Study Title

Allogeneic Stem Cell Transplantation of NiCord®, Umbilical Cord Blood-Derived Ex Vivo Expanded Stem and Progenitor Cells, in Patients with Hemoglobinopathies

Clinical Phase	Pilot Study
Product:	NiCord®
IND Number:	14459
EudraCT Number:	2014-000074-19

Sponsor
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Director, Medical Affairs	Einat Galamidi Cohen, M.D.
Protocol No.	GC P#02.01.020
Dated	December 8, 2011
Amendment #	VI
Dated	December 13, 2017

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
The information in this document is considered privileged and confidential, and may not be disclosed to others except to the extent necessary to obtain Institutional Review Board (IRB)/Ethics Committee (EC) approval, written informed consent and the approval of local regulatory authorities as required by local law.

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List of Abbreviations

AE	Adverse Events
AIBW	Adjusted Ideal Body Weight
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
BM	Bone Marrow
CBB	Cord Blood Bank
CBU	Cord Blood Unit
CF	Cultured Fraction
CFU	Colony-forming Units
CMV	Cytomegalovirus
CNS	Central Nervous System
CoA	Certificate of Analysis
CRFs	Clinical Report Forms
CRO	Contract Research Organization
CSA	Cyclosporine A
CTCAE	Common Terminology Criteria for Adverse Events
DCC	Data Coordinating Center
DLCO	Diffusing Lung Capacity of Carbon Monoxide
DMC	Data Monitoring Committee
EBV	Epstein–Barr Virus
EC	Ethics Committee
FPQC	Final Process Quality Controls
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
GFR	Glomerular Filtration Rate
GvHD	Graft-versus-host Disease
HbS	Hemoglobin S
HCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPC	Hematopoietic Progenitor Cell
HSC	Hematopoietic Stem Cells
HSCT	Hematopoietic Stem Cell Transplantation
HTLV	Human T-Lymphotropic Virus
IBW	Ideal Body Weight
IC	Informed Consent
ICH	International Conference on Harmonization
IPQC	In-process Quality Controls
IRB	Institutional Review Board
ITT	Intent to Treat
IV	Intravenous
LVEF	Left Ventricular Ejection Fraction

List of Abbreviations

MAC	Myeloablative conditioning
mARTs	Mono-ADP-ribosyltransferases
MM	Medical Monitor
MMF	Mycophenolate Mofetil
MRA	Magnetic Resonance Angiogram
MRI	Magnetic Resonance Imaging
NAD^+	Nicotinamide Adenine Dinucleotide
NAM	Nicotinamide
NF	Non-cultured Fraction
NK	Natural Killer
NMDP	National Marrow Donor Program
OOS	Out of Specification
PARPs	Poly-ADP-ribose Polymerases
PB	Peripheral Blood
PBSC	Peripheral Blood Stem Cell
PCR	Polymerase Chain Reaction
PP	Per Protocol
PRBC	Packed Red Blood Cells
QC	Quality Control
RBC	Red Blood Cell
SAE	Serious Adverse Event
SC	Sickle-Hemoglobin C
SCD	Sickle Cell Disease
SCF	Stem Cell Factor
SCT	Stem Cell Transplant
SLM	Study Logistics Manager
SOPs	Standard Operating Procedures
SRC	SCID Repopulating Cells
SS	Sickle-Cell Anemia
TCD	Trans-Cranial Doppler
TPO	Thrombopoietin
TRM	Transplant-related Mortality
UCB	Umbilical Cord Blood
UCBT	Umbilical Cord Blood Transplantation

SPONSOR PROTOCOL APPROVAL PAGE

Protocol Title: Allogeneic Stem Cell Transplantation of NiCord®, Umbilical Cord Blood-Derived Ex Vivo Expanded Stem and Progenitor Cells, in Patients with Hemoglobinopathies

Clinical Phase	Pilot Study
Protocol Number:	GC P#02.01.020
Amendment Number:	VI
Dated:	December 13, 2017

Approved by:

Director, Medical Affairs

Einat Galamidi Cohen, M.D.

_____ _____

Signature Date

Protocol Title: Allogeneic Stem Cell Transplantation of NiCord®, Umbilical Cord Blood-Derived Ex Vivo Expanded Stem and Progenitor Cells, in Patients with Hemoglobinopathies

Clinical Phase Pilot Study

Protocol Number: GC P#02.01.020

Amendment Number: VI

Dated: December 13, 2017

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 designated time frame.

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#02.01.020

Protocol Title
Allogeneic Stem Cell Transplantation of NiCord®, Umbilical Cord Blood-Derived Ex Vivo Expanded Stem and Progenitor Cells, in Patients with Hemoglobinopathies

Number of Centers and Planned Geographical Distribution
Up to 5 centers in the U.S.

Clinical Phase
Pilot study

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.

In Part 1 of this study, NiCord® will be administered to the patient in conjunction with a second, unmanipulated CBU.

In Part 2 of this study, NiCord® will be administered to the patient without a second, unmanipulated CBU.

Study Duration
Total study duration per patient is approximately 270 days from signing of informed consent to last visit on day 180 post-transplant.

Study Objectives
Part 1: The overall study objectives are to evaluate the safety and efficacy of co-transplantation of NiCord® and an unmanipulated CBU in patients with Hemoglobinopathies (Sickle Cell Disease (SCD), or thalassemia major) following myeloablative therapy.

Part 2: The overall study objectives are to evaluate the safety and efficacy of transplantation of NiCord® in patients with Hemoglobinopathies (Sickle Cell Disease (SCD), or thalassemia major) following myeloablative therapy.

Primary Objectives

- Assessment of the acute toxicity associated with the infusion of NiCord®, within 24 hours post-infusion
- Part 1: Assessment of cumulative incidence of donor-derived neutrophil engraftment by day 42 following co-transplantation of NiCord® and unmanipulated cord blood grafts
- Part 2: Assessment of cumulative incidence of donor-derived neutrophil engraftment by day 42 following transplantation of NiCord®

Secondary Objectives

- Proportion of transplant-related mortality at 100 days
- Event-free survival at 100 days (death, autologous recovery, primary or secondary graft failure will be considered events for this endpoint)
- Overall survival at 180 days

Exploratory Objectives

- Incidence of donor cell chimerism (>10%) from either donor at 100 and 180 days
- Percentage donor chimerism in whole blood, CD3+ and myeloid (CD15+ or CD33+) fractions at 7, 14, 21, 28, 42, 70, 100,180 days
- Time from infusion to neutrophil (>500/uL) and platelet (>50K/uL) engraftment
- Incidence of platelet engraftment (>50K/uL) at 180 days
- Incidence of acute GvHD grade II-IV and III-IV at 100 days
- Incidence of chronic GvHD (limited or extensive) at 180 days
- Incidence of regimen-related toxicity
- Incidence of life-threatening and fatal infections at 180 days
- Immune reconstitution at 100 days, and 180 days

Post-study Analysis

- Event-free survival at 1 year (death, autologous recovery, primary or secondary graft failure will be considered events for this endpoint)
- Overall survival at 1 year
- Percentage donor chimerism in whole blood, CD3+ and myeloid (CD15+ or CD33+) fractions at 1 year
- Incidence of chronic GvHD (limited or extensive) at 1 year
- Incidence of life-threatening and fatal infections at 1 year
- Immune reconstitution at 1 year

Study Hypothesis
Part 1: Co-transplantation of NiCord® and an unmanipulated unrelated cord blood graft in patients with hemoglobinopathies (SCD, or thalassemia major) following myeloablative preparative therapy will be safe and will enable cord blood engraftment.

Part 2: Transplantation of NiCord® in patients with hemoglobinopathies (SCD, or thalassemia major) following myeloablative preparative therapy will be safe and will enable cord blood engraftment.

Study Design
This is an open-label, non-randomized, interventional, single group assignment study of NiCord® in patients suffering from hemoglobinopathies. In Part 1, the patients will be transplanted both with NiCord® and an unmanipulated CBU. In Part 2, the patients will be transplanted with NiCord® only.

Once the best available cord blood units (CBUs) have been identified and the patient or legal guardian has signed the informed consent (IC), the patient will be screened for the study. The trial consists of four phases:

(I) Eligibility/Screening Phase
Patient clinical assessment and eligibility review: 45 days prior to CBU shipment for the start of manufacturing.

The selected CBU for ex-vivo expansion will be shipped from the Cord Blood Bank (CBB) to the production site and received no later than two days before the start of production.

[redacted]

(II) Baseline Phase
Baseline clinical assessments: within 4 weeks prior to start of conditioning regimen.
Confirm patient suitability for transplant: 1 week prior to start of conditioning regimen.

(III) Preparative and Conditioning Phase
Once the patient is consented to the study and found to be eligible, the patient is started on hydroxyurea: 30mg/kg/day orally, beginning on day -35 (may be extended if transplant is delayed) until one day prior to the start of conditioning.

In Part 1: The unmanipulated CBU will be shipped from the CBB to the clinical site prior to the initiation of conditioning.

[redacted]

The myeloablative conditioning regimen will consist of:

- Busulfan:
    - For patients <21 years old: 1mg/kg/dose IV q 6h on days -9 to -6 for 16 doses
    - For patients >21 years old: 0.8mg/kg/dose IV q 6h on days -7 to -4 for 16 doses
- Cyclophosphamide:
    - For patients < 21 years old: 50mg/kg/day IV on days -5 to -2
    - For patients >21 years old: 60mg/kg/day IV on days -3 and -2
- Fludarabine:
    - For patients <21 years old: 35 mg/m2 IV daily x 5 days (days -14 through -10)
    - For patients ≥21 years old: 35 mg/m2 IV daily x 5 days (days -12 through -8)

The GvHD prophylaxis regimen will be:

- Mycophenolate Mofetil (MMF): beginning day –3 for at least 45 days

  AND
- Cyclosporine: beginning day -3 to at least day 180

(IV) Transplantation and Post Transplantation Follow-up Phase
NiCord® CF + NF and Infusion Solutions will be shipped to the clinical site before transplantation.

Day 0:
Part 1: Transplantation of the unmanipulated CBU followed by NiCord® with a minimal interval of four hours between the infusions of the two units. With regards to NiCord® infusion: the NiCord® CF will be infused first, followed by the NiCord® NF starting no later than 1 hour post NiCord® CF infusion.

Days +1 to +180: Post-transplant supportive care and follow-up.

Throughout the study, all AEs, concomitant medications and clinically significant procedures will be recorded in both patient's medical charts and CRF.

Post-study Follow-up
Clinical outcomes including secondary graft failure, chronic GvHD, cardiac and pulmonary function tests, chimerism, Hb-electropheresis, incidence of life-threatening infections, immune reconstitution, routine labs, vital signs, physical exam, performance scale, and survival status (including causes of death), will be collected from the center at six months post study completion (1 year post transplantation), as per site practice.

Number of Patients

Part 1: Up to fifteen (15) patients who are evaluable for the engraftment endpoint. Part 1 will be closed to enrollment at the time that this amendment is approved.

Part 2: Up to five (5) patients who are evaluable for the engraftment endpoint.

Inclusion Criteria

1. Patients must be 2 – 45 years of age and at least 10 kg
2. Patient is a candidate for allogeneic SCT for treatment of SCD or thalassemia:
   a. Patient must have clinically severe SCD (e.g., SS, SC or SBeta^0 Thal) with at least one of the following clinical complications:
      - Recurrent painful events (at least 3 in the 2 years prior to enrollment) that cannot be explained by other causes. Pain may occur in typical sites associated with vaso-occlusive painful events and cannot be explained by causes other than SCD. Pain lasts at least 4 hours and requires parenteral narcotic treatment, equianalgesic dose of oral narcotics or parenteral nonsteroidal anti-inflammatory drugs. These painful events may be treated in any setting, but events managed at home will be considered only if there is documentation of the event in a clinical record that may be reviewed by an investigator. These events must occur despite adequate supportive care measures (e.g., hydroxyurea therapy).
      - Acute chest syndrome (ACS) with at least two episodes with the development of a new infiltrate on chest radiograph and/or having a perfusion defect demonstrable on a lung radioisotope scan within the past two years that required hospitalization, oxygen therapy, and red blood cell (RBC) transfusion. These episodes must occur despite adequate supportive care measures (e.g., hydroxyurea therapy). At least one episode of acute chest syndrome per year while on hydroxyurea therapy unless patient is unable to take hydroxyurea due to toxicity.
      - Any combination of painful events and ACS episodes that total three or more events within the two years before transplantation
      - SCD related and clinically significant neurologic event (stroke or hemorrhage) or SCD related neurologic defect lasting more than 24 hours
      - Abnormal cerebral magnetic resonance imaging (MRI) and/or abnormal cerebral magnetic resonance angiography (MRA)
      - Abnormal Transcranial Doppler (TCD), as defined by a TCD velocity that exceeds 200 cm/sec by the non-imaging technique (or TCD measurement of >185 cm/sec by the imaging technique) measured at a minimum of two separate occasions one month or more apart
      - Patients on chronic PRBC transfusion therapy, defined as receiving 8 or more transfusions per year for > 1 year to prevent vaso-occlusive clinical complications

(e.g., pain, stroke, and acute chest syndrome), with a history of alloimmunization which compromises the delivery of adequate transfusion therapy

OR;

b. Patients with thalassemia major requiring ≥8 (or >100 ml/kg) RBC transfusions per year in the two years preceding enrollment.

3. Part 1: Patients must have two partially HLA-matched CBUs. Units 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 subject and 3-6/6 HLA-A, B, DRB1 loci with each other (using same resolution of typing). Double mismatch at any one locus (A, B, or DRB1) is not permitted.

   Part 2: Patients must have one partially HLA-matched CBU. 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 subject. Double mismatch at any one locus (A, B, or DRB1) is not permitted.

   a. For patients weighing ≥ 25 kg, the manipulated CBU must have a pre-cryopreserved (post processing) total nucleated cell dose of ≥$1.8x10^9$ and ≥$1.8x10^7$cells per kg body weight.

      For patients weighing < 25 kg, the manipulated CBU must have a pre-cryopreserved (post processing) total nucleated cell dose of ≥$1.6x10^9$.

      Part 1: The unmanipulated CBU should contain a pre-cryopreserved (post processing), nucleated cell dose of at least $3.5x10^7$/kg. The better matched unit will be the unmanipulated unit (as per investigator's discretion).

   b. The manipulated CBU should contain a pre-cryopreserved (post processing), total CD34+ cell count of ≥ $8x10^6$ for patients weighing ≥ 25 kg and a pre-cryopreserved (post processing), total CD34+ cell count of ≥$7x10^6$ for patients weighing < 25 kg.

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

   d. The CBU should be procured from a public bank that meets local applicable regulations.

   e. The selected units should be typed twice (i.e., initial typing and verification typing). Verification typing (confirmatory typing) should be in a laboratory that is ASHI/EFI accredited and must come from an attached segment.

4. Patients' Performance score ≥70% by Lansky or Karnofsky performance status scale

5. Patient has sufficient physiologic reserves including:

   - Cardiac: Left ventricular ejection fraction (LVEF) > 50% by echocardiogram radionuclide scan or cardiac MRI; or LV shortening fraction > 26%

- Pulmonary: Pulse oximetry with a baseline O2 saturation of ≥ 85% is required for all patients; DLCO > 60% of predicted for age (corrected for hemoglobin) for patients in whom pulmonary function testing can be performed. cDLCO value should be from testing performed before the administration of a bronchodilator if applicable. FVC and FEV1 > 60% of predicted for age.
- Renal: Serum creatinine ≤ 1.5 x upper limit of normal for age and GFR > 100 mL/min/1.73 m^2. For patients ≥16 years of age, GFR should be >70 mL/min/1.73 m^2. Note, estimated GFR value not acceptable; nuclear GFR testing must be performed.
- Hepatic: Serum conjugated (direct) bilirubin < 2 x upper limit of normal for age as per local laboratory in the absence of gall bladder disease or prior cholecystectomy; Hepatic transaminases (ALT and AST) < 5 x upper limit of normal range

6. In SCD patients, HbS should be ≤ 45% within 7 days prior to initiation of conditioning regimen. If the HbS level is >45% then the patient must receive RBC transfusions or erythrocyte exchange prior to conditioning regimen initiation.
7. Patient must have at least one graft source as a backup in case of graft failure:
    a. Autologous stem cells harvested from bone marrow; OR
    b. A related, haplo-identical family member who is suitable for bone marrow or peripheral blood stem cell donation and has agreed to do so in the event of graft failure; OR
    c. An additional HLA-matched CBU, or two CBUs, reserved as a backup.
8. Females of childbearing potential, defined as any female who has experienced menarche and is not postmenopausal or permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy), agree to use an appropriate method of contraception from at least 7 days prior to Hydroxyurea administration until completion of follow-up procedures. An appropriate method of contraception is defined as one that results in a low failure rate (i.e., less than 1 percent per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine contraceptive devices (IUDs), sexual abstinence, or a vasectomized partner.
9. Patient and/or legal guardian signs the written informed consent after being made 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. Evidence of uncontrolled bacterial, viral or fungal infections or severe concomitant diseases, which in the judgment of the Principal Investigator, indicate that the patient could not tolerate transplantation.
2. Evidence of HIV infection or HIV positive serology.
3. Evidence of active Hepatitis B or Hepatitis C as determined by serology or PCR.

