  - Lymphoma patients:
    - Clinical evaluation for relapse per physician's judgement (Days [redacted])
    - CT scan or PET-CT (Days [redacted])
    - When clinically indicated: BM morphology (Day [redacted])
- CMV PCR: at the weekly protocol specified visits [redacted] and then on day [redacted] and day [redacted] or more frequently as clinically indicated.
- EBV PCR: at protocol specified visits [redacted] (or more frequently as clinically indicated) and at days [redacted] (if patient is on immunosuppression).

- HHV6 DNA assessment by PCR at each weekly protocol specified visit after transplantation until ANC >500 or until visit at day [redacted].
- Peripheral blood collection for whole blood or myeloid donor/host chimerism (at day [redacted] and at days [redacted] only). Bone marrow chimerism is an acceptable alternative to peripheral blood.
- Lymphocyte subsets (CD3, CD4, CD8, CD19, CD56/16) on days [redacted].
    - Additional assessments requested (but not required) are: CD123+ (dendritic lymphocytes), CD11c+ (dendritic myeloid cells), CD3+CD56+CD16+ (NKT cells), CD45RA+/CD62L+(RTE), CD25+/CD62L+(T-Reg), Total CD25+, CD57+/CD28+(CTL), HLA-DR+(Activated), and quantitative immunoglobulins (in case quantitative immunoglobulins are assessed, a record of the most recent IVIG administrations is required).
- GvHD assessment:
    - Acute: At every visit up to day 180 post transplant, or more frequently as clinically indicated, Acute GvHD will be assessed according to the Consensus Conference on Acute GvHD grading (Appendix B). Day [redacted] GvHD assessment must be done on day [redacted].
    - Chronic: on the day of diagnosis, as well as on days [redacted] post transplant or more frequently as clinically indicated. Chronic GvHD will be assessed and classified mild, moderate, or severe, according to the 2014 National Institute of Health consensus grading criteria (Appendix B).

      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; Unless approved by the sponsor, either the provided worksheet or an equivalent EMR adaptation of the form approved by the sponsor must be used to document chronic GvHD.
- GvHD prophylaxis as specified in section 6.4
- G-CSF administered as specified in section 6.8
- Infection prophylaxis as specified in section 6.11
- Beginning after the Day 100 visit, the site will continue at least monthly contact with the subject until the day [redacted] visit. If there is no hospital or clinic visit scheduled at the transplant center for more than 30 days, then a member of the study team will contact the subject via phone or email within 35 days from the last contact to inquire about adverse events, hospitalizations, infections, and medication changes (including transfusions). This contact will be documented in the subject's medical or research record.

- The patient survival and relapse status should be assessed at 15 months or later post-randomization.

Optional supplemental immune reconstitution sub-study

An optional supplemental immune reconstitution sub-study will explore immune biomarkers potentially predicting clinical outcomes such as relapse, engraftment and viral reactivation/disease. Blood samples for exploratory research of immune reconstitution will be collected from the patients who consent to this sub-study for immunophenotyping and MultiPlex analyses (on days [redacted] visits) as well as for T cell receptor analysis (at screening and on days [redacted] visits). These samples will be sent to a central laboratory for analysis as detailed in a separate research study plan.

7.9.3. Administration of Health-Related Quality of Life Measures

The self-report questionnaires and patient declaration page will be completed prior to randomization and subsequently at [redacted] days from transplantation or until death or discontinuation from the study. For patients who were not transplanted within 90 days post randomization, or for those who relapsed or had graft failure, the completion of these questionnaires is requested if possible, but not mandatory; the FACT-BMT can be completed from home via a computer if needed (the URL will be provided by the site). Surveys are completed by participants using self-completed instruments made available during routine scheduled clinic visits. The method of survey completion, the date, and the language will be recorded in the database. Surveys may not be completed by surrogates. It is recommended to complete the surveys prior to any other physical testing required at the visit.

Only patients able to read and speak one of the languages available in the developer-approved translations are eligible to participate in the HQL component of this trial. Likewise, if the paper version of the EQ-5D questionnaire is not available in the developer-approved translation at the patient's transplant center, and the self-completed instrument cannot be made available, the patient will not be required to complete these questionnaires.

Table 6: Required Patient-reported Outcomes Data Collection[a]

Instrument	[redacted]					
FACT-BMT						
EQ-5D						
TOTAL						
ANTICIPATED TIME		25-30 min	25-30 min	25-30 min	25-30 min	25-30 min

[a] For patients who were not transplanted within [redacted] days post randomization these assessments are requested (but not required) at [redacted] days post randomization. The completion of the questionnaires is also requested, but not mandatory for the following: 1) after relapse post transplant 2) after the [redacted] questionnaire for patients who did not have primary engraftment, 3) after secondary graft failure.
* For patients <18 years old, number of items = 43

7.9.4. Assessment of Medical Resource Utilization (MRU)

MRU will be captured throughout the study by recording units of medical resources consumed during the trial period on study case report forms to examine potential differences between treatment groups in drivers of MRU that are not driven by protocol. The types of MRU data that will be recorded include hospital resources (hospitalizations by setting), specialty procedures, drugs and supportive care, and complications.

7.9.5. Evaluation and Treatment of Graft Failure

Evaluation of Graft Failure: Should a patient suffer 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;
- Chimerism studies;
- Viral/bacterial cultures including serology and PCR analysis for Herpes viruses (including fun and HHV6); and
- Anti-HLA antibody measurements.

For primary graft failure, the assessments listed above are recommended on day 21 if WBC is <= 0.1 $x10^9$/L.

Treatment of Graft Failure: If the patient has less than 100 PMN 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 performed.

7.9.6. 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 randomized. Patients will be defined as screening failures when withdrawn from the study before randomization. Reason for screening failures will be outlined in the study reports.

Patients who were randomized but do not receive a stem cell transplant within 90 days post randomization are part of the intent to treat analysis and should be followed for Grade 2 and 3 infections, survival status, relapse, and HQL at [redacted]days post randomization with an additional assessment of survival and relapse status at 15 months post randomization, according to section 7.5. All other assessments are not required for these patients unless they receive a stem cell transplant within 90 days post randomization, at which point they would be followed according to section 7.9. For early withdrawal patients who withdraw or are withdrawn from the study post transplant, any assessments due at the time of withdrawal (according to Table 4) are requested.