4. Pregnancy as indicated by a positive serum human chorionic gonadotrophin (HCG) test or lactation.
5. Patients with 8/8 HLA-matched related family donor or unrelated donor able to donate.
6. Severe alloimmunization with inability to guarantee a supply of adequate PRBC donors
7. Evidence of donor specific anti-HLA antibodies to the selected NiCord® CBU (MFI>2000 to HLA A, B, C, or DRB1).
8. Prior myeloablative allogeneic hematopoietic stem cell transplant within last 12 months or reduced intensity transplant within the past 6 months.
9. Allergy to bovine products, Gentamicin, or to any product which may interfere with the treatment.
10. Psychologically incapable of undergoing bone marrow transplant (BMT) with associated strict isolation or documented history of medical non-compliance and/or psychiatric illness and/or social situations that would limit compliance with study requirements.
11. Enrolled in another clinical trial or received an investigational treatment within 30 days prior to CBU shipment to the production facility, unless documented approval obtained from Sponsor.

Statistical Considerations

The data from Part 1 and Part 2 will be analyzed separately. A secondary analysis combining the data will be provided; this combined analysis will also present the results from each part separately.

Primary End-point and Principal Analysis: Cumulative incidence of donor-derived neutrophil engraftment by day 42. Time-to-neutrophil engraftment is defined as the first of three (3) consecutive measurements on different days that the patient has an absolute neutrophil count (ANC) greater than, or equal to, 500/uL following conditioning regimen-induced nadir. The ANC recovery must be of donor origin documented by peripheral blood chimerism assays indicating:

a. Mixed chimerism – >10% host cells and <90% host cells

OR

b. Donor chimerism – ≤10% host cells

Interim Analysis and Safety Assessment Guidelines:

Part 1: The data emerging from this study will be reviewed by an independent DMC. In Part 1, this committee will review the accumulated data after 3 6 (and 10, if still recruiting) patients have entered the study and have been assessed at day 100 following the transplant. The committee will make recommendations to the Sponsor regarding early stopping or study modification.

Early safety assessment guidelines will be used to monitor the following events, and alert the DMC. The following events will prompt consideration of early stopping or modification of the protocol:

- Serious (grade 4 or 5) acute toxicities: if ≥2 out of the first 7 or ≥3 out of the first 14 patients experience grade 4 or 5 acute toxicity
- Neutrophil engraftment: if ≥3 of the first 5 patients or ≥4 out of the first 8 patients or ≥5 of the first 11 patients or ≥6 of the first 14 patients fail to achieve neutrophil engraftment (from either NiCord®, the unmanipulated CBU or both). Additionally, early consideration will be given by the DMC if 2 out of the first 2 patients fail to engraft
- Secondary graft failure: If ≥3 of the first 5 patients, ≥4 out of the first 8 patients, or ≥5 of the first 11 patients or ≥6 of the first 14 patients experience secondary graft failure, as defined in section 4.3.2
- Treatment-related mortality at 100 days: if ≥3 out of the first 5 patients or ≥4 out of the first 8 patients or ≥5 out of the first 11 patients or ≥6 of the first 14 patients die before 100 days from treatment-related causes

Part 2: The data emerging from Part 2 of the study will be reviewed by the DMC. In Part 2, a DMC review will occur after 3 patients receive NiCord® as a standalone graft and have been assessed at day 100 following transplant. Recruitment may continue during the follow-up of the third cryopreserved NiCord® recipient.

Early safety assessment guidelines will be used to monitor the following events, and alert the DMC. The following events will prompt consideration of early stopping or modification of the protocol in Part 2:

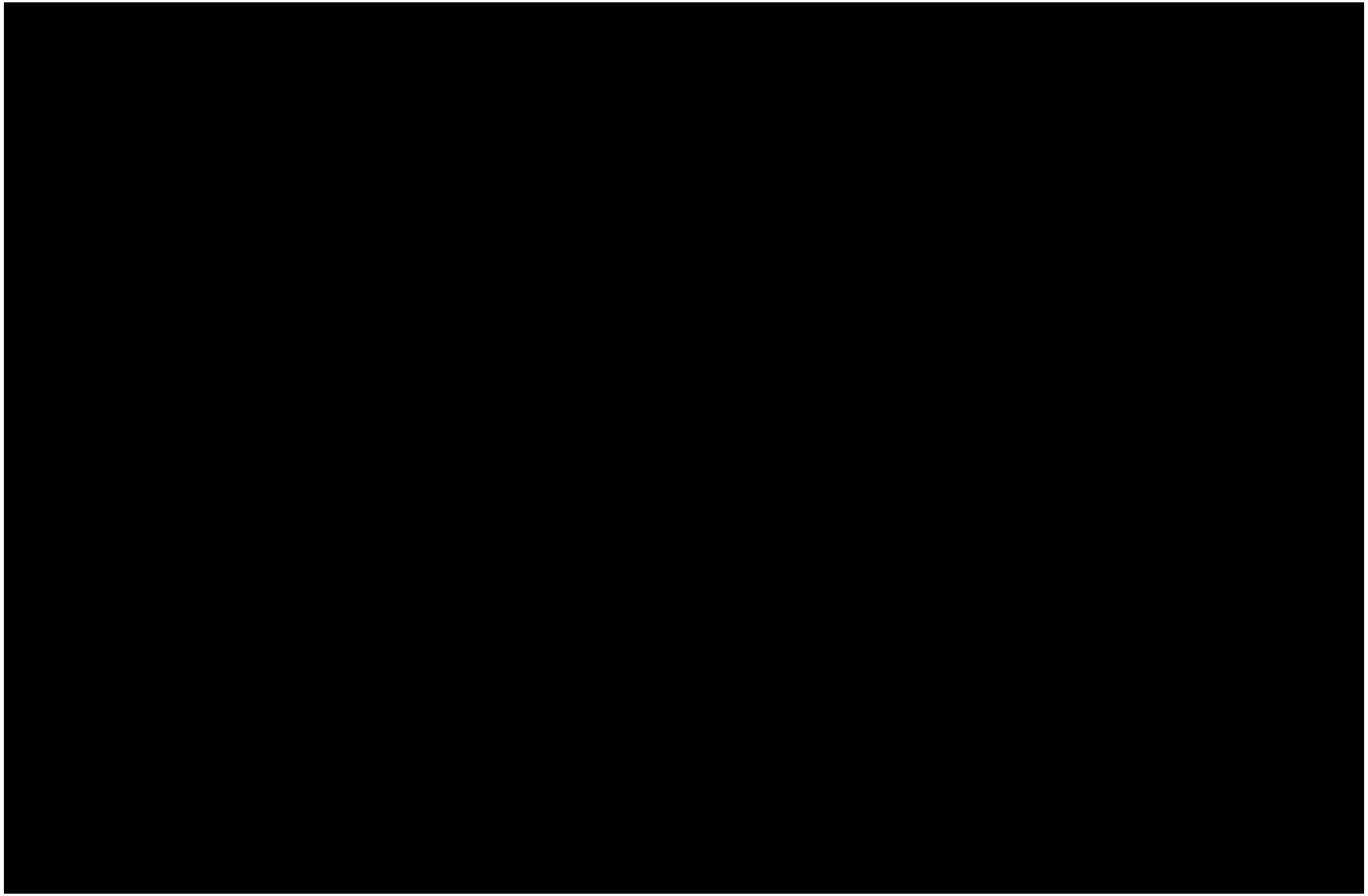
- Serious (grade 4 or 5) acute toxicities: if 1 out of the first 1, or ≥2 out of the first 5 patients experience grade 4 or 5 acute toxicity
- Neutrophil engraftment: if 2 out of the first 2, or ≥3 of the first 5 patients fail to achieve neutrophil engraftment. Additionally, early consideration will be given by the DMC if the first patient fails to engraft
- Secondary graft failure: if 2 out of the first 2, or ≥3 of the first 5 patients experience secondary graft failure, as defined in section 4.3.2
- Treatment-related mortality at 100 days: if 2 out of the first 2, or ≥3 of the first 5 patients die before 100 days from treatment-related causes

Statistical Notes

The guidelines in Part 1 and 2 are formulated so that an alert will occur if the posterior probability is sufficiently high that the chance of an event exceeds a given threshold. Specifically:

- Acute toxicity: posterior probability that chance of grade 4 or 5 acute toxicity is greater than 5% exceeds 0.95. Prior distribution: Beta (0.05, 0.95).

- Neutrophil engraftment: posterior probability that chance of no neutrophil engraftment is greater than 20% exceeds 0.95. Prior distribution: Beta (0.2, 0.8).
- Secondary Graft Failure: posterior probability that chance of secondary graft failure is greater than 20% exceeds 0.95. Prior distribution: Beta (0.2, 0.8).
- Treatment-related mortality: posterior probability that chance of treatment-related mortality within 100 days of transplant is greater than 20% exceeds 0.95. Prior distribution: Beta (0.2, 0.8).



3. BACKGROUND AND RATIONALE

3.1. Overview

Allogeneic hematopoietic stem cell transplantation (HSCT) is a potentially curative procedure for a number of hematologic malignancies, non-malignant hematologic diseases, bone marrow failure syndromes and inherited metabolic disorders. The application of allogeneic HSCT is limited by donor availability of suitably HLA-matched family donors. Alternative donors include mismatched family members or matched unrelated donors, but these approaches are often complicated by an increased risk of graft-versus-host disease (GvHD) or prolonged and cumbersome search and procurement processes. In addition, far fewer subjects of racial minorities find suitable HLA-matched donors.

Umbilical Cord Blood (UCB) has been increasingly used as an alternative source of stem cells; however, in nearly every large single center or registry analysis of outcomes after umbilical cord blood transplantation (UCBT), cell dose is identified as an important factor influencing the incidence and rate of hematopoietic recovery, risk of transplant-related mortality (TRM) and probability of survival and therefore, is a key hurdle precluding broader use of this potentially beneficial stem cell source.

To improve outcomes and extend applicability of UCBT, one potential solution is ex vivo expansion of UCB-derived stem and progenitor cells.

Gamida Cell Ltd. is engaged in the development of NiCord®, an expanded hematopoietic UCB-derived stem/progenitor cell graft, as a potential medicinal product for the treatment of subjects with high-risk hematological malignancies.

The manufacturing of the fresh and the cryopreserved NiCord® cultured fraction is exactly the same apart for the re-suspension on the last manufacturing day, the cryopreservation and the suspension before transplantation. 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.

3.2. Sickle cell disease morbidity and mortality

SCD is an autosomal recessive genetic disease caused by a single mutation in the beta globin gene, which leads to a multitude of pathophysiologic changes including sickling of hemoglobin and vasculopathy resulting in a clinically heterogeneous multisystem disease.[1] The original case report of SCD was published in 1910.[2] SCD was the first inherited disease attributed to a molecular defect – a single amino acid substitution (glutamine replaced by valine) at the sixth position of the β-globin chain of hemoglobin A ($\beta^{6\ glu \rightarrow val}$).[3] Despite being clinically identified more than a century ago, and being the first disease to be known to have a molecular basis, effective therapies based on knowledge of molecular defects are lacking.[4, 5] It is one of the most common inherited disorders worldwide. SCD affects 1 in every 400 African-American live births translating into a prevalence of 70,000 in the U.S. alone, and over 50,000 in Europe. When sickle

hemoglobin (hemoglobin S) is deoxygenated, it aggregates into large polymers, leading to distortion in shape and rigidity of red cells, which in turn is responsible for vaso-occlusion, the hallmark of pathophysiology. Vaso-occlusion underlies the development of symptoms in various target organs including but not limited to the central nervous system, lungs, bones, joints, kidneys, and eyes. The most catastrophic clinical syndrome is the development of cerebral infarction. Cerebrovascular accidents, including cerebral infarction (ischemic stroke) and cerebral hemorrhage (hemorrhagic stroke) are a leading cause of death in children and adults with SCD. Nearly 10% of patients have a stroke by 20 years of age. In addition, silent stroke is also prevalent in 20% of patients with SCD. Once patients have an episode of stroke, recurrent strokes are common in two-thirds of patients without intervention. Other serious complications of SCD include chronic lung disease, pulmonary hypertension and cor pulmonale (as a result of recurrent acute chest syndromes), severe vaso-occlusive painful crises, and osteonecrosis of bones and joints. Children with SCD are also known to have cognitive impairments because of overt or often, silent strokes. These morbidities significantly decrease the quality of life and also predict a more severe phenotype, such as development of stroke and recurrent acute chest syndromes.[6, 7, 8]

Median survival of patients with SCD in the 1970s was 14.3 years.[9, 10] As a result of a number of clinical advances in management of SCD, such as newborn screening, early institution of antibiotics, immunizations, early identification of patients at risk for strokes, chronic transfusions, and hydroxyurea, the median survival in the 1990s had improved to 42 years and 48 years in males and females respectively.[11] While this is a significant improvement from the past, it still represents a decrease in life span by 2-3 decades as compared to the general population. Furthermore, patients often are medically and psychologically debilitated from the years of chronic problems occurring from childhood and frequently cannot become self-sufficient productive members of society as young adults. Taken together, the morbidity and mortality related to SCD represent a public health burden of great magnitude.

3.3. Conventional approaches and their limitations

Chronic transfusion has been shown to decrease the risk of recurrent strokes and even employed in primary stroke prevention.[12, 13] However, despite regular chronic transfusions, approximately 20% patients developed a second stroke in one study.[14] Besides, several patients continue to have silent infarcts in spite of receiving chronic transfusions.[15] Thus, chronic transfusion has limitations in treatment of SCD and is not without risks, the most well-known of which are iron overload, alloimmunization, allergic reactions and infections. Hydroxyurea has also been shown to ameliorate some disease manifestations in some patients with SCD.[16] However, many patients do not respond to hydroxyurea and the role in stroke prevention is unclear. Thus, neither chronic transfusions nor hydroxyurea represent a curative therapy for sickle cell anemia.

3.4. Role of Hematopoietic stem cell transplantation (HSCT)

HSCT is the only therapy demonstrated to be curative for patients with SCD. Studies from Belgium, France, and the U.S. have shown that HSCT from HLA-identical or matched related donors (MRD), using bone marrow or cord blood as graft source, and myeloablative conditioning (MAC) consisting of busulfan, cyclophosphamide and ATG (Bu/Cy/ATG) is associated with event-free survival of 80-85% in patients with SCD.[17, 18, 19, 20] Further analysis

of 26 long-term survivors in the American cohort with a median follow-up of 56 months demonstrated stabilization of underlying vasculopathy, and resolution of other complications related to SCD e.g., further episodes of pain, stroke, or acute chest syndrome in most patients who had stable engraftment.[21] Thus, HSCT clearly modifies the natural course of SCD patients in a curative manner. Barriers to wider applicability of HSCT for SCD patients include the lack of HLA-identical related donors and inherent resistance to engraftment in the setting of alternative donor HSCT.

3.4.1. Barriers to wider applicability of HSCT for SCD

The main barrier to wider applicability of HSCT for SCD is the lack of HLA-identical related or non-related donors. HLA-identical related donors are available for only 10-20% of the patients and there are no reports of matched unrelated donor HSCT likely because of the difficulty finding a suitable matched unrelated donor for SCD patients.[22] Results obtained with an HLA-matched sibling cord blood (CB) transplantation are remarkable but the chances of finding a related HLA-identical CB unit are no better than that of finding an HLA-matched sibling. Available data involving the use of mismatched unrelated CBT indicates primary graft failure and GvHD as a major concern.[23] Patients with SCD, like other hemoglobinopathies, have an inherently increased risk to reject mismatched grafts and therefore, primary graft failure. This is because of various factors such as marrow hyperactivity attempting to compensate for the chronic anemia, high incidence of alloimmunization resulting from frequent exposure to packed red cell transfusions, and lack of exposure to prior chemotherapy leaving the patient immunocompetent immediately prior to transplant. Therefore, there is an urgent need to develop protocols that will enable successful engraftment of grafts derived from mismatched donors. If partially mismatched, unrelated umbilical cord blood grafts would be considered, the majority of the patients would have at least a 4/6 HLA-matched donor available.

3.4.2. Hematopoietic stem cell transplantation for patients with thalassemia

Allogeneic hematopoietic stem cell transplantation (HSCT) still remains the only potentially curative treatment for patients with thalassemia, which represents the most frequent inborn genetic disorder in the Mediterranean countries.[24] Since the first successful allogeneic HSCT, performed in Seattle more than 20 years ago by Thomas and colleagues on an Italian child, hundreds of patients with thalassemia have been cured of their original disorder after receiving an allograft, in most cases from an HLA-identical family donor.[25, 26, 27] In view of this result, allogeneic HSCT represents an attractive therapeutic alternative, especially for those patients, and their families, who do not accept the prospective of a lifelong disease, requiring continuing treatment with blood transfusion and drugs.[28]

The extensive experience accumulated in the field of HSCT from an HLA-identical sibling for patients with thalassemia has allowed to identify clinical parameters influencing post-transplant outcome, thus permitting more refined prognostic counseling to the patients considering the option of HSCT or to their parents.[26, 27, 28, 29, 31] In particular, the risk of dying of transplant-related complications has been clearly shown to be mainly dependent on patient age, iron overload and liver viral infections. In fact, adults, especially when affected by chronic active hepatitis, have a worse outcome than children, the probability of survival with transfusion independence having been reported to be 58%;[29] among children below the age of 17, three

classes of risk have been identified on the basis of regularity of previous iron chelation, liver enlargement and presence of portal fibrosis.[26] In the most recent update of the Pesaro group's experience, the probability of thalassemia-free survival of patients younger than 17 years at time of bone marrow transplantation (BMT) who received the allograft from an HLA-identical relative and belonging to class I and II was 87% and 85%, respectively.[30.] Worse results have been reported in pediatric patients who had low compliance with iron chelation favoring the occurrence of iron-induced organ damage, in whom the probability of thalassemia-free survival was initially reported to be 53%. Reducing the dosage of cyclophosphamide, used together with busulfan in the preparative regimen of these patients, it has been possible to document a lower incidence of transplant-related mortality for children in class III, which remained, however, in the order of 25%.[31] A most recent survey, reporting on a limited number of class 3 patients, has suggested that the adoption, during the 2 months preceding HSCT, of a hypertransfusion regimen, intended to reduce the expansion pressure on the erythron, together with the use of azathioprine and hydroxyurea to suppress hematopoiesis and fludarabine for reducing the risk of rejection may lower the probability of treatment failures and improve post-transplant outcome also in this subgroup of patients.[32]

The results obtained by the Pesaro team in patients transplanted from an HLA-compatible relative have been substantially reproduced by other groups, whose studies have confirmed that the majority of patients with thalassemia given HSCT from an HLA-identical sibling can be cured of their disease and that both iron overload and old age unfavorably affect post-transplant outcome.[33, 34]

One impediment to the success of allogeneic HSCT for the cure of thalassemia is represented by graft rejection, whose incidence is considerably higher than that observed in patients transplanted for leukemia.[30, 31] Several factors may contribute to the occurrence of this complication, including avoidance of any immunosuppressive or myeloablative treatment before transplantation, possible allo-immunization related to erythrocyte transfusions and large spleen size, especially in older patients. Notably, in patients transplanted from an HLA-identical sibling, the incidence of rejection is directly correlated with the patient's class of risk, an incidence of 4%, 8% and 12% being observed in patients belonging to risk class I, II and III, respectively.[30, 31]

Stable mixed chimerism is also not uncommon among patients transplanted for thalassemia from a compatible sibling,[35] as seen also in patients with acquired aplastic anemia following BMT.[36] Patients with thalassemia developing stable chimerism, even with a low percentage of donor marrow progenitors (20-30%), have been reported to experience marked enrichment for donor cells in the mature red blood cell compartment, which makes them transfusion-independent.[35] This observation has provided a strong biological and clinical rationale for considering the use of reduced-intensity preparative regimens in patients with thalassemia. Thalassemia patients with liver/heart damage could represent the ideal candidates for well-controlled, clinical trials of less toxic conditioning regimens by centers experienced in HSCT. So far, few reports have demonstrated the feasibility of using reduced-intensity preparative regimens (which may also help reduce the incidence of late effects, in particular those concerning growth and fertility, resulting from high-dose chemotherapy used for conventional HSCT) for successfully treating patients with haemoglobinopathies.[37, 38, 39, 40] Although transplant-related toxicity was mild in all

cases reported, a significant proportion of these patients did not have sustained engraftment. This finding indicates that, using non-myeloablative strategies, stable donor engraftment is more difficult to achieve in patients with hemoglobinopathies than in adults with malignancy and it does not encourage the use of this approach in young and well-fitted patients, who deserve more intensive myeloablative treatment.

3.4.3. Unrelated Umbilical Cord Blood as an alternative graft source for HSCT

Among the most significant advances in HSCT over the past decades have been explorations into the use of alternate hematopoietic grafts, to include allogeneic unrelated UCB.[41, 42, 43] UCB, the residual baby's blood in the placenta, is a by-product from childbirth that historically had been discarded. Experimental studies have demonstrated that UCB is enriched in primitive hematopoietic progenitors compared with adult bone marrow (BM) and mobilized peripheral blood stem cell grafts (PBSC). Notably, long-term engrafting cells are almost eightfold enriched among UCB CD34+ cells compared to those in CD34+ cells from PBSC. These biological features may well explain the curious clinical finding that despite a slower pace of myeloid engraftment after UCB transplantation there is a higher prevalence of early progenitors in the marrow space in those children who were given UCB as opposed to BM transplant.[44]

UCBT is associated with a decreased incidence as well as severity of both acute and chronic GvHD. There are other advantages such as easy availability and lesser chance of viral transmission through the product. Unrelated 4/6 HLA-matched UCBT is an acceptable stem cell graft for patients with hematological malignancies for whom matched related or unrelated donors are not available. The main drawback of UCBT result from the relatively low dose of total nucleated cells and $CD34^+$ cells within an umbilical cord blood unit. Infusion of high cell dose relative to the size of the patient strongly correlates with time to engraftment and probability of overall engraftment and thus, survival.[45] Results of UCBT for hematological malignancies have been substantially improved in the last years and rate of successful engraftment is relatively high in patients transplanted with an adequate cell dose of $2.5\text{-}3x10^6$/kg. However, delayed hematopoietic recovery still substantially contributes to increased morbidity and transplant-related mortality.[46] For patients without a single UCB unit with adequate cell dose, double UCBT is an acceptable alternative.[47] Yet, the problem of delayed hematopoietic recovery persists and the risk of GvHD is increased.

3.4.4. UCB in hemoglobinopathies: increased graft failure – a function of lower cell dose

Unrelated CBT has been used in a limited number of patients with hemoglobinopathies and with limited success so far. Cell dose is even more critical for the successful of UCBT in SCD and thalassemia patients. It has been reported that cell dose of the UCB graft is an independent predictor of engraftment and subsequent event-free survival in hard to engraft patients. Combined registry data from Eurocord, CIBMTR and New York Blood Center on patients with hemoglobinopathies undergoing UCBT was recently published.[23] Sixteen patients with SCD and 35 patients with thalassemia were reported to have undergone an unrelated UCB transplant. Patients with SCD had an overall survival probability of 94%, but only 50% event-free survival. Seven of 16 SCD patients received a reduced-intensity conditioning. Primary graft failure was the predominant cause of treatment failure occurring in 7 of 16 patients with SCD and 20 of 35

patients with thalassemia. In multivariate analysis of the overall cohort, engraftment rate and EFS were higher with cell dose >5 x 10^7/kg. The 2-year probability of EFS was 45% in patients who received grafts with cell dose >5 x 10^7/kg and 13% with lower cell dose. These results highlight the critical importance of adequate cell dose in patients with hemoglobinopathies undergoing unrelated UCB transplants and suggest more successful results to be obtained by implementing new strategies that would allow adequate cell dose in the UCB graft.

3.4.5. Strategies to augment cell dose: use of dual UCB grafts

With the realization of critical importance of cell dose in engraftment and survival after single UCBT, and with the aim of increasing the cell dose for adults and adolescents who could not find a single cord with adequate cell dose, transplantation was performed in adults with hematologic malignancies with a combination of 2 UCB units that were partially HLA-matched with the recipient (4-6/6 HLA match) and with each other.[56] Phase II non-comparative studies, and retrospective comparisons, suggest that by adding a second CBU, successful engraftment can be achieved at a rate that is comparable to a UCBT using a single adequately sized CBU.[48] Outcomes of single versus double cord in pediatric patients with high risk leukemia undergoing myeloablative conditioning demonstrated similar outcomes with no survival advantage in recipients of a double UCBT as compared to those transplanted with an adequately dosed single UCB unit.[49] While recipients of two units had a higher incidence of acute GvHD, relapse risk was unchanged. Therefore, single UCBT was recommended as the standard approach in children with hematologic malignancies for whom a single unit containing ≥2.5 x 10^7nucleated cells/ kg matched at zero, one or two HLA-loci is available. Double UCBT however remains a suitable alternative in the absence of an adequately dosed single UCB unit in children with hematologic malignancies.

Importantly, despite the increased cell dose provided by DCBT, time-to-neutrophil and platelet engraftment (engraftment kinetics) and engraftment rates appear to be comparable between single and double CBT.[50] Thus the use of DCBT does not appear to improve the hematopoietic recovery following transplantation and the risk of GvHD is increased.

Another confounding topic to consider is that in DCBT usually only one of the two CBUs engrafts. Early after transplantation (day 21) both CBUs contribute to hematopoiesis in 40–50% of patients, but by day 100, one CBU predominates in the vast majority of patients[51] and the dominant CBU cannot yet be predicted. It has been postulated that graft-versus-graft immune interactions are the principal mechanism promoting the engraftment of a single CBU in patients undergoing DCBT. Delaney et al[52] have demonstrated that early $CD3^+$ PB chimerism predicts the long-term engrafting CBU following myeloablative DCBT. The correlation of higher early post-transplant donor $CD3^+$ PB chimerism with the dominant CBU suggests a rapid immune mediated response as a primary mechanism of action for long-term single donor dominance. *In vivo*[53] and *in vitro*[54] studies also suggest that the predominant CBU in the setting of double CBT is the CBU able to develop a prevalent cytotoxic activity directed against activated lymphocytes and HSC graft of the other CBU. It is therefore possible that a discordant dominance between the two CBUs, in terms of stem cell potency and graft-versus-graft alloreactivity, could result in graft failure, i.e., when the dominant CBU with respect to alloreactive capacity eradicates the CBU able to support a more efficient and robust hematopoietic engraftment.[54]

3.4.6. Combining 2 UCB grafts: a newly emerging and successful strategy to augment cell dose

With the realization of critical importance of cell dose in engraftment and survival after single UCBT, and with the aim of increasing the cell dose for adults and adolescents who could not find a single cord with adequate cell dose, transplantation was performed in adults with hematologic malignancies at University of Minnesota with a combination of 2 UCB units that were partially HLA-matched with the recipient (4-6/6 HLA match) and with each other.[55, 56, 57] Twenty-three patients with a median age of 24 years received 2 UCB units with a median infused cell dose of 3.5 x 10^7/kg after TBI-based myeloablative conditioning. Engraftment was achieved in all 21 evaluable patients at a median of 23 days. Mixed chimerism was noted in 24% of patients at day 21, however by day 100, only one of the two units predominated. While a significantly higher CD3+ dose was noted in the predominating unit, this observation has not been confirmed in subsequent larger data from the same institution. Understanding the kinetics of engraftment with double UCBT is an area of active research. Incidence of grade II GVHD was increased but not that of severe grades III-IV (13%). Disease-free survival was 57% at 1 year, with 72% of patients alive if they received transplants while in remission. With safety and feasibility of double UCBT demonstrated, increasing number of double UCBT have been performed at several institutions with similar observations – reproducible engraftment, low transplant related mortality (TRM), and comparable progression free survival (PFS).[58, 59] A multicenter, randomized, open label study, comparing outcomes of single versus double cord in pediatric patients with high risk leukemia undergoing myeloablative conditioning, through the NHLBI/NCI-sponsored Blood and Marrow Transplant Clinical Trials Network (BMT CTN, Study 0501) has been completed.[60] The study demonstrated similar outcomes with no survival advantage in recipients of a double UCB transplant as compared to those transplanted with an adequately dosed single UCB unit. While recipients of two units had a higher incidence of acute GvHD, relapse risk was unchanged. Therefore, single UCB transplant was recommended as the standard approach in children with hematologic malignancies for whom a single unit containing ≥2.5 x 10^7nucleated cells/ kg matched at zero, one or two HLA-loci is available. Double UCB transplant however remains a suitable alternative in the absence of an adequately dosed single UCB unit in children with hematologic malignancies.

3.5. Ex Vivo Expansion Of Cord Blood Cells

Attempts to increase the UCB graft cell dose and particularly the $CD34^+$ progenitor cell dose by ex-vivo expansion led to numerous clinical trials addressing the clinical implications of expansion of an UCB unit using various methods of expansion (Table 1). The double cord approach, used in those trials, serves as safe modality for evaluating the safety and potential efficacy of graft manipulation.

Laboratory studies characterizing the expanded cell populations have shown promise and some of the clinical trials may suggest more rapid hematopoietic recovery in UCB recipients.

Table 1: Methods of Expansion

Type of expansion	Authors	Subjects	Cytokines	Days in culture	Fold expansion		Days to ANC >500	Days to plts >20,000	Survival (median length) and GvHD
					TNC	CD34+			
Liquid suspension	Shpall et al.	*n* = 37, adults and children	SCF, TPO, G-CSF	10	56	4	28	106	32% survival (minimum 17 months) 67% grade II-IV aGvHD 40% grade III and IV GvHD
	de Lima and Shpall	*n* = 35, adults and children	SCF, TPO, G-CSF	14	23	2.3	14	34	48% survival (11 months) 43% grade II–IV aGVHD 7% grades III and IV
	de Lima and Shpall	*n* = 10, adults and children	SCF, FL, IL-6, TPO, TEPA	21	219	6	30	48	30% survival (25 months) 44% grade II aGVHD No grade III and IV aGVHD
	Delaney et al.	*n* = 5, adults and children	Notch ligand δ-1, SCF, FL, IL-6, TPO, IL-3	16	660	160	14		83% survival (277 days)
Stromal co-culture	de Lima and Shpall	*n* = 6, adults and children	SCF, TPO, G-CSF	14	12	12	14.5	30	83% survival (12 months) 33% grade II aGVHD No grade III or IV aGVHD
Continuous perfusion system	Jarosak et al.	*n* = 27, children, few adults	PIXY321, FL, EPO	12	2.4	0.5	22	71	39% survival (41 months) 36% grade II–IV aGVHD 22% grade III and IV aGVHD
	Pecora et al.	*n* = 2 adults	PIXY321, FL, EPO	12	2.2	1.6, second did not expand	28	56	100% survival (13 months) No aGVHD

Abbreviations: aGVHD = acute GVHD; FL = Flt-3 ligand; TEPA = tetraethylenepentamine; TNC = total nucleated cell; UCB = umbilical cord blood.