Patients who experience graft failure or relapse post transplant will continue to be followed according to the study visit schedule for hospitalizations, grade 2 and 3 infections, relapse (except patients with prior post-transplant relapse), graft failure (except patients with prior post-transplant graft failure), survival status, and HQL. For these patients, all SAEs will be reported until at least 30 days post transplant. After day 30 post transplant and following date of relapse or graft failure only SAEs resulting in death or with suspected causal relationship to the infused product will be reported. No other study related assessments are required for these subjects after the date of graft failure or relapse.

7.9.7. 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 trial center on the clinical outcomes as assessed during the usual clinical management of their disease over the study period. This will allow us to continue to gather clinical information on patients who subsequently discontinue active participation and did not withdraw informed consent, and to include them in the analyses of all clinical endpoints.

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

7.10. Optional Long term follow-up

For patients enrolled in the optional long term follow-up sub-study, information on the following, performed as per the standard of care at individual institutions, will be collected:

- Vital signs and physical examination
- Donor/host chimerism and secondary graft failure
- Lab analysis: CBC and Immunophenotyping (lymphocytes subsets and additional Immunophenotyping as per site practice)
- Karnofsky/Lansky performance status score
- GvHD assessment
- Survival and disease status (progression/relapse, new malignancy, non-relapse mortality, primary and contributing cause of death)

Data may be obtained by review of medical records from the transplant center, through the patient's primary care physician, and/or contact by phone at the time points 2 years, 3 years, 4 years and 5 years post-transplantation.

7.11. Data reporting

7.11.1. Criteria for Forms Submission

Criteria for timeliness of submission for all study forms are detailed in the Data Management Handbook and [redacted] User's Guide. Forms not entered into [redacted] within the specified time will be considered delinquent. A missing form will continue to be requested either until the form is entered into [redacted] and integrated into the Data Coordinating Center's (DCC) master database or until a form exception is granted and entered into the missing form exception file, as detailed in the Data Management Handbook. Adverse Events will be reported as outlined in section 9 of this protocol.

8. STUDY MEDICATION

8.1. Description

8.1.1. NiCord®

NiCord® is a cryopreserved cell-based product of allogeneic, *ex vivo* expanded, umbilical cord blood-derived, hematopoietic CD34+ progenitor cells (NiCord® CF) and the non-expanded cell fraction of the same cord blood unit (NiCord® NF) consisting of mature myeloid and lymphoid cells. See further details on the cell expansion process in section 3.4.

Briefly, production of NiCord® involves *ex vivo* culture of purified CD133+ cells derived from a single CBU for 21 (±2) days in the presence of the cytokines [redacted]

On day 21 (±2) the cells are washed twice and cryopreserved in CryoStor®CS10. On the day of transplantation, the cells are thawed and reconstituted by a 1:5 dilution with the infusion solution. Harvest can be carried out from day 19 and up to day 23 if the patient's clinical condition or logistical considerations require an earlier transplantation date or a delay.

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

NiCord® 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

NiCord® 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.

Quality control (QC) tests are performed throughout the course of the manufacturing and on the final product and their results are documented. The testing includes in-process quality controls (IPQC) and final process quality controls (FPQC) performed according to the relevant Manufacturer's SOP. The IPQC and FPQC tests are performed according to written analytical methods either by QC employees or by trained outsourcing testing labs.

IPQC samples from NiCord® are taken at different identified stages during the process.

FPQC samples from NiCord® NF are taken prior to cryopreservation on day 0 of production. FPQC samples from NiCord® CF are taken prior to cryopreservation on the

harvest day. FPQC samples from infusion solution are taken at the end of the manufacturing day.

FPQC tests include both bioassays ([redacted]) and safety tests([redacted]).

All safety and some of the IPQC and FPQC bioassay tests have specifications and the results should be within the provided specifications. Some of the IPQC and FPQC bioassays do not have specifications and results are only collected and documented.

The results of the final process quality control tests for NiCord® and the infusion solution will be provided by Gamida Cell in the certificate of analysis sent for each batch of product

Upon the release of NiCord® CF, some of the quality control tests results may not be available. Hence, two certificates of analysis will be issued for each clinical batch according to the relevant Manufacturer's SOP - a preliminary certificate and a final certificate.

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

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

8.3.1. Out of Specification Results

In a case 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.

[redacted]

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.

8.3.1.1. NiCord® CF OOS

- IPQC OOS:

If NiCord® CF does not meet the specification of one of the quality control tests and the test result is confirmed by investigation, results are reported to the clinical site and production is stopped. In case no further investigation on the product is required both fractions (NiCord® CF and NiCord® NF) will be discarded by the production site, and will not be transplanted under any circumstances. A backup graft will be transplanted if patient conditioning has already started. Otherwise, a replacement CBU can be considered for NiCord production.

- FPQC OOS:
  - [redacted]

[redacted]

- If the OOS result is either CF sterility and/or mycoplasma FPQC test, the microorganism is identified, and the clinical site is notified. In the event of an OOS result in the CF obtained after transplantation, the following steps will be implemented by the investigator:
  - Blood cultures will be drawn
  - Antibiotic coverage will be modified such that the known isolate will be adequately covered
  - Antibiotic coverage will be discontinued if blood cultures prove negative and antibiotic cessation is clinically indicated

8.3.1.2. NiCord® NF OOS

If NiCord® NF does not meet the specifications of one of the quality control tests, and the test result is confirmed by investigation, it will be discarded at the production site prior to its shipment and will not be transplanted under any circumstances. In such an event, the production of the NiCord® CF will be stopped and the investigator will immediately be informed.

A backup graft will be transplanted if patient conditioning has already started. Otherwise, a replacement CBU can be considered for NiCord production.

8.4. Handling of NiCord®

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

Packaging of NiCord® CF, NiCord® NF and the infusion solutions will be performed according to the Sponsor's procedures.

8.5. Shipment

NiCord® 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 NiCord® 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 NiCord® 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 the graft infusion and 24 hours after the end of the graft 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. [redacted].

- 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.

For this study, primary and secondary graft failure events should be reported as SAEs; Disease progression/relapse should be reported as an SAE.

Serious adverse events require reporting (see section 9.2) within 24 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[60] and National Institute of Health consensus grading criteria for chronic GvHD (Appendix B).

Infections will be graded according to the grading scale provided in Appendix G.

All other AEs will be graded using NCI's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. The categories for grade 1 and 2 events will be combined 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 three (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 hours of knowledge of the event (note that all SAEs require reporting within 24 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 CFR312.32 and Directive 2001/20/EC

The Sponsor is required to report SUSARs in the NiCord arm only to regulatory authorities within statutory deadlines. In these cases, for reporting purposes, the Sponsor is unblinded with respect to the treatment arm.