Summary of clinical trials evaluating UCB that has been expanded *ex vivo*

3.5.1. Ex-Vivo Expansion by Liquid Suspension Culture

In an effort to expand HSCs ex vivo, one method has been liquid culture, in which UCB-derived progenitor cells (primarily CD133+ or CD34+) are cultured with combinations of cytokines growth factors, serum or serum free medium in various flasks, bags or containers. In the attempts to stimulate the proliferation of primitive hematopoietic progenitors, various "cocktails" of growth factors and cytokines were tested but the proper mixture has not yet been determined. Pre-clinical and clinical results with cytokine only expansion cultures were not satisfactory and prompted attempts to further optimize ex vivo culture conditions[61, 62, 63, 64, 65, 66, 67] as well as the development of new technologies aimed at attenuating in vitro differentiation, enhancing expansion of less differentiated progenitor cells and increasing the numbers of short and long term repopulating cells. This included the use of histone deacetylases, thought to promote HSC self-renewal,[68] the use of glycogen synthase kinase-3 inhibitors reported to maintain the pluripotency of stem cells[69] and the use of an immobilized, engineered form of the Notch ligand δ-1to stimulate ex vivo UCB expansion.[70] The latter was tested on a small number of patients[71] with promising results suggesting that the expanded unit may provide short-term repopulating cells that may facilitate and improve speed of engraftment of the non-cultured unit. Later clinical studies have further supported the use of *ex vivo* cultured umbilical cord blood stem cells to shorten the time to hematopoietic recovery following myeloablative chemotherapy.[72, 73] Myeloid engraftment occurred at a median time of about 15-16 days and platelet engraftment at a median of about 40-42 days. This is accomplished by increasing the frequency of lineage committed

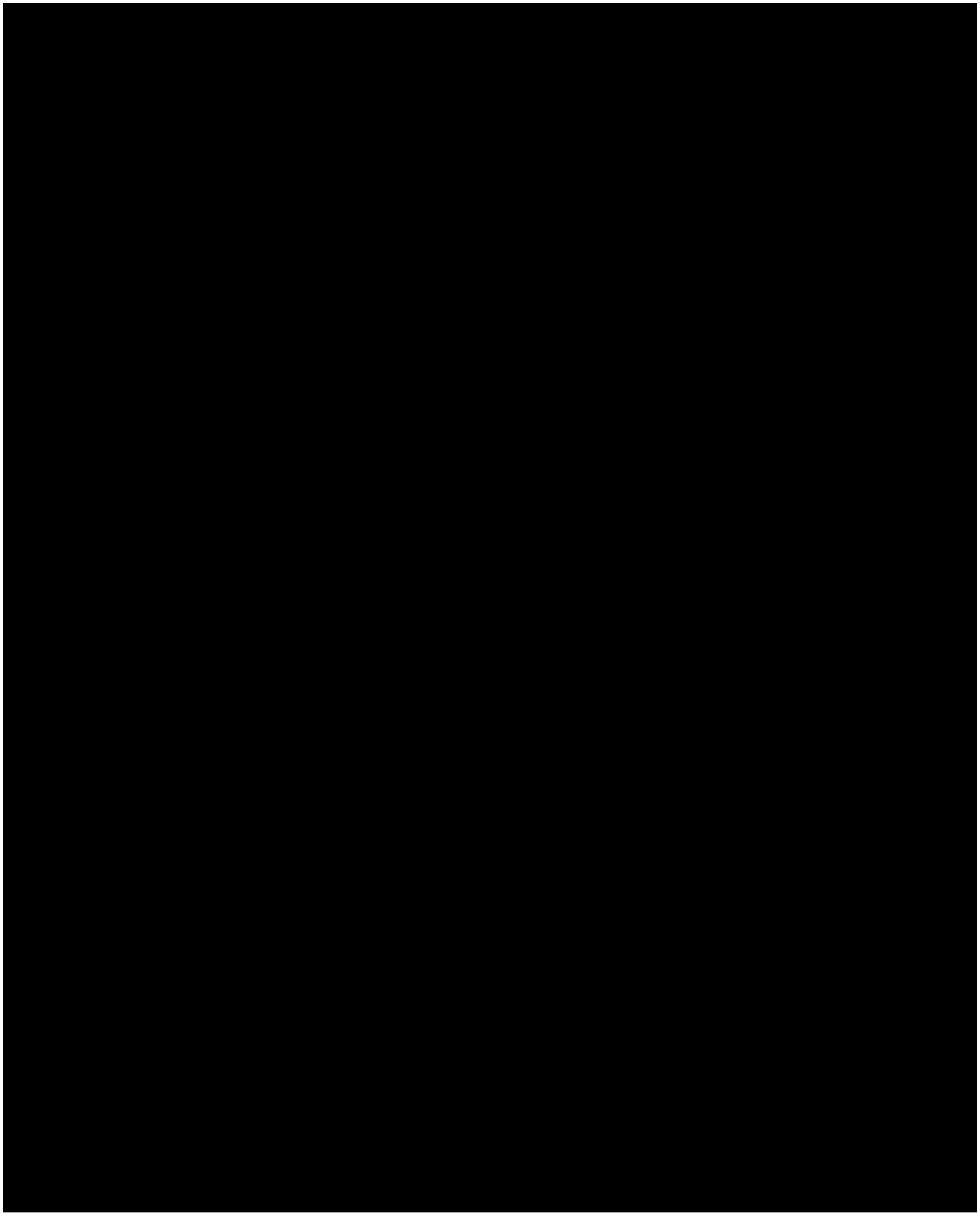
short-term repopulating hematopoietic stem cells. However, the expanded cells which were observed as early as one week post transplantation were lost before or after engraftment. In all cases, the co-infused unmanipulated cord blood unit provided long-term hematopoiesis.

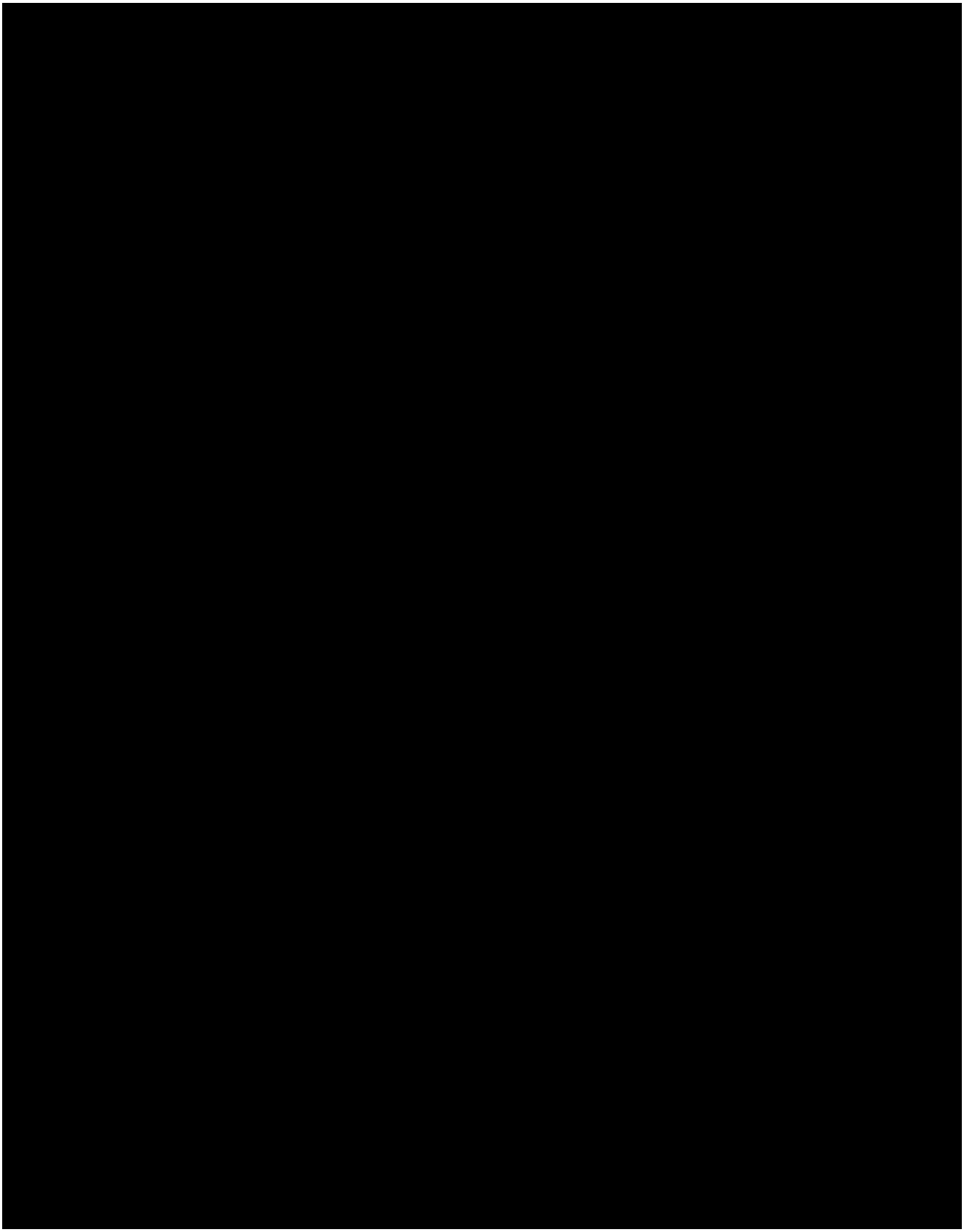
Gamida Cell Ltd. introduced the use of tetraethylenepentamine, a copper chelator thought to modulate the proliferation and differentiation of primitive hematopoietic progenitors.[74, 75, 76] This method was tested in a phase III study of 100 patients with encouraging results.[77]

Gamida Cell Ltd. has undertaken to develop NiCord®, a novel product of ex vivo expanded CBU to be transplanted with or without a second, unmanipulated CBU. As discussed above, the incidence of neutrophil engraftment and time to engraftment following transplantation of either single large CB unit or double CB units are still lower and delayed compared to BM or PB transplantations. By increasing the number of short and long-term reconstitution progenitor cells transplanted, NiCord® has the potential to ameliorate this limitation, enabling broader application of UCBT in adults and adolescents, and improving the clinical outcomes of transplantation.

3.5.2. Gamida Cell Expansion Technology

[redacted]





3.6. Rationale for the administration of NiCord® as a single expanded CBU

Ideally, a successful expansion technology would obviate the need for DCBT, and in most cases would enable the clinician to choose a single, best HLA-matched 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; while the main concern still remains for preservation of long-term repopulating cells in *ex vivo* conditions[106, 107, 108] . The concern is not only related to the persistence of such unique cells in culture, but also to their potential to differentiate and reconstitute all blood cell lineages including myeloid, T, NK and B cells, as efficiently as the long-term repopulating cells before expansion.[109]

Until the advent of NiCord® expansion technology, *ex vivo* expansion studies have only been successful in demonstrating short-term early hematopoietic reconstitution.

In light of the accumulated data from the ongoing NiCord® clinical program in hematologic malignancies, Part 2 of the study aims to assess whether UCB transplantation of a single expanded CBU using the NiCord® technology provides donor-derived engraftment in patients with hemoglobinopathies following myeloablative therapy.

The DCBT approach adds a measure of safety to the evaluation of novel approaches to *ex vivo* expansion. However, as previously described, the drawback of this strategy is that graft-versus-graft immune interactions lead to the engraftment of one of the two CBUs transplanted and therefore potentially, the most potent CBU with respect to hematopoietic reconstitution may be eradicated by the immunologically dominant CBU. Furthermore, the use of DCBT has not demonstrated any improvement in the rates or kinetics of engraftment. Current data suggest that unrelated CBT with NiCord® may make it possible to choose the best CBU for the patient, expand it in culture and transplant it to the patient in a single CBT approach.

Clinical data to date demonstrate that patients with hematological malignancies treated with NiCord® as a standalone graft 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 detailed in section 3.7.1.2, a study of NiCord® in hematological malignancies as a standalone graft source is ongoing (GC P#03.01.020). The dataset that served as the basis for the NiCord® Phase III hematological malignancies study design comprised patients aged 12-65 years old treated at multiple international centers between August 2013 and June 2015. Sixteen patients received NiCord® as a standalone graft. All 16 NiCord®-only recipients achieved neutrophil engraftment by day 42 with full donor chimerism. Only one patient experienced secondary graft failure in the year following NiCord® transplant. The median days to neutrophil engraftment in NiCord® -only recipients was 10 days post transplant, ranging from 6 days to 26 days. All but two 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 75% and 64% respectively. Among the engrafters, the median time to engraftment to 20k/mm^3 and 50k/mm^3 was 32 days and 42 days respectively. Immune reconstitution of CD4+, CD8+, CD19+, CD56+/16+ in NiCord®-only recipients was comparable to unmanipulated cord blood transplantation in historical controls. The overall survival of NiCord®-only recipients at 180 and 365 days was 81% and 59% respectively, and the cumulative incidence of non-relapse mortality at day 100 and day 180 post transplant was 12% and 19% respectively.

Demonstration of successful, rapid and sustained engraftment of a single expanded CBU would obviate the need for the use of a second CBU, providing both potentially less GvHD and significant cost savings. NiCord® could potentially provide an accessible graft for allogeneic transplantation in patients with hemoglobinopathies who do not have a matched related donor option, thereby addressing a critical unmet need.

3.7. Clinical Experience with NiCord® and CordIn™

3.7.1. NiCord® Clinical Experience in Hematological Malignancies

The clinical experience with NiCord® in Hematological Malignancies is summarized in Table 2 below.

Table 2: 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/ Dr. Joanne Kurtzberg and Dr. Mitchell Horwitz Cardinal Bernardin Cancer Center, Loyola University/ Dr. Patrick Stiff

Protocol Number (ClinicalTrials.gov Number)	Study Title	Study Status	Institution/Principal Investigator
GC P#03.01.020 (NCT01816230[b])	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.	Enrollment completed (estimated LPLV: June 2018)	Duke University Health System/ Dr. Mitchell Horwitz Hospital Universitario y Politécnico La Fe/ Dr. Guillermo Sanz Vanderbilt University Medical Center/ Dr. Madan Jagasia Hospital Universitari Vall d'Hebrón/ Dr. David Valcárcel AOU San Luigi Gonzaga/ Dr. Daniela Cilloni Universitair Medisch Centrum Utrecht/ Dr. Jaap Jan Boelens Cedars-Sinai Medical Center/ Dr. Yulia Linares Cleveland Clinic/ Dr. Rabi Hanna University of Minnesota/ Dr. John Wagner Cardinal Bernardin Cancer Center, Loyola University/ Dr. Patrick Stiff Oregon Health & Science University/ Dr. Richard Maziarz National University Hospital/ Liang Piu Koh Singapore General Hospital/ William Hwang
GC P#04.01.020/030 (NCT02039557[c])	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/ Dr. Mitchell Horwitz and Dr. Joanne Kurtzberg Hospital Universitario y Politécnico La Fe/ Dr. Guillermo Sanz Hospital Universitari Vall d'Hebrón/ Dr. David Valcárcel

Protocol Number (ClinicalTrials.gov Number)	Study Title	Study Status	Institution/Principal Investigator
GC P#05.01.020 (NCT02730299[d])	A Multicenter, Phase III, Randomized Trial of Transplantation of NiCord®, Umbilical Cord Blood-derived Ex Vivo Expanded Stem and Progenitor Cells, versus Unmanipulated Umbilical Cord Blood for Patients with Hematological Malignancies	Ongoing	Duke University Health System/ Dr. Mitchell Horwitz Hospital Universitario y Politécnico La Fe/ Dr. Guillermo Sanz Hospital Universitari Vall d'Hebrón/ Dr. David Valcárcel Cleveland Clinic/ Dr. Rabi Hanna University of Minnesota/ Dr. John Wagner Cardinal Bernardin Cancer Center, Loyola University/ Dr. Patrick Stiff Universitair Medisch Centrum Utrecht/ Dr. Jaap Jan Boelens Dana Farber Cancer Institute/ Dr. Corey Cutler University of Kansas Cancer Center/ Dr. Joseph McGuirk

[a] http://clinicaltrials.gov/ct2/show/NCT01221857?term=nicord&rank=1.
[b] https://clinicaltrials.gov/ct2/show/NCT01816230?term=nicord&rank=4
[c] https://clinicaltrials.gov/ct2/show/NCT02039557?term=Gamida+Cell+ltd&rank=6
[d] https://clinicaltrials.gov/ct2/show/NCT02730299?term=Gamida+Cell+ltd&rank=5

The subsequent sections describe the clinical studies mentioned above.

3.7.1.1. 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 $2.5x10^7$ total nucleated cells per kilogram of the recipient's body weight. This unit was designated as the unmanipulated unit. The second unit, designated for NiCord® expansion, contained at least $1.5x10^7$ total nucleated cells per kilogram of the recipient's body weight. When 2 units with at least $2.5x10^7$ total nucleated cells per kilogram of the recipient's body weight were available, the best-matched unit was assigned as the unmanipulated unit. The cord blood units were required to match the recipient at

4 or more HLA loci by intermediate-resolution typing for HLA class I alleles (A and B) and high-resolution typing for HLA class II DRB1 alleles.

The bone marrow conditioning regimen consisted of 1,350-cGy TBI delivered in 9 fractions on days –9 to –5, and fludarabine 40 mg/m^2 was given on days –5 to –2 of the transplantation. An optional infusion of 60 mg/kg cyclophosphamide on days –4 and –3 was given at the discretion of the managing physician. GvHD prophylaxis was provided by Tacrolimus and Mycophenolate Mofetil starting 4 days before transplantation. Mycophenolate Mofetil and Tacrolimus were continued for a minimum of 60 days and 6 months following transplantation, respectively. Main results are described below and in the Clinical Study Report.