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 subject 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. The majority of this section outlines requirements for patients who receive a transplant within 90 days of randomization (see also Table 12). For patients who do not receive a transplant within 90 days of randomization see Table 13 for an outline of safety reporting requirements. Below is a broad overview of data entry requirements:

- Treated grade 1 infections after the **start of the conditioning regimen** and all grade 2 or 3 infections **post randomization** will be reported on the Infection Summary form.
- Graft versus Host Disease (GvHD) will be reported on GvHD forms.
- Common events post transplant (which are summarized in Appendix D) will be reported on a Transplant Toxicity Summary form. For these common events, the highest grade over a given interval will be recorded on a Toxicity form, with the exception of some GvHD symptoms which will be recorded on the GvHD forms.
- Non-serious uncommon events post transplant will be reported on an Adverse Event Log.
- Serious Adverse Events **post signing of consent** will be reported on SAE forms set 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. [redacted].
- For patients who do not undergo transplant within 90 days following randomization and are enrolled in the post-randomization follow-up (section 7.5): only SAEs resulting in death will be reported after Day 90.
- Hospital Admission reporting is due from time of the start of the conditioning regimen until end of study; this is reported on the Hospital Admission Summary form.

Common Events Post Transplant

Common events post transplant are summarized in Appendix D and will be reported on the Transplant Toxicity Summary form. The intervals for reporting common events on the Toxicity form are: during conditioning up to UCBU/NiCord® transplant, during and 24 hours post UCBU/NiCord® transplant, from 24 hours post UCBU/NiCord® transplant to day 7, then at weekly intervals up to day 42 post transplant. For grade 3-5 events, any suspected relationship of the event to UCBU/NiCord® will also be collected on the Toxicity form. Common events that also meet SAE criteria will be reported on SAE summary forms at all times post transplant until the end of the study unless otherwise noted.

Non-serious Uncommon Events Post Transplant

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

After day 42 post transplant grade 1 and 2 non-serious adverse events will not be reported, with the exception of certain infections and symptoms of GvHD which will continue to be reported on their respective forms. After day 42, all grade 3 and 4 non-

serious events will be reported on the Adverse Event Log form, regardless of whether or not they are common events, with the exception of infections and symptoms of GvHD which will continue to be reported on their respective forms.

Serious Adverse Events

At all times after the signing of consent, SAEs, relapse and graft failure will be reported on SAE summary forms. These events may require reporting on other forms as well (e.g., Death form when applicable), however they should not be reported on the Adverse Event Log form. **SAEs must be reported within 24hrs of the study team's knowledge of the event.**

- Reporting should be done by completing and submitting a Serious Adverse Event Form in [redacted].
- If initial SAE reporting via [redacted] is not possible within 24 hours then the site must send an email to [redacted] including the patient study ID and a brief description of the event including the PI's assessment of causality

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.

For transplanted patients, every SAE that occurs between the time of patient consent and the participant's final study visit, the investigator is responsible for reviewing all documentation (e.g., hospital progress notes, laboratory test results, and diagnostic reports) relating to the event. Except as noted above for some events that are post relapse or graft failure, the investigator or designee will then record all relevant information about an SAE onto the appropriate page of the CRF. The investigator must review, sign, and date an SAE summary report form to confirm the accuracy of the recorded information. The signed report will be maintained in the site's study files. It is not acceptable for the investigator to send photocopies of the subject's medical records in lieu of completion of the appropriate CRF pages. Unless otherwise requested, transfer of subjects' medical records with the CRF should be restricted to hospital admission and progress notes, laboratory and radiology reports, discharge summaries and autopsy reports, if available. When uploading medical records to [redacted], all subject identifiers (i.e., name, date of birth, medical record number) must be obliterated prior to uploading the documents to [redacted].

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. 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

Both the Emmes Medical Monitor (MM) and the Sponsor will be alerted via email at the time any serious adverse event is submitted to [redacted].

The MM is responsible for initial review of these events within 1 business day of email notification. The MM review will be documented in [redacted]. If the MM requires additional information to make an assessment, the transplant center will have 2 calendar days to respond to the request. As noted above, most information is due within 2 working days of the site's knowledge of the event.

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 NiCord® 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 an actual life-threatening consequence i.e., its occurrence places the subject 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 participant, or a female partner of a male study participant 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 subject 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. DMC Reporting

In addition to the DMC reporting procedures outlined in section 10.2 of this protocol, any concerns regarding the type or frequency of an adverse event will be communicated to the DMC Chair by the Sponsor. The DMC Chair will review the adverse event materials, determine if the information is complete, determine if additional DMC review is required and make recommendations to the Sponsor concerning continuation or modification of the study.

9.9. Regulatory Authorities and IRB/ECs

The Sponsor shall notify the concerned Regulatory Authorities of Suspected Unexpected Serious Adverse Reactions (SUSARs) for the 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 required to report SUSARs in the NiCord arm only to regulatory authorities within statutory deadlines. In these cases, for reporting purposes, the Sponsor is unblinded with respect to the treatment arm.

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 subjects, per country requirements.

The Sponsor or designee shall notify the investigator of potential serious risks from clinical trials 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. Study Design and Objectives

The study is designed as an open-label, controlled, multicenter, Phase III, randomized study of transplantation of NiCord® versus unmanipulated cord blood in patients with hematological malignancies.

10.1.1. Accrual

The study will enroll 120 eligible patients, randomized in a 1:1 ratio to the NiCord® and control arms. The study accrual will be managed so that no single site will provide an unusually large fraction of patients.

[redacted]

10.1.2. Randomization

The study will use a form of randomization known as minimization that is designed to ensure that the treatment groups are well balanced with respect to selected factors of prognostic importance. Such forced balance is an important advantage in a small trial such as this one (see section 10.1.5). The factors included in the minimization algorithm will include: treatment center, disease risk group, age group, and intent to perform single vs double cord transplant in the control arm.

Approximately [redacted] treatment centers are expected. The disease risk group definition, which is based on the "refined DRI" described by Armand et al.[61] will have three levels: low risk, moderate risk, and high/very high risk. The risk group will be assigned by applying the criteria of Armand et al for DRI assignment and will be further adjusted to include in high/very high risk group any AML, ALL and other leukemia (not including MDS and CML) patient with any level of Minimal Residual Disease detected by flow cytometry. For patients with rare disease types who are not classified by Armand et al, the disease risk will be assigned by the site investigator. The age group factor will have three levels ([redacted]). Although age and disease/stage may not strongly influence the primary endpoint, time to engraftment, there is an advantage in keeping them well balanced across the treatment groups for the purposes of comparing other important endpoints, including overall mortality and non-relapse mortality.

Minimization will be implemented as follows: a measure of treatment group imbalance (to be defined in a separate document) will be calculated for each new patient and the allocation that minimizes this imbalance will be chosen with a pre-selected probability. Whenever the imbalance measures are equal under the two allocations, 1:1 randomization will be used.

10.1.3. Primary Endpoint

The primary objective is to compare time from transplant to neutrophil engraftment between patients allocated to receive NiCord® transplantation and those allocated to receive unmanipulated cord blood transplantation.

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 on different days with subsequent donor chimerism [redacted].

10.1.4. Primary Hypothesis

The primary null hypothesis of the study is that there is no difference between the time to engraftment for patients allocated NiCord® and those allocated unmanipulated cord blood.

10.1.5. Sample Size and Power Considerations

The primary endpoint will be time from transplant to neutrophil engraftment. The primary analysis for comparing time to engraftment between the two treatment groups will be based on the Mann-Whitney test statistic (refer to the Statistical Analysis Plan (SAP) for details on the test statistic to be used). Although the test will be based on the re-randomization distribution, rather than the usual permutation distribution or its normal approximation, little or no statistical power is lost thereby, as confirmed by simulations. The primary sample size calculations were therefore based on the usual methods associated with the Mann-Whitney test. Noether's formula was used to calculate the sample size.[62]

[redacted].

Based on these datasets and factoring in adjustments assuming [redacted] See Appendix I for details of these calculations.

Noether's formula [redacted]

[redacted].

Although the formal sample size calculation for the primary endpoint provided above yields a size between [redacted] and [redacted], the study will be larger for the following reasons:

a. in order to provide a more extensive safety database for NiCord®;
b. to ensure that statistical significance on the primary endpoint will be very strong and highly convincing; and
c. to reduce the chance of seeing higher mortality in the NiCord® group than in the control group even if NiCord® truly has a beneficial effect on mortality (see 10.1.6 below)

For these reasons and in consideration of the orphan indications, a total sample size of 120 patients will be entered, with approximately 60 randomized to NiCord® and 60 to control. With 120 patients statistical power for the primary endpoint is estimated to be greater than 0.99.

10.1.6. Overall mortality and "reverse" results

Overall mortality remains an important endpoint in evaluating results following cord blood transplant. However, it is not possible to design the study in a way that ensures with high probability that the observed difference will be in the direction of benefit to NiCord®, even if NiCord® truly does reduce the mortality rate. This is demonstrated in Table 7.

Table 7: Probabilities of observing that the 180-day overall mortality is higher in the NiCord® group under different scenarios when total sample size is 120

Relative Reduction in Treatment-Related Mortality (%)	Overall 180-day mortality rate in NiCord® group (%)*	Overall 180-day mortality rate in control group (%)	Probability of a higher 180-day mortality observed in NiCord® group
0	[redacted]		
10			
20			
30			
40			

* [redacted]

10.2. Interim Analysis and Stopping Guidelines

10.2.1. Data Monitoring Committee

This trial will be reviewed periodically by a Data Monitoring Committee (DMC). Policies and composition of the DMC are described in the DMC Charter. Information provided to the DMC will be limited to descriptive statistics, data listings, and safety

monitoring analyses. No formal hypothesis testing of endpoints will be performed unless specifically requested by a majority of the DMC or specified below.

In addition to data provided for periodic reviews, the DMC will be provided with information regarding 130-day mortality on a monthly basis, starting the first month after the first randomization. The monitoring guideline described in section 10.2.2 below serves as a reference for expected mortality rates on this study based on historical reports of overall survival of UCBU recipients;[12] it is not a formal "stopping rule" that would mandate automatic closure of study enrollment. Along with the monthly mortality report, full data information may be provided to the DMC for complete understanding of the fatalities reported (e.g., adverse events, GvHD, toxicity). The medical monitor will also view the mortality and other safety data and may make recommendations about approaching the DMC between the monthly mortality updates if they have any concern about the number or type of events or any other concerns about the safety of participants on the trial.

10.2.2. Guidelines for Safety Monitoring

The key safety endpoint to be monitored is the overall mortality at Day 130 post-randomization. Monitoring will occur within each treatment arm according to the randomized treatment assignment. An extension of the sequential probability ratio test (SPRT) for censored exponential data will be provided for reference, as described in greater detail below. Although the SPRT will be provided for participants in each treatment arm separately, the results for both arms will be provided at the same time to the DMC along with other supporting documentation of the deaths including the individual causes of death and a comparison of the proportion of deaths between arms.

This sequential testing procedure conserves type I error at [redacted]% across all of the monthly examinations for a treatment arm. The SPRT can be represented graphically. At each monthly interim analysis, the total time on study is plotted against the total number of endpoints. The continuation region of the SPRT is defined by two parallel lines. Only the upper boundary will be used for monitoring to protect against excessive Day 130 mortality. If the graph crosses the upper boundary, the SPRT rejects the null hypothesis, and concludes that there are more events than predicted by the observed time on study. Otherwise, the SPRT continues for each arm until enrollment reaches the maximum of [redacted] patients and all patients have had at least 130 days of follow-up post randomization.

This procedure assumes a censored exponential distribution for time to mortality, and censors follow-up time after 130 days post-randomization. Note that only deaths that occur on or before the patient has been followed for 130 days are counted. Total time on study within each treatment group is computed as time from randomization until death, or 130 days, whichever comes first, summed for all randomized patients allocated that treatment.

The usual measures of performance of an SPRT are the error probabilities α and β of rejecting H_0 when $\theta = \theta_0$ and of accepting H_1 when $\theta = \theta_1$, respectively, and the expected

sample size $E(N|\theta_i)$. The tests to be used in this protocol were developed from the following SPRT:

A SPRT contrasting [redacted]% versus [redacted]% for 130-day mortality results in decision boundaries with a common slope of 0.82 and an upper intercept of 2.62, with nominal type I and II errors of 10% and 10%, respectively.

The actual operating characteristics of the truncated test, shown in Table 8, were determined in a simulation study that assumed uniform accrual of 60 individuals over a 36 month time period, exponential time to failure after randomization and 41 months of monitoring. It is expected that the 130-day post randomization mortality rate may be [redacted]-[redacted]%, however, a null rate of [redacted]% was selected for the safety monitoring for 130 day post randomization in order to have high power for rejecting if the rate is [redacted]%; the DMC will be reminded of the operating characteristics when provided with the monitoring data.