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 (one patient received an unmanipulated CBU transplant instead of NiCord®). The median days to neutrophil engraftment in NiCord® recipients achieving engraftment was 12.5 days, ranging from 7 days to 26 days. All but one of the patients who engrafted did so prior to day 20 post-transplant. 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.[110,111,112]. 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).[113]

All engrafted patients maintained full donor chimerism throughout follow-up. Seven patients maintained predominance (>90%) of NiCord® cells, three patients maintained predominance of unmanipulated CBU cells (including one who did not receive NiCord®), and one patient exhibited mixed chimerism throughout follow-up.

Platelets engraftment was achieved in nine out of eleven patients who received NiCord®. One patient died before achieving platelet recovery and one patient experienced primary engraftment failure. 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. Three patients had a grade 3 toxicity (two with hypertension and one with hematuria), two patients had grade 2 toxicity, five patients had grade 1 toxicity, and two patients had no toxicity within 24-hours post infusion.

One patient died from causes other than relapse within the first 100 days post-transplant. No NiCord® recipient developed grade III or IV GvHD. Five of eleven NiCord® recipients developed grade II GvHD. A total of 14 Serious Adverse Events (SAEs) were reported in eight of the eleven NiCord® recipients. One of the 14 SAEs (grade 3 hypertension immediately following infusion) was determined to be related to NiCord®. 1-year overall and progression-free survival rates were 82% and 73%, respectively.

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.

3.7.1.2. Study GC P#03.01.020

A clinical study of NiCord® in hematological malignancies as a standalone graft source is ongoing (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 the NiCord® Phase III hematological malignancies 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 August 2013 and June 2015. Eligibility required the availability of a cord blood unit containing at least $8x10^6$ total CD34+ cells as well as a pre-cryopreserved (post-processing) total nucleated cell count of $\geq 1.8x10^9$, and total nucleated cell dose $\geq 1.5x10^7$ TNC/kg. The cord blood unit was required to match the recipient at 4 or more HLA loci by intermediate-resolution typing for HLA class I alleles (A and B) and high-resolution typing for HLA class II DRB1 alleles.

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

Main results are described below.

Efficacy: Eighteen patients received NiCord® (16 NiCord®-only recipients and two patients who received both NiCord® and the backup CBU). All 16 NiCord®-only recipients achieved neutrophil engraftment by day 42 with full donor chimerism.

The median days to neutrophil engraftment in NiCord® -only recipients was 10 days post transplant, ranging from 6 days to 26 days. All but two 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 75% (95% CI: 43-91) and 64% (95% CI: 32-84) respectively . Two patients died prior to day 100 without $20k/mm^3$ platelet engraftment, one

patient failed to engraft platelets at 20k/mm^3 by day 100, two patients engrafted 20k/mm^3 but not 50k/mm^3 by day 100, and one 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 32 days and 42 days respectively.

The overall survival of NiCord®-only recipients at 180 and 365 days was 81% (95% CI: 51-93) and 59% (95% CI: 25-82) respectively.

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

Safety: Only one patient 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 12% (95%CI: 2-34) and 19% (95%CI: 4-42) respectively.

The incidence of acute GvHD grade II-IV and III-IV at 100 days post NiCord® only transplant was 50% (95% CI: 23-72) and 12% (95% CI: 2-34) respectively. Eight of the sixteen NiCord®-only recipients experienced chronic GvHD in the year following NiCord® transplant. One case of chronic GvHD was extensive while the other seven were limited.

Among 18 patients receiving NiCord® (16 NiCord® only recipients and two patients who received both NiCord® and the backup CBU), no grade 4 infusion toxicity occurred. One NiCord® recipient had a grade 3 toxicity (atrial fibrillation), eight patients had grade 2 toxicity, seven patients had grade 1 toxicity, and two patients had no toxicity within 24-hours post infusion. Two infusion toxicities (grade 2 serious infusion related hypersensitivity and grade 2 non-serious hypertension) were reported as related to NiCord®.

Forty SAEs were reported in 15 of the 18 NiCord® recipients. Six of the 40 SAEs reported were determined to be related to NiCord®. These six related SAEs included five GvHD events and one grade 2 infusion-related hypersensitivity.

Of the 16 NiCord®-only recipients, 14 experienced one or more post transplant grade 2 or 3 infections. Of the 30 reported post transplant grade 2 or 3 infections, a total of five grade 3 infections were reported in three NiCord® only recipients; one patient with a Klebsiella infection at day 325 post transplant, one patient with an RSV infection at day 5 post transplant, and one patient with three 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.

3.7.1.3. 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.

3.7.1.4. Study GC P#05.01.020

The study GC P#05.01.020 entitled: "A Multicenter, Phase III, Randomized Trial of Transplantation of NiCord®, Umbilical Cord Blood-derived Ex Vivo Expanded Stem and Progenitor Cells, versus Unmanipulated Umbilical Cord Blood for Patients with Hematological Malignancies" is an open-label study 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.

3.7.2. CordIn™ Clinical Experience in Hemoglobinopathies

Table 3: Overview of ongoing clinical studies of CordIn™

Protocol Number (ClinicalTrials.gov Number)	Study Title	Study Status	Institution/Principal Investigator
GC P#01.01.030 [a] (NCT02504619 [b])	Allogeneic Stem Cell Transplantation of CordIn™, Umbilical Cord Blood-Derived Ex Vivo Expanded Stem and Progenitor Cells, in Patients with Hemoglobinopathies	Ongoing	Robert Debré Hospital/ Dr. Jean-Hugues Dalle UCSF Benioff Children's Hospital/ Dr. Mark Walters Children's National Medical Center, Washington/ Dr. Allistair Abraham

[a] IND Number: 16245
[b] https://clinicaltrials.gov/ct2/show/NCT02504619?term=GC+P%2301.01.030&rank=1

3.7.2.1. 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 an open-label study to evaluate the safety and efficacy of CordIn™ in patients with Hemoglobinopathies following conditioning therapy with Busulfan, Thiotepa, and Fludarabine. As of 09Oct2017, one patient has been transplanted on this protocol.

3.8. Rationale for Study Design & Dosages

For HSCT to become a realistic therapeutic option available to a majority of patients with severe SCD and thalassemia, effective and safe use of alternative donors such as umbilical cord blood

needs to be established. Given that previous attempts with UCB grafts result in too high a level of graft failure, this study proposes an innovative strategy for unrelated allogeneic transplantation of SCD patients and thalassemia patients using an ex-vivo expanded UCB graft utilizing a novel technology (NiCord®), with or without a second unmanipulated CBU, following preparative conditioning. This approach aims to address the need for improved donor access, as well as the CD34 cell dose limitation. We will gain information about engraftment and safety of unrelated UCB transplantation with NiCord® grafts, as well as additional aspects, including immune reconstitution and GvHD.

3.8.1. Study Population

This study will include patients who are candidates for myeloablative HSCT for treatment of SCD or thalassemia. As described above allogeneic HSCT with sibling donor cell engraftment can ameliorate SCD or thalassemia symptoms, improve quality of life, and stabilize vasculopathy with acceptable rates of early and late toxicities. Unfortunately, for a very large number of patients such a match is not available. CBUs are widely available but their limited cell dose is associated with limited stem/progenitor cell subpopulations and is a key hurdle precluding broader use of this stem cell source in this population. Therefore, the study population of SCD or thalassemia using expanded cord blood will be included in this study. For ethical reasons, the study will only enroll patients who do not have an adequate suitably matched and readily available stem cell donor.

3.8.2. CBU Cell Dose

Part 1 only: as a safety precaution, the unmanipulated UCB unit is required to contain at least $3.5x10^7$ TNC/kg body weight.

Part 1 and Part 2:
The manipulated UCB unit is required to contain $\geq 1.8x10^9$ TNC and $\geq 1.8x10^7$ TNC/kg body weight for patients weighing ≥25kg, and TNC $\geq 1.6x10^9$ for patients weighing <25kg.

The manipulated CBU should contain a pre-cryopreserved (post processing), total CD34+ cell count of $\geq 8x10^6$ for patients weighing ≥ 25 kg and a pre-cryopreserved (post processing), total CD34+ cell count of $\geq 7x10^6$ for patients weighing < 25 kg.

3.8.3. 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.

4. STUDY OBJECTIVES, HYPOTHESIS & STUDY ENDPOINTS

4.1. Objectives

Primary Objectives

- Assessment of the acute toxicity associated with the infusion of NiCord®, within 24 hours post-infusion
- Part 1: Assessment of cumulative incidence of donor-derived neutrophil engraftment by day 42 following co-transplantation of NiCord® and unmanipulated cord blood grafts
- Part 2: Assessment of cumulative incidence of donor-derived neutrophil engraftment by day 42 following transplantation of NiCord®

Secondary Objectives

- Proportion of transplant-related mortality at 100 days
- Event-free survival at 100 days (death, autologous recovery, primary or secondary graft failure will be considered events for this endpoint)
- Overall survival at 180 days

Exploratory Objectives

- Incidence of donor cell chimerism (>10%) from either donor at 100 and 180 days
- Percentage donor chimerism in whole blood, CD3+ and myeloid (CD15+ or CD33+) fractions at 7, 14, 21, 28, 42, 70, 100 and 180 days
- Time from infusion to neutrophil (>500/uL) and platelet (>50k/uL) engraftment
- Platelet engraftment (>50k/uL) at 180 days
- Incidence of acute GvHD grade II-IV and III-IV at 100 days
- Incidence of chronic GvHD (limited or extensive) at 180 days
- Incidence of regimen-related toxicity
- Incidence of life-threatening and fatal infections at 180 days
- Immune reconstitution at 100 days and 180 days

Post-study Analysis

- Event-free survival at 1 year (death, autologous recovery, primary or secondary graft failure will be considered events for this endpoint)
- Overall survival at 1 year
- Percentage donor chimerism in whole blood, CD3+ and myeloid (CD15+ or CD33+) fractions at 1 year
- Incidence of chronic GvHD (limited or extensive) at 1 year
- Incidence of life-threatening and fatal infections at 1 year

- Immune reconstitution at 1 year

4.2. Hypothesis

Part 1: Co-transplantation of NiCord® and an unmanipulated unrelated cord blood graft in patients with hemoglobinopathies (SCD or thalassemia major) following a preparative therapy will be safe and will enable cord blood engraftment.

Part 2: Transplantation of NiCord® in patients with hemoglobinopathies (SCD or thalassemia major) following myeloablative preparative therapy will be safe and will enable cord blood engraftment.

4.3. Definition of Study Endpoints

4.3.1. Acute Toxicity

Acute toxicity will be assessed and graded as per site practice, guidelines and forms and in line with CTCAE v.4.03 as specified in Appendix D.

4.3.2. Neutrophil Engraftment

Neutrophil engraftment is defined as achieving an Absolute Neutrophil Count (ANC) of ≥500 mm^3 for 3 consecutive measurements on different days by day 42 inclusive (the day of engraftment will be defined as the first of these 3 days). The ANC recovery must be of donor origin documented by peripheral blood chimerism assays indicating a. Mixed chimerism - >10% host cells and <90% host cells or b. Donor chimerism – ≤10% host cells.

Primary graft failure is defined as failure to achieve neutrophil engraftment by day 42 as described above. Death prior to day 14 will be considered insufficient follow-up to determine graft failure. Infusion of a second stem cell product on or prior to Day 42 will be considered primary graft failure. 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.

Secondary graft failure consists of documented engraftment as defined above, followed by neutropenia (< 500/µL for three or more consecutive laboratory values on separate days), without subsequent improvement occurring either spontaneously or after growth factor treatment. Infusion of a second stem cell product after documented neutrophil engraftment will be considered secondary graft failure.

4.3.3. 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 >$50x10^9$/L with no platelet transfusions in the preceding 7 days (count day of engraftment as one of the preceding 7 days). The first day of the three measurements will be designated the day of platelet engraftment.

4.3.4. Autologous Recovery

Autologous recovery is defined in patients recovering from an aplastic phase as achieving ANC ≥500 mm^3 for 3 consecutive measurements on different days with ≥90% host chimerism in the peripheral blood or >70% Hb S level on Hemoglobin electrophoresis.

Autologous recovery is defined in patients who have previously recovered as presenting with ANC ≥500 mm^3, and RBC and platelet transfusion independence in the past month with ≥90% host chimerism in the peripheral blood or >70% Hb S level on Hemoglobin electrophoresis.

4.3.5. Transplant Related Mortality

Transplant related mortality is defined as any death not preceded by autologous recovery.

4.3.6. Acute and Chronic GvHD

Incidence of acute GvHD grade II-IV and III-IV will be assessed based on the Consensus Conference on Acute GvHD grading (Appendix A) on day 100. Chronic GvHD will be assessed on day 180 and will be classified as limited or extensive according to Appendix A.

4.3.7. Immune Reconstitution

The humoral system will be assessed based on levels of immunoglobulins (IgG, IgA, IgM). 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, CD16/56), as well as additional immunophenotyping as per site practice. T-Cell Receptor Excision Circles (TREC) analysis will be performed.

4.3.8. Chimerism of the Two CBU Grafts

Percent engraftment of both NiCord® and the unmanipulated CBUs will be assessed by peripheral blood Chimerism test using RFLP or microsatellite with separate assessment of the lymphoid and myeloid fractions post neutrophil engraftment and optionally an assessment of erythroid chimerism at 180 days post-transplant in patients with mixed chimerism.

4.3.9. Life-threatening/Fatal Infection

Any infection that involves:

- Bacteremia with deep organ involvement (e.g., with new or worsening pulmonary infiltrates; endocarditis)
- Severe sepsis with bacteremia
- Fasciitis requiring debridement
- Pneumonia requiring intubation
- Brain abscess or meningitis without bacteremia
- C. Difficile toxin positive stool with toxic dilatation or renal insufficiency with/without diarrhea
- Fungemia including Candidemia
- Proven or probable invasive fungal infections (e.g., Aspergillus, Mucor, Fusarium, Scedosporium, resistant candida species)

- Disseminated infections (defined as multifocal pneumonia, presence of urinary or blood antigen, and/or CNS involvement) with Histoplasmosis, Blastomycosis, Coccidiomycosis, or Cryptococcus
- Pneumocystis jiroveci pneumonia (regardless of PaO2 level)
- Severe VZV infection (coagulopathy or organ involvement)
- CMV end-organ involvement (pneumonitis, enteritis, retinitis)
- EBV PTLD
- Adenovirus with end-organ involvement (except enteritis, conjunctivitis and upper respiratory tract)
- Lower tract respiratory viruses
- Any viral encephalitis or meningitis
- CNS or other organ toxoplasmosis
- Strongyloides hyperinfection
- Severe sepsis without an identified organism

4.3.10. Regimen Related Toxicities

Post transplant grade 3-5 toxicities assessed using CTCAE v4.03 as specified in Appendix D.

5. STUDY POPULATION

5.1. Number of Patients

The sample size is up to 20 evaluable patients (up to 15 evaluable patients who enrolled and received NiCord® and an unmanipulated CBU plus up to 5 evaluable patients who enrolled and received NiCord® only). In addition, patients must have met all of the following criteria:

- Did not receive any stem cells up to day 28 except for the NiCord® and, if in Part 1, the unmanipulated CBU (e.g., second unmanipulated CBU)
- Did not die prior to day 14
- Received conditioning therapy as specified in the protocol
- Did not seriously contravene the eligibility criteria specified in section 5.2 below
- Did not receive a NiCord® transplant that was outside the final process quality control (FPQC) limits specified in section 8.3

Enrolled patients who have received a transplant of CB cells but did not meet all of the above criteria will enter the main statistical analysis (ITT) but will be considered non-evaluable for the per protocol analysis. For completing the per protocol analysis such patients can be replaced.

Any patient may be removed from the study at any time if in the judgment of the Investigator further treatment 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 withdrawn from the study before receiving NiCord®. All screening failures will be replaced.

Patients will be defined as early termination/discontinuation, if dropout occurs after transplantation of NiCord®.

For early termination/discontinuation patients, termination visit should be completed. In case such patients did not withdraw consent, study investigator will make all efforts to gather information on the clinical outcomes as assessed during the usual clinical management of their disease over the first 180 days following transplantation and to capture this information in the CRF.