Table 8: Operating characteristics of sequential testing procedure for 130 Day Mortality from a simulation study with 100,000 replications

True 130-Day Rate	[redacted]
Probability of Rejecting Null	
Mean Month of Crossing Boundary	
Mean # Events	
Mean # Patients Randomized	

For example,

[redacted].

10.2.1. Interim Analysis for Efficacy and Futility

There will be no interim analyses for efficacy or futility but there will be pre-specified interim safety monitoring as described above. Timing of final analyses is specified in section 10.4.1 below.

10.3. Analysis Populations

The screened population consists of all subjects who signed informed consent.

Intent-to-Treat (ITT) population includes all patients who are randomized into the trial, classified in the treatment groups to which they were allocated. Analysis of the ITT population provides the primary analysis of the primary endpoint, and also the primary

analyses of the secondary endpoints, tertiary endpoint, and the analyses of the exploratory endpoints unless otherwise stated.

Transplanted (TP) population includes all patients randomized who received a cord blood transplant within 90 days following randomization. Patients are, in assigned to the treatment groups to which they were allocated. Analysis of the TP population provides the analyses for the exploratory endpoints that depend on transplant, such as graft versus host disease.

As treated (AT) population includes all patients randomized who received a cord blood transplant within 90 days following randomization, grouped by treatment actually performed. Analysis of the AT population is for supportive purposes.

ANC engrafted population (AEP) includes all subjects who received a cord blood transplant within 90 days following randomization and achieved ANC engraftment; analysis is focused on the treatment actually performed. Analysis of the AEP population is for supportive purposes.

Platelets-engrafted population (PEP) includes all subjects who received a cord blood transplant within 90 days following randomization and achieved platelet engraftment; analysis is focused on the treatment actually performed. Analysis of the PEP population is for supportive purposes.

Safety population (SP) is identical with to the AT population defined above.

10.3.1. Demographics and Baseline Characteristics

Demographics and relevant baseline information (e.g., medical history, HCT-specific comorbidity index,[63] center, disease, disease risk group, intended treatment (single or double CBT)) will be presented and summarized with appropriate descriptive statistics. The comparability of the baseline factors between the treatment groups will be assessed.

These summaries will be based on the ITT population.

10.4. Analysis Plan

10.4.1. Timing of final analyses and statistical significance levels

The final analysis of the primary endpoint will be conducted after all randomized patients have completed follow-up to 45 days post-transplant (or 90 days post randomization if the patient does not receive a transplant). The final analysis of the secondary and tertiary endpoints and all exploratory endpoints will be conducted after all randomized patients have completed follow-up to the later of 210 days post-randomization or 180 days post transplant. An additional analysis of 15-month post randomization and 1-year post transplant endpoints will be performed when all study patients have completed their study follow-up. Follow-up on the long-term follow-up sub-study will be ongoing after the last patient completes their last core study assessment (at the latest 15 months post randomization). However, the core study database will be cleaned, locked, and analyzed at the time the last patient completes their last core study visit and will not remain open during the additional long term follow-up period. A separate study database will be used

to capture data on the long term follow-up sub-study and a separate SAP will be developed to describe the planned analyses for that sub-study.

All statistical tests will be conducted against a two-sided alternative hypothesis, employing a significance level of 0.05. For the secondary endpoints, p-values will be adjusted for multiple testing using Hommel's method that controls the family-wise error rate.[64] The results of the tertiary and exploratory endpoints will be assessed to provide a broad picture of the efficacy and safety of NiCord® in comparison with un-manipulated CB transplant; the p-values will be presented but the family-wise error rate for these endpoints will not be controlled.

Some of the outcomes (survival and relapse) are more naturally measured in relation to time from randomization, and other transplant-related outcomes (hospitalization, engraftment, infections, graft versus host disease, immune reconstitution) in relation to time from transplantation. When time from transplantation is used then it has been traditional in this field to consider survival or disease events up to 100 days or 180 days post-transplant. Since there is approximately a 30-day gap between randomization and transplantation, when using time from randomization, we use 130 days or 210 days instead.

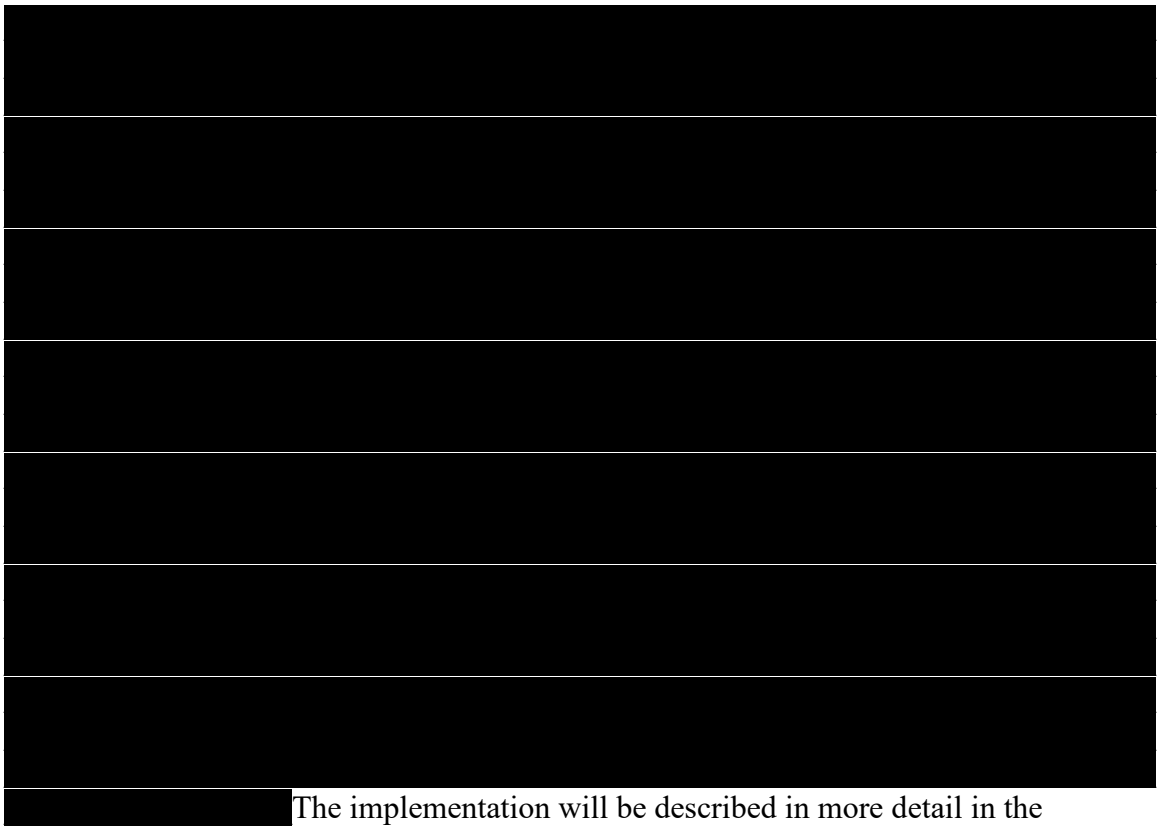
The primary endpoint, time to neutrophil engraftment, and the secondary endpoints will be evaluated from transplantation, although they will take into account events occurring between randomization and transplant. See the subsections below for details.

In the remainder of section 10.4, whenever the protocol mentions relapse, if the relapse occurs after randomization but before transplant, and the transplant is carried out within 90 days of randomization, then the relapse will not be counted as a primary event or competing risk event. However, in addition, secondary analyses will also be provided where the relapse occurring before transplant will be treated as a relapse and applied to the analysis of the primary, secondary, and tertiary endpoints. (See the SAP for more details.)

10.4.2. Analysis of the Primary Endpoint

The study will compare the distribution of times to engraftment in the NiCord® vs Control groups.

[redacted]



The implementation will be described in more detail in the Statistical Analysis Plan.

10.4.2.1. Secondary Analysis of Time to Neutrophil Engraftment

Three secondary analyses of the time from transplant to engraftment will be conducted. Statistical methods analogous to those described above will be used but on different populations. The first will be based on the as-treated (AT) population and will exclude patients who do not receive a transplant within 90 days following randomization. The second will in addition exclude patients who do not achieve ANC engraftment, forming the ANC-engrafted population (AEP). The third will compare time to neutrophil engraftment using a logrank test statistic for the ITT population. These secondary analyses (a) provide information supportive of the primary analysis, and (b) the first and second provide estimates of median time from transplant to engraftment that are commonly used in the literature.

Analyses of the primary and secondary endpoints in the following subgroups will also be conducted: (a) disease risk group; (b) age group; (c) intention to perform single vs double CB transplant; (d) disease (ALL, AML, CML, MDS, and lymphoma); (e) HCT-specific Comorbidity Index (0, 1-2 and 3+).; (f) gender; (g) race/ethnicity; (h) geographical region. See section 10.4.6 for more details.

10.4.3. Analysis of Secondary Endpoints

The secondary endpoints are those that will be subjected to formal statistical testing with adjustment for multiple testing. In this subsection, we list the statistical analyses of those secondary endpoints. All statistical tests comparing NiCord® to unmanipulated cord

blood will be based on the re-randomization distribution. Confidence intervals for the test statistics will be provided in all cases. The method for computing confidence intervals will be described in the Statistical Analysis Plan. The following outlines the primary analyses that will be performed. Details of secondary analyses are fully described in the SAP.

10.4.3.1. Incidence of bacterial infection grades 2-3 or invasive fungal infection by 100 days following transplantation

This analysis will be performed on the ITT population.

The proportion of patients suffering a grade 2-3 bacterial infection or invasive fungal infection between randomization and 100 days following transplantation will be estimated in each treatment group in the following manner.

[redacted]

Secondary analyses will be performed on the TP and AT populations, as specified in the SAP.

10.4.3.2. Days alive and out of hospital in the first 100 days following transplantation

The primary analysis will be performed on the ITT population.

The number of days that the patient is alive and out of hospital in the first 100 days post-transplant, will be counted. Patients who are lost to follow-up during the first 100 days, but have not relapsed or had graft failure, will have their value imputed as follows:

[redacted]

[redacted].

Secondary analyses will be performed on the TP and AT populations, as specified in the SAP.

10.4.3.3. Platelet engraftment by 42 days following transplantation

This analysis will be conducted on the ITT population. The proportion of patients with platelet engraftment by day 42 post-transplant in each group will be estimated for each treatment group from the cumulative incidence curve, with competing risks as follows:
[redacted]

Secondary analyses will be conducted on the TP and AT populations, as specified in the SAP.

10.4.4. Analysis of Tertiary Endpoint

10.4.4.1. Non-relapse mortality by 210 days following randomization

The primary analysis will be performed on the ITT population.

[redacted]. A secondary analysis conducted on the ITT population will be performed as described in the SAP.

10.4.5. Analysis of Exploratory Endpoints

10.4.5.1. Neutrophil engraftment by 16 days following transplantation

This analysis will be conducted on the ITT population.

[redacted].

10.4.5.2. Time from transplantation to platelet engraftment

The primary analysis of this endpoint will be conducted on the PEP (platelet engrafted population) and will estimate the distribution and median of time to platelets engraftment

among the platelet engrafters.

[redacted]. A secondary analysis conducted on the ITT population will be performed as described in the SAP.

10.4.5.3. Duration of primary hospitalization

The primary analysis will be performed on the transplanted (TP) population.

[redacted].
A secondary analysis conducted on the AT population will be performed as described in the SAP.

10.4.5.4. Non-relapse mortality by 130 days following randomization

The primary analysis will be performed as described in section 10.4.4.1 except that the time-period will be limited to 130 days. A secondary analysis conducted on the ITT population will be performed as described in the SAP.

10.4.5.5. Non-relapse mortality by 15 months following randomization

The primary analysis will be performed as described in section 10.4.4.1, except that the time-period will be extended to15 months. A secondary analysis conducted on the ITT population will be performed as described in the SAP.

[redacted].

10.4.5.6. Overall survival at 210 days following randomization

The primary analysis will be performed on the ITT population.

[redacted]. A secondary analysis conducted on the ITT population will be performed as described in the SAP.

10.4.5.7. Overall survival by 15 months following randomization

The analysis will be performed as described in section 10.4.5.6 except that the time-period will be extended to15 months post randomization for the primary analysis.

10.4.5.8. Disease-free survival by 15 months following randomization

This analysis will be performed on the ITT population.

[redacted].

10.4.5.9. Neutrophil engraftment by 42 days following transplantation

The primary analysis will be conducted on the ITT population.

[redacted]

[redacted]. A secondary analysis conducted on the TP population will be performed as described in the SAP.

10.4.5.10. Acute GvHD grade II-IV by 100 days following transplantation

This analysis will be conducted on the transplanted population (TP).

[redacted]. A secondary analysis, based on the cumulative incidence curve, will be described in the SAP.