5.2. Eligibility Criteria

Inclusion Criteria

1. Patients must be 2 – 45 years of age and at least 10 kg.
2. Patient is a candidate for allogeneic SCT for treatment of SCD or thalassemia:

a. Patient must have clinically severe SCD (e.g., SS, SC or SBeta^0 Thal) with at least one of the following clinical complications:

- Recurrent painful events (at least 3 in the 2 years prior to enrollment) that cannot be explained by other causes. Pain may occur in typical sites associated with vaso-occlusive painful events and cannot be explained by causes other than SCD. Pain lasts at least 4 hours and requires parenteral narcotic treatment, equianalgesic dose of oral narcotics or parenteral nonsteroidal anti- inflammatory drugs. These painful events may be treated in any setting, but events managed at home will be considered only if there is documentation of the event in a clinical record that may be reviewed by an investigator. These events must occur despite adequate supportive care measures (e.g., hydroxyurea therapy)
- Acute chest syndrome (ACS) with at least two episodes with the development of a new infiltrate on chest radiograph and/or having a perfusion defect demonstrable on a lung radioisotope scan within the past two years that required hospitalization, oxygen therapy, and red blood cell (RBC) transfusion. These episodes must occur despite adequate supportive care measures, (e.g., hydroxyurea therapy). At least one episode of acute chest syndrome per year while on hydroxyurea therapy unless patient is unable to take hydroxyurea due to toxicity
- Any combination of painful events and ACS episodes that total three or more events within the two years before transplantation
- SCD related and clinically significant neurologic event (stroke or hemorrhage) or SCD related neurologic defect lasting more than 24 hours
- Abnormal cerebral magnetic resonance imaging (MRI) and/or abnormal cerebral magnetic resonance angiography (MRA)
- Abnormal Transcranial Doppler (TCD), as defined by a TCD velocity that exceeds 200 cm/sec by the non-imaging technique (or TCD measurement of >185 cm/sec by the imaging technique) measured at a minimum of two separate occasions one month or more apart
- Patients on chronic PRBC transfusion therapy, defined as receiving 8 or more transfusions per year for > 1 year to prevent vaso-occlusive clinical complications (e.g., pain, stroke, and acute chest syndrome), with a history of alloimmunization which compromises the delivery of adequate transfusion therapy

  OR;

b. Patients with thalassemia major requiring ≥8 (or >100 ml/kg) RBC transfusions per year in the two years preceding enrollment.

3. Part1: Patients must have two partially HLA-matched CBUs. Units 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 subject and 3-6/6 HLA-A, B, DRB1 loci with each other (using same resolution of typing). Double mismatch at any one locus (A, B, or DRB1) is not permitted

   Part 2: Patients must have one partially HLA-matched CBU. 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 subject. Double mismatch at any one locus (A, B, or DRB1) is not permitted

a. For patients weighing ≥ 25 kg, the manipulated CBU must have a pre-cryopreserved (post processing) total nucleated cell dose of ≥$1.8x10^9$ and ≥$1.8x10^7$cells per kg body weight.

   For patients weighing < 25 kg, the manipulated CBU must have a pre-cryopreserved (post processing) total nucleated cell dose of ≥$1.6x10^9$.

   Part 1: The unmanipulated CBU should contain a pre-cryopreserved (post processing), nucleated cell dose of at least $3.5x10^7$/kg. The better matched unit will be the unmanipulated unit (as per investigator's discretion).

b. The manipulated CBU should contain a pre-cryopreserved (post processing), total CD34+ cell count of ≥ $8x10^6$ for patients weighing ≥ 25 kg and a pre-cryopreserved (post processing), total CD34+ cell count of ≥$7x10^6$ for patients weighing < 25 kg.

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

d. The CBU should be procured from public banks that meet local applicable regulations

e. The selected unit should be typed twice (i.e., initial typing and verification typing). Verification typing (confirmatory typing) should be in a laboratory that is ASHI/EFI accredited and must come from an attached segment

4. Patients' Performance score ≥70% by Lansky or Karnofsky performance status scale.
5. Patient has sufficient physiologic reserves including:

- Cardiac: Left ventricular ejection fraction (LVEF) > 50% by echocardiogram radionuclide scan or cardiac MRI; or LV shortening fraction > 26%
- Pulmonary: Pulse oximetry with a baseline O2 saturation of ≥ 85% is required for all patients; DLCO > 60% of predicted for age (corrected for hemoglobin) for patients in whom pulmonary function testing can be performed. cDLCO value should be from testing performed before the administration of a bronchodilator if applicable. FVC and FEV1 > 60% of predicted for age.
- Renal: Serum creatinine ≤ 1.5 x upper limit of normal for age and GFR > 100 mL/min/1.73 m^2. For patients ≥16 years of age, GFR should be >70 mL/min/1.73 m^2. Note, estimated GRF value not acceptable; nuclear GFR testing must be performed.
- Hepatic: Serum conjugated (direct) bilirubin < 2 x upper limit of normal for age as per local laboratory in the absence of gall bladder disease or prior cholecystectomy; Hepatic transaminases (ALT and AST) < 5 x upper limit of normal range

6. In SCD patients, HbS should be ≤ 45% within 7 days prior to initiation of the conditioning regimen. If the HbS level is >45% then the patient must receive RBC transfusions or erythrocyte exchange prior to conditioning regimen initiation.
7. Patient must have at least one graft source as a backup in case of graft failure:
    a. Autologous stem cells harvested from bone marrow; OR
    b. A related, haplo-identical family member who is suitable for bone marrow or peripheral blood stem cell donation and has agreed to do so in the event of graft failure; OR
    c. An additional HLA-matched CBU, or two CBUs, reserved as a backup
8. Females of childbearing potential, defined as any female who has experienced menarche and is not postmenopausal or permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy), agree to use an appropriate method of contraception from at least 7 days prior to Hydroxyurea administration until completion of follow-up procedures. An appropriate method of contraception is defined as one that results in a low failure rate (i.e., less than 1 percent per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine contraceptive devices (IUDs), sexual abstinence, or a vasectomized partner.
9. Patient and/or legal guardian signs the written informed consent after being made 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. Evidence of uncontrolled bacterial, viral or fungal infections or severe concomitant diseases, which in the judgment of the Principal Investigator, indicate that the patient could not tolerate transplantation.
2. Evidence of HIV infection or HIV positive serology.
3. Evidence of active Hepatitis B, Hepatitis C or EBV as determined by serology or PCR.
4. Pregnancy as indicated by a positive serum human chorionic gonadotrophin (HCG) test, or lactation.
5. Patients with 8/8 HLA-matched related family donor or unrelated donor able to donate.
6. Severe alloimmunization with inability to guarantee a supply of adequate PRBC donors.
7. Evidence of donor specific anti-HLA antibodies to the selected NiCord® CBU (MFI>2000 to HLA A, B, C, or DRB1).
8. Prior myeloablative allogeneic hematopoietic stem cell transplant within last 12 months or reduced intensity transplant within the past 6 months.
9. Allergy to bovine products, Gentamicin, or to any product which may interfere with the treatment.

10. Psychologically incapable of undergoing bone marrow transplant (BMT) with associated strict isolation or documented history of medical non-compliance and/or psychiatric illness and/or social situations that would limit compliance with study requirements.
11. Enrolled in another clinical trial or received an investigational treatment within 30 days prior to CBU shipment to the production facility, unless documented approval obtained from Sponsor.

5.3. Reproductive Restrictions

The long term effect of stem cell product on fetal development has not been studied. Consequently, precautions must be taken to avoid any pregnancy that could potentially occur during drug exposure to EITHER male OR female patients.

Female patients should be either post-menopausal (amenorrhea for at least 12 consecutive months), surgically sterile or, if a woman of child-bearing potential (WOCP), have a negative urine beta human chorionic gonadotropin (HCG) pregnancy test prior to entering the study and agree to use acceptable methods of contraception during the study. An acceptable method of contraception is defined as one that results in a failure rate less than 1 percent per year when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine contraceptive devices (IUDs), sexual abstinence, or a vasectomized partner.

WOCP must be advised to use acceptable contraceptives throughout the study period. If hormonal contraceptives are used, they should be taken according to the package insert. WOCP who are not currently sexually active must agree to use acceptable contraception, as defined above, if they decide to become sexually active during the period of the study and for 4 weeks after the last dose of stem cell therapy.

5.4. Patient Withdrawals

5.4.1. Withdrawal of Patients from the Study

Any patient may be removed from the study at any time if in the judgment of the Investigator further treatment is not in the best interests of the patient. The primary reason for withdrawal must be recorded in the patient's medical record and in the CRF. If a patient is withdrawn for more than one reason, each reason should be documented in the source document and the most medically significant reason should be entered on the CRF.

Patients may also withdraw themselves from the study at any time and for any reason, without prejudice to their future medical care by the physician or at the institution.

Patients will be defined as screening failures if they are withdrawn from the study before receiving NiCord®, or as early termination/discontinuation, if dropout occurs after transplantation of NiCord®. Screening failures can be replaced.

5.4.2. Criteria for Withdrawal

Patients who are prematurely discontinued 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 first 6 months following treatment. This will allow us to continue to gather clinical information on patients who subsequently withdraw from 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 or legal guardian withdrew consent
- Sponsor requested patient to be withdrawn
- Pregnancy
- Request of primary care physician or Investigator, based on the patient's best interests
- Occurrence of an AE or SAE, which, in the judgment of the investigator, justifies withdrawal due to its nature, severity or requirement for treatment, regardless of the causal relationship to the IMP
- Non-compliance (per investigator judgment)
- Lost to follow-up

At least three documented attempts must be made to contact any patient lost to follow-up (e.g., calling the patient at last known phone number, sending a certified letter to the patient's last known address).

5.4.3. Early Discontinuation of Follow-up

For early termination patients that withdraw/are withdrawn from the study post transplant, any assessments due at the time of withdraw (according to Table 4) are requested.

6. CONCOMITANT MEDICATIONS & SUPPORTIVE CARE

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.

6.2. Disallowed Concomitant Medications

The following medications should not be given post transplant:

- Methotrexate (unless approved in advance by Sponsor)
- Any cytokines except G-CSF or GM-CSF should not be used (including IL-2 or others, unless approved by Sponsor); bio-identical substitutions are allowed.
- The use of Bactrim is discouraged on or after day -2 and prior to engraftment as it may delay engraftment, and is reserved only in cases where it is assessed to be essential and superior to all alternative medications
- Investigational agents, unless previously approved by the sponsor

6.3. Preparative & Conditioning Regimen

All patients will receive one of two conditioning regimens, depending on the patient's age, as shown in the tables below. GvHD prophylaxis will consist of cyclosporine and mycophenolate in both regimens.

Patients <21 years old

Days	Agent	Dose
-35 to -15	Hydroxyurea[1]	30mg/kg/day orally
-14 to -10	Fludarabine	35 mg/m2 IV daily x 5 days
-9 to -6	Busulfan	1mg/kg/dose IV q 6h x 16 doses
-5 to -2	Cyclophosphamide[2]	50mg/kg/day x 4 doses

[1] Hydroxyurea may be extended if transplant is delayed. If patient is already on HU, the dose will be maintained at the prescribed level if it is at least 30mg./kg/day.
[2] If treatment with Cyclophosphamide is contraindicated, substitute Melphalan 45 mg/m2/day IV x 3 days (-4 to -2)

Patients >21 years old

Days	Agent	Dose
-35 to -13	Hydroxyurea[1]	30mg/kg/day orally
-12 to -8	Fludarabine	35 mg/m2 IV daily x 5 days
-7 to -4	Busulfan	0.8 mg/kg/dose IV q 6h x 16 doses
-3 and -2	Cyclophosphamide	60mg/kg/day x 2 doses

[1] Hydroxyurea may be extended if transplant is delayed. If patient is already on HU, the dose will be maintained at the prescribed level if it is at least 30mg./kg/day.

6.3.1. Hydroxyurea Administration

Start at 30mg/kg/day, once daily as a liquid or capsule. Monitor CBC, ANC and LFTs weekly. Hold hydroxyurea for Platelets < 50,000/uL, ANC < 1000, or if AST/ALT > 4x Upper limit of

normal. Resume at 20% lower dose when laboratory values improve. Start no later than day -35 and continue until one day prior to the start of conditioning. The administration period may be extended if transplant is delayed. If the patient is already on a lower dose of hydroxyurea, adjust the dose to 30 mg/kg/day and continue. If the patient is already on a higher dose hydroxyurea, no adjustment is necessary.

Refer to Appendix E, 'Drug Labels', for risks and toxicities of Hydroxyurea administration

6.3.2. Fludarabine Administration

Fludarabine 35 mg/m2/day will be administered as a 15-30 minute IV infusion. Fludarabine will be dosed as per adjusted ideal body weight (see below for cyclophosphamide).
Refer to Appendix E, 'Drug Labels', for risks and toxicities of Fludarabine administration.

6.3.3. Busulfan Administration

For patients <21 years old, administer 1 mg/kg/dose intravenously as a 2-hour infusion every 6 hours for 16 doses. For patients ≥21 years old, administer 0.8 mg/kg/dose intravenously as a 2-hour infusion every 6 hours for 16 doses. Dilute in normal saline to a concentration of 0.5mg/ml. Busulfan pharmacokinetic sampling will be obtained after the 1st dose. Dose modification will target a steady state concentration (Css) of 600-900 ng/ml.

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

6.3.4. Cyclophosphamide (CY) Administration

Dose will be calculated using adjusted ideal body weight*, if actual body weight is more than 125% of ideal body weight. For patients <21 years old, the dose is 50mg/kg/day for 4 days (60mg/kg/day for 2 days for patients ≥21 years old) diluted in normal saline and administered intravenously as a 60 minute infusion. Provide adequate hydration 3000 ml/m2/day of appropriate maintenance IV solution during CY administration. Mesna 50 mg/kg/day is given IV as a continuous infusion beginning 30 min prior to CY and continuing until 24 hours after the last administered CY dose.

Refer to Appendix E, 'Drug Labels', for risks and toxicities of CY administration.

* Ideal Body Weight Formulas:

For patients 1 to 18 years of age: (ht = cm, IBW = kg)

Less than 60 inches (152.4 cm): IBW = (ht2 x 1.65)/1000

More than 60 inches (152.4 cm): Males IBW = 39.0 + [2.27 x (ht - 60)]

Females IBW = 42.2 + [2.27 x (ht - 60)]

For patients over 18 years old:

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 Ideal Body Weight Formula for all patients:
AIBW = IBW + [(0.25) x (ABW - IBW)]

6.3.5. Melphalan

If treatment with cyclophosphamide is contraindicated in patients <21 years old, substitute melphalan 45 mg/m2/day IV as a 15-20 minute infusion x 3 days (-4 to -2). Melphalan must be infused within 60 minutes of preparation.

Refer to Appendix E, 'Drug Labels', for risks and toxicities of Melphalan administration.

6.3.6. Methylprednisolone

If methylprednisolone is substituted for ATG, administer IV as a 1 hour infusion.

Refer to Appendix E, 'Drug Labels', for risks and toxicities of Methylprednisolone administration.

6.4. GvHD Prophylaxis Medications

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

Cyclosporine A (CSA)

CSA will be administered beginning on Day –3. If administering via continuous IV infusion, it is recommended to target cyclosporine trough levels of 200-400 ng/mL by TDX method (or 100-250 ng/mL by Tandem MS or equivalent level for other CSA testing methods). For intermittent dosing, it is recommended to target cyclosporine trough levels of 150-300 ng/mL by TDX method (or equivalent level for other CSA testing methods).

Dose adjustments will be made on the basis of toxicity and high or low CSA levels. Once the patient can tolerate oral medications and has a normal gastro-intestinal transit time, CSA can be converted to an oral form at 2-3x the current IV dose. CSA dosing will be monitored and altered as clinically appropriate.

In the absence of actual toxicity, patients will receive CSA until Day +180 or graft failure. Following day +180 patients will receive CSA according to institutional protocols.

In the event of toxicity or GvHD, centers may switch to Tacrolimus. Dosing should be adjusted to maintain a tacrolimus trough blood level of 5-15 ng/mL. In the event of toxicity to Tacrolimus, treat per institutional practice.

Refer to Appendix E, 'Drug Labels', for risks and toxicities of CSA administration.

Mycophenolate Mofetil (MMF)

MMF will be given at a dose of 15 mg/kg/dose IV q 8 hours beginning the morning of Day –3. (If renal failure and GFR < 25 mL/min do not exceed dose of 1 gm q 8 hours. No dose adjustment is required for liver disease.) MMF should be given IV until patient can tolerate oral medications and has a normal gastro-intestinal transit time. Capsules/tablets or suspension may

be used to achieve calculated doses, and the site is allowed to round the dose up or down to accommodate the nearest capsule/tablet size per standard of care at the site. MMF will be dosed based on the patient's actual body weight.

MMF should be continued for 45 days or 7 days after engraftment, whichever day is later, if acute GvHD or graft failure has not occurred. If GvHD occurs before Day 45, treat according to institutional protocols.

In the event of toxicity to MMF, dosing may be adjusted or discontinued per institutional practice.

Refer to Appendix E, 'Drug Labels', for risks and toxicities of MMF 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. The following guidelines are suggested:

- The diagnosis of acute GvHD will be made on clinical and histological grounds (see Appendix A for grading system). Acute GvHD, manifest as skin rash (ranging from palmar erythema to bullous dermatitis), mucositis (manifest most dramatically as diarrhea), hepatitis, and delayed hematopoietic recovery, usually occurs within the first 100 days but may occur later on. Patients with grade II or greater acute GvHD may receive as first-line therapy methylprednisolone, 1-10 mg/kg/day (IV or PO) for 7 to 14 days, and then tapered as clinically indicated every 5-7 days. An alternative first-line regimen of methylprednisolone 500 mg/m2/dose q 12 hours x2 doses, repeated every 48-72 hours for up to 4 courses may also be used. If acute GvHD persists, or does not respond to institution of steroids, treatment should be instituted at the discretion of the attending physician.
    - Enrollment in phase I/II studies of novel anti-GvHD therapy is permitted per approval of the Sponsor.
- Chronic GvHD, seen much more frequently in patients who have had acute GvHD, is manifested by sclerodermatous and atrophic skin changes, xerophthalmia, xerostomia, weight loss, and immunodeficiency (with particular susceptibility to sinopulmonary infections), and will be diagnosed by clinical and histologic criteria. Treatment with prednisone and cyclosporine or azathioprine or other medications per institutional guidelines should be instituted if systemic disease is diagnosed; this therapy may contribute to the susceptibility to infection.

6.6. Supportive Care

Institutional standard of care practice guidelines will be followed after transplantation for nutritional support, treatment of infections, and blood product support. Supportive care guidelines are detailed below.

6.6.1. 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.

6.6.2. 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.

6.6.3. Seizure Prophylaxis for SCD Patients

Prophylaxis against seizures is mandatory in all SCD patients and should be commenced at the start of conditioning. Suitable drugs for prophylaxis include phenytoin, clonazepam, or levetiracetam, and should be administered according to institution guidelines. Seizure prophylaxis should be continued in SCD patients until cyclosporine or any other calcineurin inhibitor is discontinued. In patients with pre-existing seizures, continued prophylaxis may be given per standard of care.

Serum magnesium level should be maintained >1.5 mg/dL in all SCD patients during the period of treatment with calcineurin inhibitors cyclosporine or tacrolimus to reduce the risk of seizures.

6.6.4. Hypertension

Hypertension should be strictly controlled to prevent CNS toxicity. Blood pressure should be monitored closely and both systolic and diastolic hypertension should be treated promptly to maintain blood pressure at the patient's pre-transplant baseline ± 20%.

6.6.5. Growth Factor

G-CSF (e.g., Filgrastim, Neupogen, Granix, Zarxio) therapy will be given IV starting Day +1 at dose of 5 µg/kg/day (rounding to nearest vial dose). G-CSF will be continued until the absolute neutrophil count (ANC) is > 2,000/µL on 3 consecutive days after the nadir.

6.6.6. Blood Products

All blood products (except the unmanipulated UCB and NiCord®) 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.

In all SCD patients, the hemoglobin level must be maintained between 9.0 and 11.0 g/dL for at least 100 days post-transplant and platelet count > 50,000/μL post-transplant until recovered to avoid neurological adverse events (AEs), as described previously.[114]

6.6.7. Infection Prophylaxis and Surveillance

Institution guidelines will be followed to provide prophylaxis for infections. Strict guidelines for hygiene and care will be applied. Before starting the pre-transplant conditioning there should be no evidence of mucosal or cutaneous infections. All dental caries should be resolved and abscesses eliminated. Supervised dental prophylaxis is recommended. 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.

6.6.7.1. Anti-viral Prophylaxis

Acyclovir 400 mg PO BID is recommended for anti-viral prophylaxis with conditioning through the duration of neutropenia and then at 800 mg PO BID until 1year post transplant or until 6 months after immunosupression 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.

6.6.7.2. Anti-bacterial Prophylaxis

Anti-bacterial prophylaxis is required. Ciprofloxacin 500 mg PO BID day 0-100 is recommended. Other anti-bacterial prophylaxis regimens may be administered per institutional guidelines.

6.6.7.3. PCP Prophylaxis

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

6.6.7.4. Fungal Prophylaxis

Anti-fungal prophylaxis against Aspergillus sp. is recommended with agents such as itraconazole, voriconazole, or posaconazole.

6.6.7.5. 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 up through Day 42, and then at day 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 may be considered to prevent marrow suppression.

6.6.7.6. 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 with cidofovir or other active agents per institution guidelines.

6.6.7.7. Intravenous Immune Globulin

Intravenous immune globulin may be administered according to institutional practice guidelines. Weekly IVIG infusions (500 mg/kg/dose) are recommended for immunoprophylaxis through Day 100 to maintain IgG levels in the normal range for age. Alternatively, if IVIG is not given on a regular schedule, IgG levels should be monitored and IVIG infusions given to maintain IgG level in the normal range for age.

6.6.8. Treatment of Infections

Patients undergoing the myeloablation 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, it will be treated per institutional practice and will be recorded in the source documents and in the e-CRF.

6.6.9. 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 clinical center should attempt weekly contact with patients through day 70 to ask about infectious symptoms and any other medical events or treatments. Clinical centers will continue with monthly contact from day 70 to the completion of follow-up.

6.6.10. Supportive Care Guidelines for CNS Toxicities

Patients with SCD and cerebral vasculopathy have a high incidence of new CNS toxicities (seizures, labile hypertension, RPLS, PRES, intracranial hemorrhage, stroke, etc.) during the entire transplant process, beginning with the conditioning regimen and lasting through the time that immunosuppression is eventually discontinued. In order to minimize or avoid these risks, adherence to the following guidelines is strongly recommended for all patients:

1. The baseline blood pressure in patients with SCD is often less than “normal” for age. Hypertension can ensue following fluid infusions, or with the use of medications such as corticosteroids and calcineurin inhibitors, even after short term use. Blood pressure (both systolic and diastolic) should be monitored closely (at least every 4 hours) and strictly maintained within 20% of the baseline blood pressure of the patient – aggressive (and often parenteral) use of anti-hypertensive drugs may be required to control hypertension.

2. Seizure prophylaxis is mandatory. Prophylaxis with phenytoin, gabapentin or levetiracetam should be commenced with conditioning therapy per standard guidelines and continued for 180 days after transplant or until cyclosporine or any other calcineurin inhibitor is discontinued, whichever is later. In patients with pre-existing seizures, continued prophylaxis may be given per standard of care.

3. Platelet counts will be monitored frequently after starting the conditioning therapy and platelet transfusions will be administered as needed to keep levels > 50,000/μL.

6.6.11. Nutrition

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

6.6.12. Guidelines for Infusing a Second Stem Cell Product or Donor Cellular Infusion

A second transplant or donor cellular infusion (DCI) should not be considered unless the patient has graft failure. If graft failure occurs then the patient may be treated per institutional guidelines.

6.7. Investigational Agents

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

6.8. 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 administered, from time of signature on the ICF and until the end of the study, will be recorded in the source documents and the reason for administration should be clearly stated in the indications and if needed also documented as AEs.

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 & Examinations Flow Sheet

NiCord® Study for Hemoglobinopathies - Schedule of Assessments Summary														
	Before transplant			Days Post-transplant										
	Eligibility / Screening Phase	**Baseline Phase**	**Preparative and Conditioning Phase**	**Transplantation and Post Transplantation FU Phase**										Post-Study FU
Days	Within 45 days prior to CBU shipment	Within 4 weeks prior to start of conditioning[1]	-35 to -15/-13 Preparative -14/-12 to -2 Conditioning[2]	0	1	7	14 ±3	21 ±3	28 ±3	35 ±3	42 ±3	70 ±3	100 ±14	180 ±21	365 ±21
Part 1: Identify two UCB matching units [3] Part 2: Identify one UCB matching unit [3]	X														
Written Informed Consent[4]	X														
Backup Identification /BM Harvest[5]	X														
Eligibility Criteria	X														
hCG Test for Pregnancy (if of child bearing potential)	X	X													
Ship selected CBU for manipulation to arrive at the production site preferably no later than two days before the start of manufacturing	X														
Medical History	X	X													
Historical Medications	X														
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Karnofsky/Lansky performance scale	X	X							X			X	X	X	X
Confirm Eligibility within one week prior to conditioning		X													

NiCord® Study for Hemoglobinopathies - Schedule of Assessments Summary														
	Before transplant			Days Post-transplant										
	Eligibility / Screening Phase	**Baseline Phase**	**Preparative and Conditioning Phase**	**Transplantation and Post Transplantation FU Phase**										Post-Study FU
Days	Within 45 days prior to CBU shipment	Within 4 weeks prior to start of conditioning[1]	-35 to -15/-13 Preparative -14/-12 to -2 Conditioning[2]	0	1	7	14 ±3	21 ±3	28 ±3	35 ±3	42 ±3	70 ±3	100 ±14	180 ±21	365 ±21
Physical Examination	X	X	X[6]	X	X				X			X	X	X	X
Vital Signs[7]	X[8]	X[8]	X[6]	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory CBC & Chemistry[9]	X	X	X[6]	X	X	X	X	X	X	X	X	X	X	X	X
Complete urinalysis with microscopic examination	X														
CBU confirmatory HLA typing[10]	X														
Infectious disease markers[11]	X	X													
Viral Screening		X													
Radionuclide GFR[12]	X	X													
Anti-HLA antibodies[23]	X														
CMV PCR			X[13]			X	X	X	X	X	X	X	X		
Immunophenotyping Lymphocyte subsets[14, 15]		X											X	X	X
Immunoglobulins (IgG, IgA, IgM)[15]		X											X	X	X
T-cell Receptor Excision Circles (TREC)[15]		X											X	X	X
Peripheral blood baseline sample for Chimerism[16]		X													
Peripheral blood chimerism[17]						X	X	X	X		X	X	X	X	X
Hb-electrophoresis[18]		X												X	X

NiCord® Study for Hemoglobinopathies - Schedule of Assessments Summary														
	Before transplant			Days Post-transplant										
	Eligibility / Screening Phase	**Baseline Phase**	**Preparative and Conditioning Phase**	**Transplantation and Post Transplantation FU Phase**										Post-Study FU
Days	Within 45 days prior to CBU shipment	Within 4 weeks prior to start of conditioning[1]	-35 to -15/-13 Preparative -14/-12 to -2 Conditioning[2]	0	1	7	14 ±3	21 ±3	28 ±3	35 ±3	42 ±3	70 ±3	100 ±14	180 ±21	365 ±21
Preparative and Conditioning regimen as per protocol			X												
NiCord® CF, NF, and infusion solutions shipped to transplant center			X												
NiCord® CF thawing and infusion				X											
NiCord® NF thawing and infusion				X											
Toxicity assessment 24 hours post infusion[19]				X	X										
GvHD prophylaxis[20]			X	X	X	X	X	X	X	X	X	X	X	X	
G-CSF Therapy[21]					X	X	X	X	X	X	X				
Infection prophylaxis[22]			X			X	X	X	X	X	X				
Cardiac: • ECG[23] • Echocardiography LVEF or shortening fraction, tricuspid regurgitation, and jet velocity (if present)[24]	X												X	X	
CT scan sinus, chest, abdomen, pelvis[23]		X													
Chest X-ray[25]		X													
MRA/MRI[26]		X													
Pulmonary Function Test with cDLCO, FEV1, FVC, O2[23]	X												X	X	

NiCord® Study for Hemoglobinopathies - Schedule of Assessments Summary																
	Before transplant			Days Post-transplant												
	Eligibility / Screening Phase	**Baseline Phase**	**Preparative and Conditioning Phase**	**Transplantation and Post Transplantation FU Phase**												Post-Study FU
Days	Within 45 days prior to CBU shipment	Within 4 weeks prior to start of conditioning[1]	-35 to -15/-13 Preparative -14/-12 to -2 Conditioning[2]	0	1	7	14 ±3	21 ±3	28 ±3	35 ±3	42 ±3	70 ±3	100 ±14	180 ±21	365 ±21
Assess Acute GvHD[27]						X	X	X	X	X	X	X	X	X	X	X
Assess Chronic GvHD													X	X	X	
Hospital Admission			From initiation of conditioning regimen until end of study													
RBC and platelet transfusion record			RBC and platelet transfusion recording from transplant until d180													
Infections			Report all grade 2/3 infections from initiation of conditioning regimen until end of study. Report life threatening infections through the 6-month post study follow-up.													
Serious adverse events			From initiation of conditioning regimen until end of study													

[1] Baseline assessments should be completed and resulted prior to initiation of the conditioning regimen.
[2] Transition from preparative to conditioning phase is dependent on the patient's age. Conditioning begins at day -12 for patients ≥21 years of age whereas conditioning begins on day -14 for patients <21 years of age.
[3] Before signing informed consent and according to CBU matching criteria as detailed in Section 7.1 of the protocol.
[4] Signing informed consent can be done before screening, as per site practice. Signed consent is required prior to performing any protocol specific tests or procedures that are not part of the standard site practice. Standard of care hydroxyurea dose adjustment is permitted prior to consent if it is in the best interest of the patient regardless of the patient's participation in the trial.
[5] Autologous stem cells harvested from bone marrow should be obtained, or related haploidentical donor/back-up CBU(s) to be identified (as detailed in inclusion criteria), in case of engraftment failure. If Autologous stem cells harvest from BM is chosen as the backup graft source, the backup BM harvest can be obtained during Baseline, but prior to the start of conditioning treatment, for patients who have an alternative back-up stem cell source identified.
[6] As per site practice.
[7] Temperature, blood pressure, pulse, respiratory rate; saturation (pulse oxymetry) required through the Day 42 visit.
[8] Including height, weight and BSA.
[9] CBC performed daily from Day 0 until neutrophil engraftment. Differentials not required if WBC<0.2. Blood chemistries include (at a minimum): serum creatinine, total bilirubin, alkaline phosphatase, AST, ALT, and magnesium at screening, baseline (before start of conditioning), day -1, day 0, and then at least twice weekly until Day 28, and weekly after Day 28 until 12 weeks post-transplant, 6 months and 1 year post-transplant).
[10] HLA -A, -B, -C, -DRB1 must be typed at high resolution and patient must also have ABO and Rh typing performed.
[11] Infectious disease markers include: CMV, Hepatitis panel (HepB sAg, HepB Core Ab, HepC Ab), EBV Ab, herpes simplex virus, syphilis Ab (such as RPR), HIV and HTLV I/II antibody, and varicella zoster.
[12] Tests from 90 days prior to screening are acceptable for eligibility, provided the patient has been asymptomatic since the time of the tests. For baseline testing, can be done up to 90 days prior to initiation of the conditioning regimen, provided the patient has been asymptomatic since the time of the tests.
[13] After start of chemotherapy.
[14] CD3, CD4, CD8, CD19, CD16/56 and others as per site practice.
[15] Blood sample collection may be done at any time before the start of the conditioning regimen as long as the tests are resulted before the initiation of conditioning.
[16] Sample can be collected during screening if more convenient.

[17] Measured by molecular methods, in whole blood and fractionated for lymphoid and myeloid components; Bone marrow chimerism is an acceptable alternative. Optional: Red cell chimerism measured after day 180 and 365 when RBC transfusion independence has been achieved for a minimum of 2 months.

[18] Hb-electrophoresis only needed pre-transplant (within 7 days prior to initiation of conditioning) in SCD non-chronically RBC transfused patients. If the HbS level is >45% then the patient must receive RBC transfusions or erythrocyte exchange prior to conditioning initiation. Post transplant Hb-electrophoresis at day 180 and 365 in SCD patients unless host reconstitution has occurred.

[19] (fever, chills, allergic reaction/hypersensitivity, anaphylaxis, sinus bradycardia, sinus tachycardia, hypertension, hypotension, nausea, vomiting, diarrhea, dyspnea, hypoxia, hemoglobinuria, infection, flank pain and any other skin, CNS, cardiac, pulmonary or other toxicity manifestations).