10.4.5.11. Acute GvHD grade III-IV by 100 days following transplantation

The analyses will be performed as described in section 10.4.5.10, except that the time to the event will be the first time to aGvHD grade III-IV, instead of grade II-IV. A secondary analysis, based on the cumulative incidence curve, is described in the SAP.

10.4.5.12. Chronic GvHD (mild/moderate/severe) by 180 days following transplantation

This analysis will be conducted on the transplanted population (TP).

[redacted]

[redacted]. A secondary analysis will be based on the cumulative incidence curve as described in the SAP. The reason for performing both primary and secondary analyses of this endpoint is given at the end of section 10.4.5.10.

10.4.5.13. Chronic GvHD (mild/moderate/severe) by 1 year following transplantation

The analysis will be performed as described in section 10.4.5.12, except that the time-period will be extended to 365 days. A secondary analysis will be based on the cumulative incidence curve as described in the SAP.

10.4.5.14. Secondary graft failure by 1 year following transplantation

This analysis will be conducted on the transplanted population (TP).

[redacted]. A secondary analysis will be based on the Kaplan-Meier curve as described in the SAP.

10.4.5.15. Grade 3 viral infections by 180 days following transplantation

[redacted]. Secondary analyses will be performed on the TP and AT populations, as specified in the SAP.

10.4.5.16. Grade 3 viral infections by 1 year following transplantation

The analysis will be conducted as described in section 10.4.3.1. Secondary analyses will be performed on the TP and AT populations, as specified in the SAP.

10.4.5.17. Relapse by 15 months following randomization

This analysis will be conducted on the ITT population.

[redacted].

[redacted]. A secondary analysis will be based on the cumulative incidence curve as described in the SAP.

[redacted].

10.4.5.18. Relapse mortality by 15 months following randomization

This analysis will be conducted on the ITT population.

The same approach as in section 10.4.5.17 will be used to overcome possible biases arising from the timing of the BM assessment.

[redacted]. A secondary analysis will be based on the cumulative incidence curve as described in the SAP.

[redacted].

10.4.5.19. Immune Reconstitution

Summary statistics of the numbers and proportions of different lymphocyte subpopulations at days 28, 70, 100, 180 and 365 post-transplant (mean, standard deviation, median and quartiles) will be presented for each treatment group. This will be performed on the AEP population.

[redacted].

10.4.5.20. Health-Related Quality of Life

Patient-reported health-related quality of life outcomes will be assessed on the ITT population using two standardized measures including the FACT BMT and the EuroQol EQ-5D. The self-report questionnaires will be completed prior to transplantation and subsequently at 42, 100, 180 and 365 days from transplantation or until death or

discontinuation from the study. Questionnaires are requested but not required after failure to transplant by Day 90, graft failure, or relapse. The instruments will be scored according to the recommendations of the developers.

[redacted].

10.4.6. Subgroup Analysis

Descriptive statistics calculated based on the primary analyses of the primary and secondary endpoints will be provided for the following subgroups:

1. Disease risk group as defined in section 10.1.2 (low, moderate and high/very high risk).
2. Age group as defined in section 10.1.2 ([redacted]).
3. Intention to perform single vs. double CB transplant
4. Disease (ALL, AML, CML, MDS and lymphoma)
5. HCT-specific Comorbidity Index (0, 1-2 and 3+)
6. Gender
7. Race/ethnicity
8. Geographical region

These data are intended to serve as supportive analyses. P-values for comparing the treatment groups within subgroups will not be provided, since in a trial with limited sample size they can be misleading. The subgroup results will be presented as forest plots.

10.5. Missing data

Sections 10.4.2 and 10.4.3 have included details regarding the handling of missing data that can occur because [redacted]. In addition, survival analyses of time-related endpoints specify that loss-to-follow up will be regarded as a censoring event and the usual survival analysis assumptions will be applied in those cases. In what follows we describe our

approach [redacted].

10.5.1. Loss to follow-up in the primary analysis of the primary endpoint

[redacted].

10.5.2. Loss to follow-up in the primary analyses of the secondary endpoints

[redacted]

[redacted].

10.5.3. Sensitivity analyses for missing data

[redacted].

10.6. Safety and Tolerability of NiCord® transplantation

This analysis will be conducted on the safety population (SP).

The analysis of adverse events, serious adverse events, and toxicities will be primarily descriptive. Formal comparisons between treatment groups will be performed to assess whether there is strong evidence of a differential safety signal.
[redacted].

Adverse events (AEs) and serious adverse events (SAEs) are collected as described in section 9. Toxicities, adverse events, and serious adverse events are not unexpected in the setting of stem cell transplantation. As such, events can be broken into several categories: infusion reactions, common events post-transplant, uncommon adverse events.

Infusion reactions:

[redacted].

Common events post-transplant:

[redacted].

Uncommon events post-transplant:

[redacted]

Pregnancies on study will be followed until outcome and described. Clinical laboratory evaluations will not be analyzed per se, but rather clinically significant abnormal values will be reported as adverse events and analyzed as referenced above.

10.7. Analysis Plan Deviations

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

10.8. Statistical Software

SAS® version 9.1 or higher software and R version 2.10.0 or higher will be used for statistical analysis and data presentation of the information collected in this study.

10.9. Long-term Follow-up (optional)

For patients who received transplantation and agreed to enroll in the observational long term follow-up sub-study, long-term outcomes will be collected at 2 years, 3 years, 4 years and 5 years post transplantation.

The overall research goals for this sub-study are:

- Describe long term sustained donor chimerism
- Describe survival and disease free survival
- Describe characteristics of patients with secondary graft failure or disease relapse
- Describe long term immune reconstitution
- Describe incidence of chronic GvHD

Details of the statistical analysis plan are provided in Appendix J.

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

11.2. Data Collection

Investigators or designees will enter the information required by the protocol onto the 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.

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, depending on the trial; also, current medical records must be available.

Direct access to source data - documents

- The investigator / institution will permit trial-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 trial 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.

11.5. Data Monitoring

CRAs will be responsible for monitoring CRFs and source documents for accuracy, protocol compliance, subject 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. SCREENING SCHEDULE

APPENDIX B. GVHD CLASSIFICATION

Acute GvHD Definition

Acute GvHD will be assessed at every visit from transplantation (day 0) until day 180 or more frequently as clinically indicated. GvHD will be classified according to the Consensus Conference on Acute GvHD grading.[60]

Table 9: 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 10: 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.

[c] 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 365 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[65] summarized below:

Table 11: 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.[65] 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).

APPENDIX C. SAFETY DATA REPORTING

Table 12: Safety Data Reporting for transplanted patients

From the time of Consent	From the time of Randomization	During Conditioning up to Start of NiCord® or CBU Infusion	During NiCord® or CBU Infusion through 24 hours Post NiCord® or CBU Infusion	> 24 hours Post NiCord® or CBU Infusion through Day 42	Day 43 through Day 365[a]
[redacted]					

[*] See Appendix D for a list of common adverse events
[#] With the exception of infections and GvHD symptoms which are reported on the Infection form and GvHD forms respectively.
[a] An additional assessment of survival and relapse status is required on or after month 15 post randomization. Death and or Relapse forms are required during this time period as applicable. In the event of death, SAE forms are also required.
[b] After day 30 post transplant and following date of relapse or graft failure only SAEs resulting in death or suspected to be related to the infused product will be reported.

Table 13: Safety Data Reporting for Post Randomization Patients Who Do Not Receive a Transplant Within 90 Days following Randomization

From the time of Consent	From the time of Randomization through Day 90 post Randomization	Day 91 through Day 365 post Randomization	Day 366 post Randomization through Month 15 post Randomization

APPENDIX D. COMMON ADVERSE EVENTS

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 E. COMMON TERMINOLOGY CRITERA FOR ADVERSE EVENTS V4.03 (CTCAE) (U.S.DEPARTMENT_OF_HEALTH_AND_HUMAN_SERVICES 2009)[66]

Document available upon request (for site personnel, document available on the Gamida Cell Studies Coordinating Center website [redacted])

APPENDIX F. DRUG LABELS

Documents available upon request (for site personnel, documents available on the Gamida Cell Studies Coordinating Center website [redacted])

APPENDIX G. 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,

Type of infection/ severity grade	Grade 1	Grade 2	Grade 3
			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)
	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	
Viral infections continued		Enterocolitis with enteric viruses Symptomatic upper tract respiratory virus	Lower tract respiratory viruses

Type of infection/ severity grade	Grade 1	Grade 2	Grade 3
	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
Nonmicrobiologically 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 Typhlitis	Any acute pneumonia requiring mechanical ventilation 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 >38.5C ***or*** < 36C
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 > 3ºC
  - 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 ≤ 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 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: [redacted]
- VZV, HZV: [redacted]
- Bacterial, non-C. difficile: [redacted]
- Bacterial, C. difficile: [redacted]
- Yeast: [redacted]
- Molds: [redacted]
- Helicobacter: [redacted]
- Adenovirus, Enterovirus, Influenza, RSV, Parainfluenza, Rhinovirus: [redacted]
- Polyomavirus (BK virus): [redacted]

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 > 38ºC or < 36ºC 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.

APPENDIX H. EUROPEAN LEUKEMIANET GUIDELINES

The following table summarizes the criteria for response as outlined in the European LeukemiaNet Guidelines.[67]

Table 14: CML Response Criteria

	Optimal response	Suboptimal response	Failure
Month 3	CHR and at least minor CyR	No CyR (>95% Ph+ cells)	No CHR
Month 6	At least pCyR	Less than pCyR	No CyR (>95% Ph+ cells)
Month 12	cCyR	Less than cCyR	Less than pCyR
Month 18	MMR	Less than MMR	Less than cCyR
At any time	Stable or improving MMR	Loss of MMR, *BCR-ABL* mutation	Loss of CHR, loss of cCyR, Clonal evolution

Definitions:

Complete Hematologic response (CHR)= normalized peripheral blood counts, white blood cell count below 10×10^9/L, platelets below 450×10^9/L, immature cells absent or normalized differential, no signs and symptoms of disease

Cytogenetic response:

Cytogenetic response (CyR) = 0-95% Ph+ cells

Complete Cytogenetic response (cCyR) = absence of Ph+ cells

Partial Cytogenetic response (pCyR) = 1–35% Ph+ cells

Minor Cytogenetic response (mCyR) = 35-65% Ph+ cells

Molecular response:

Complete Molecular Response (CMR)= complete absence of BCR-ABL gene transcripts

Major Molecular Response (MMR)= a 3-log decrease or a reduction to 0.1% compared with the baseline level of BCR-ABL transcripts

APPENDIX I. STATISTICAL ANNEX

Further Details on Sample Size Calculation (Appendix to section 10.1.5 in the Protocol)

The primary endpoint will be time from transplant to neutrophil engraftment.

[redacted]

APPENDIX J. LONG TERM FOLLOW-UP OBSERVATIONAL STUDY STATISTIC PLAN

All analyses mentioned below will be conducted separately within each randomized treatment. Estimated quantities will be provided together with their standard errors or 95% confidence intervals.

Chimerism
Peripheral blood chimerism will be assessed. Descriptive statistics (e.g., min, q1, median, q3, max) will be provided for chimerism at 2, 3, 4, and 5 years post transplant. Patients who have progressed/relapsed, had autologous recovery, had graft failure, or who die before target day (2, 3, 4, and 5 years) will be excluded from this analysis after that event.

Overall Survival
The proportion of patients alive at 2, 3, 4, and 5 years post transplant will be estimated using the Kaplan-Meier method.

Disease Free Survival
The proportion of patients alive and without progression/relapse or autologous recovery at 2, 3, 4, and 5 years post transplant will be estimated using the Kaplan-Meier method.

Secondary Graft Failure and Disease Relapse
The cumulative incidence of patients with secondary graft failure and with disease relapse will be estimated. For secondary graft failure, death, relapse, and primary engraftment failure will be considered competing events. For relapse, death without relapse will be considered a competing event. Characteristics of patients with secondary graft failure will be described separately from those patients without secondary graft failure. Similarly, characteristics of patients with disease progression/relapse or autologous recovery will be described separately from those who remain disease free.

Immune Reconstitution
The distributions of the numbers and proportions of different lymphocyte subpopulations at 2, 3, 4, and 5 years (mean, standard deviation, median, quartiles) will also be estimated. Patients who have progressed/relapsed or experienced autologous recovery, had graft failure, or who die before target day (2, 3, 4, and 5 years) will be excluded from this analysis after that event.

Chronic GvHD
The cumulative incidence of patients who experience chronic GvHD will be computed at 2, 3, 4, and 5 years post transplant. Death and second transplant will be considered as a competing risk in the estimation.

APPENDIX K. PROTOCOL AMENDMENT SUMMARY

Table 15: Protocol Amendment Summary

Protocol Version	Main Reason(s) for Amendment
Original	N/A
Amendment I	[redacted]
Amendment II	
Amendment III	
Amendment IV	
Amendment IV.1	
Amendment IV.2	
Amendment V	
Amendment V.1	
Amendment VI	

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