[20] GVHD prophylaxis with CSA and MMF beginning on day -3.

[21] Rounded to the nearest vial starting day +1 until the ANC is >2,000/µl x 3 consecutive days.

[22] As per site practice.

[23] Tests performed 30 days prior to screening are acceptable.

[24] It is recommended that these tests be performed ≤ 90 days prior to the initiation of conditioning regimen. However, provided the patient has been asymptomatic since the time of the tests, they can be done up to 6 months prior to the initiation of conditioning regimen.

[25] It is recommended that the X-ray be performed ≤ 30 days prior to the initiation of the conditioning regimen. However, it can be done < 60 days prior to the initiation of the conditioning regimen, provided the patient has been asymptomatic since the time of the X-ray scan.

[26] The requirement for a baseline MRI/MRA of the brain to assess for radiologic disease applies only to the patients with SCD; it is not required for patients with Thalassemia. Tests from within 6 months prior to screening are acceptable, provided no clinical signs of change were observed since the time of the tests. For patients with a past history of CNS complications tests from up to within 30 days prior to screening are recommended.

[27] GVHD and other morbidity assessments at every visit post- transplant.

7. DETAILED STUDY PLAN

7.1. Pre-Screening Activities: Search for Matching CBUs

In Part 1: potential candidates for double CBT for whom a search yielded matched unmanipulated and manipulated CBUs will be identified as screen candidates for the study.

In Part 2: potential candidates for single CBT for whom a search yielded a matched CBU will be identified as screen candidates for the study.

Units 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 and, for Part 1, 3-6/6 HLA-A, B, DRB1 loci with each other (using same resolution of typing). Double mismatch at any one locus (A, B, or DRB1) is not permitted.

The manipulated CBU should contain a pre-cryopreserved (post-processing) total nucleated cell dose of $\geq 1.8 \times 10^9$ and $\geq 1.8 \times 10^7$/kg for patients weighing ≥ 25 kg or a pre-cryopreserved (post-processing) total nucleated cell dose of $\geq 1.6 \times 10^9$ for patients weighing < 25kg. In Part 1: the unmanipulated CBU should contain a pre-cryopreserved (post-processing), nucleated cell dose of at least 3.5×10^7 per kilogram. The unmanipulated unit will be the best matched unit (as per Investigator's discretion).

The manipulated CBU should contain a pre-cryopreserved (post-processing), total CD34+ cell count of $\geq 8 \times 10^6$ for patients weighing ≥ 25 kg and a pre-cryopreserved (post-processing), total CD34+ cell count of $\geq 7 \times 10^6$ for patients weighing < 25 kg. The manipulated CBU will have undergone volume reduction (both plasma and red blood cell depletion) prior to cryopreservation.

All CBUs should be procured from public banks that meet local 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 or with unusual findings, the clinical site should fill out an urgent medical need document.

The selected units should be typed twice (i.e., initial typing and verification typing). Verification (confirmatory) typing should be in a lab that is ASHI/EFI accredited and must come from an attached segment.

An acceptable CBU (meeting CBU acceptance criteria as defined above) must be identified and available prior to patient's screening.

7.2. 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 by other designated qualified person (according to local regulations) that has been delegated by the principal investigator.

Standard of care workup for transplant may be done prior to patient consent. Prior to performing any study activities/evaluations that are not part of the site's routine clinical practices, the patient and/or his/her legal guardian must be thoroughly informed about all aspects of the study, including scheduled study visits and activities, and must sign the

written informed consent. 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.

Standard of care hydroxyurea dose adjustment is permitted prior to consent if it is in the best interest of the patient regardless of the patient's participation in the trial.

[redacted]

7.2.1. Consent of minors

As a rule, a pediatric subject is legally unable to provide informed consent. Therefore, pediatric study participants are dependent on their parent(s)/legal guardian to assume responsibility for their participation in clinical studies. Fully informed consent should be obtained from the legal guardian in accordance with regional laws or regulations. All participants should be informed to the fullest extent possible about the study in language and terms they are able to understand. Where appropriate, participants should assent to enroll in a study (age of assent to be determined by IRB's/EC's or be consistent with local legal requirements). Participants of appropriate intellectual maturity should personally sign and date either a separately designed, written assent form or the written informed consent. In all cases, participants should be made aware of their rights to decline to participate or to withdraw from the study at any time. Attention should be paid to signs of undue distress in patients who are unable to clearly articulate their distress. Although a participant's wish to withdraw from a study must be respected, there may be circumstances in therapeutic studies for serious or life-threatening diseases in which, in the opinion of the investigator and parent(s)/legal guardian, the welfare of a pediatric patient would be jeopardized by his or her failing to participate in the study. In this situation, continued parental (legal guardian) consent should be sufficient to allow participation in the study. Emancipated or mature minors (defined by local laws) may be capable of giving autonomous consent.

7.3. Eligibility/Screening Assessments (within 45 days prior to CBU shipment to the production site)

Tests performed during 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:

- Routine screening evaluation:
  - Medical history including primary and concomitant disease and historical medications
  - Concomitant medications will be recorded in the patient's medical record
  - Patients' Performance score by Karnofsky (age ≥16) or Lansky Play-Performance scale (age < 16)
  - Physical examination and vital signs (including height, weight and BSA)

- Laboratory: CBC with WBC differential
- Blood chemistry (serum creatinine, total bilirubin, alkaline phosphates, AST, ALT, and magnesium at a minimum)
- Serum beta hCG (females of childbearing potential)
- Complete urinalysis with microscopic examination
- Anti-HLA antibodies (tests from within 30 days prior to screening are acceptable)
- Radionuclide GFR is strongly recommended as the test of choice. Measurement of 24-hour urine creatinine clearance is acceptable if the former is not available. Estimated GFR using the serum creatinine and patient weight/age/sex is not an acceptable alternative. Tests from 90 days prior to screening are acceptable for eligibility, provided the patient has been asymptomatic since the time of the tests
- Serologic infectious disease markers for: CMV, Hepatitis panel (HepB sAg, HepB Core Ab, HepC Ab), EBV Ab, herpes simplex virus, syphilis Ab (such as RPR), HIV and HTLV I/II antibody, and varicella zoster
- Dental Consultant (recommended, optional)
- Physiologic reserves assessment:
  - Pulmonary Function Tests including Carbon Monoxide Diffusing Capacity (DLCOc), FEV1, FVC, and oxygen saturation, if the patient is able to perform. (If PFT testing included the use of bronchodilators, then the baseline results prior to the administration of any medications should be used when determining eligibility). It is recommended that these tests be performed ≤ 90 days prior to initiation of the conditioning regimen. However, provided the patient has been asymptomatic since the time of the tests they can be done up to 6 months prior to initiation of the conditioning regimen
  - 12 lead ECG (tests performed within 30 days prior to screening are acceptable)
  - Baseline echocardiography for left ventricular ejection fraction (LVEF), left ventricular shortening fraction and presence or absence of tricuspid regurgitation. If present, measure jet velocity as a measure of pulmonary hypertension. It is recommended that these tests be performed ≤ 90 days prior to initiation of the conditioning regimen. However, provided the patient has been asymptomatic since the time of the tests, they can be done up to 6 months prior to initiation of the conditioning regimen
- Autologous stem cells harvest from BM should be obtained as per site practice, or related haploidentical donor/back-up CBU(s) to be identified (as detailed in the inclusion criteria), in case of engraftment failure. If Autologous stem cells harvest from BM is chosen as the backup graft source, the backup BM harvest can be obtained during Baseline, but prior to the start of conditioning treatment, for patients who have an alternative back-up stem cell source identified.

- CBU match:
  - Patient and CBU ABO and Rh typing
  - Patient HLA class I & II high resolution typing
  - Peripheral blood baseline sample for chimerism laboratory

- CBU HLA class I (A, B, and C) & II (DRB1) high resolution typing. Note that although the matching requirement per protocol only requires low resolution A and B matching, high resolution DNA based typing is required for loci A, B, C as well as DRB1

All above mentioned activities should be completed prior to sending the CBU to the production site for expansion. Sites may perform standard of care preparation for transplantation (i.e., hydroxyurea administration) during the eligibility/screening phase in order not to delay the date of transplantation.

7.4. Baseline Assessments (Within 4 weeks prior to start of conditioning)

All tests must be performed during baseline period unless exception as detailed below.

Baseline activities will be performed as detailed in Table 4 and will include:

- Medical history including primary and concomitant disease
- Concomitant medications will be recorded in the patient's medical record
- Patients' Performance score by Karnofsky (age ≥16) or Lansky Play-Performance scale (age < 16)
- Physical examination and vital signs (including height, weight and BSA)
- Laboratory: CBC with WBC differential, blood chemistry (serum creatinine, total bilirubin, alkaline phosphates, AST, ALT, and magnesium at a minimum)
- Serum beta hCG (females)
- Peripheral blood baseline sample for chimerism laboratory. Sample can be collected during screening if more convenient.
- Radionuclide GFR is strongly recommended as the test of choice. Measurement of 24-hour urine creatinine clearance is acceptable if the former is not available. For baseline testing, can be done up to 90 days prior to initiation of the conditioning regimen, provided the patient has been asymptomatic since the time of the tests
- Immunophenotyping – Lymphocyte subsets: CD3, CD4, CD8, CD19, CD16/56 and additional immunophenotyping as per site practice
- Immunoglobulin levels (IgG, IgA, IgM)
- Blood sample for T-cell Receptor Excision Circles (TREC)
- Chest X-ray. It is recommended that the X-ray be performed ≤ 30 days prior to the initiation of the conditioning regimen. However, it can be done < 60 days prior to the initiation of the conditioning regimen, provided the patient has been asymptomatic since the time of the X-ray scan.
- CT sinus, chest, abdomen, pelvis (Tests performed 30 days prior to screening are acceptable)
- Serologic tests for: CMV, Hepatitis panel (HepB sAg, HepB Core Ab, HepC Ab), EBV Ab, herpes simplex virus, syphilis Ab (such as RPR), HIV and HTLV I/II antibody, and varicella zoster
- MRA/MRI of the brain to assess for radiologic disease- applies only to SCD patients; it is not required for patients with Thalassemia. MRA/MRI tests from within 6 months prior to screening are acceptable, provided no clinical signs of change were observed since the time of the tests. For patients with a past history

of CNS complications tests from up to within 30 days prior to screening are recommended.

All above mentioned activities should be completed and resulted prior to initiation of the conditioning regimen.

[redacted]

7.6. Preparative Phase (Day –35 to one day prior to start of conditioning regimen)

In Part 1: Prior to the initiation of the conditioning regimen (i.e., Day -10 for patients on Regimen #1 or Day -15 for patients on Regimen #2), the unmanipulated CBU must be present at the Clinical Site. Patient's monitoring during the preparative period (including physical examination, vital signs, CBC and blood chemistry) will be evaluated per section 6.3.1.

In SCD patients, Hb-electrophoresis (Hb F, Hb S, Hb A2) will be assessed within 7 days prior to administration of conditioning regimen.

In SCD patients, in order to begin the conditioning phase, Hb S must be ≤45% or the patient must receive appropriate therapy calculated to reduce Hb S to ≤45%. Viral screening is suggested prior to administration of the conditioning regimen to confirm absence of infection. Patients with fever or suspected minor infection should await resolution of symptoms before starting the conditioning regimen.

7.7. Eligibility Confirmation: (one week prior to start of conditioning regimen)

Confirm that all previous eligibility tests are still up to date, and repeat any tests that are outside of the acceptable timeframe for eligibility. 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.

7.8. Conditioning Phase

The preparative & conditioning regimen will be administered as detailed in section 6.3. The choice of conditioning regimen will be at the Investigator's discretion. GvHD prophylaxis will be administered as detailed in section 6.4[redacted]Patient monitoring during the conditioning phase (including physical examination, vital signs, CBC and blood

chemistry) will be evaluated as per site practice. CMV PCR is required as outlined in section 6.6.7.5).

7.9. Pre-Transplantation Day (Day 0)

Safety Assessment

Prior to transplantation, the patient will be evaluated by the Investigator or designee including:

- Physical Examination including weight
- CBC, blood chemistry
- Vital Signs: temperature, blood pressure, pulse, respiratory rate and oxygen saturation

7.9.1. Preparation and Infusion of the Unmanipulated CBU and NiCord®

7.9.1.1. Unmanipulated CBU Preparation (Part 1)

The unmanipulated CBU should be thawed and diluted by trained personnel using institutional procedures.

The CBU will be placed in a sterilized zip lock bag. The bag will then be submerged in a 37°C water bath and agitated until almost all ice crystals have dissolved followed by volume dilution (as per institutional practice) to preserve cell viability. The thawed and diluted CBU should be next weighed and centrifuged, supernatant should be removed and the CBU pellet should be re-suspended (as per institutional practice). An aliquot from the unmanipulated CBU will be removed prior to infusion to measure the total number of nucleated cells, percent of cell viability and percentage of the $CD34^+$ cell population. As per institutional practice, additional tests may include CFU, ALDHbr, 7-AAD, glyA cell content and FACS analysis for the percentage of the $CD133^+$, $CD45^+$, $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, $CD16^+CD56^+$ cell populations. The CBU should be labeled with the patient identification information and transferred to the bedside for infusion.

7.9.1.2. Preparation of NiCord® Non-cultured Fraction (NF)

[redacted]

NiCord® NF will be kept frozen until the day of transplantation. It will be shipped to the clinical site, together with NiCord® CF, in a cryoshipper equipped with a calibrated data logger, prior to transplantation. The SLM will fax/email the NiCord® NF final CoA to the clinical site. NiCord® NF will be sent with the required documentation according to the manufacturer's SOP.

Upon arrival, NiCord® NF should be kept in a controlled Liquid Nitrogen freezer (≤ -150°C) until transplant.

[redacted]

[redacted]

[redacted]

7.9.1.3. Preparation of NiCord® Cultured Fraction (CF)

Upon completion of the manufacturing process, final QC tests of NiCord® CF are initiated, and NiCord® CF is labeled and cryopreserved according to the Manufacturer's SOPs. The QC tests performed are divided into bioassays and safety tests. The results of the tests should meet predefined specifications.

NiCord® CF will be kept frozen until the day of transplantation.

In parallel to product testing and prior to transplantation, NiCord® CF and NF will be shipped with all available CBU segments to the clinical site in a cryoshipper equipped with a calibrated data logger, and with any other required documentation according to the manufacturer's SOP.

[redacted]

Upon arrival, NiCord® CF should be kept in a controlled Liquid Nitrogen freezer (≤ -150°C).

[redacted]

7.9.1.4. Infusion of the Unmanipulated CBU and/or NiCord® on Day 0

The unmanipulated CBU and/or NiCord® should not be irradiated under any circumstances.

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.

In Part 1: NiCord® and the unmanipulated CBU will be transplanted on the same day with a minimal interval of 4 hours between the infusions. The unmanipulated CBU will be transplanted first followed by NiCord®.

The unmanipulated CBU should be infused via the patient's central venous catheter using an in-line filter as per site practice. Rate of infusion will be according to site practice

With regards to the NiCord® infusion: NiCord® CF will be infused first, followed immediately (up to 1 hour) by the infusion of NiCord® NF.

Prior to its infusion, NiCord® must be identified at the Clinical Site according to the Sponsor's SOP and designated Form. The Clinical Site should check the product labels as well as the CoAs and will make sure that all NiCord® fractions & the infusion solutions were shipped in appropriate conditions and are within their shelf life time prior to infusing them. 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 not exceed 5 cc/kg/h. NiCord® CF and NiCord® NF should be infused as soon as possible after thaw.

- Total duration of NiCord® CF infusion should target a maximum of 2 hours from end of thaw to end of infusion, while considering the minimal infusion time specified in the product's CoA.
- Total duration of NiCord® NF infusion should not exceed 1 hour from end of thaw to end of infusion, while considering the minimal infusion time specified in the product's CoA.
- The minimal infusion time is calculated based on the actual endotoxin test result and the endotoxin limit of 5 EU/Kg weight/60 minutes.

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. Vital signs should be monitored before beginning the infusion and every 30 minutes during the infusion. Pre-medication and hydration prior to cord blood infusion should be administered per institutional procedure. 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.

7.9.2. Evaluation and Treatment of Mycoplasma Safety Test Failure

The mycoplasma safety test results may not be available at the time the patient is transplanted. In the event that this test proves positive after transplantation, the clinical 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 clinical site will receive a final CoA containing all test results.

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

Safety assessment including:

- Physical Examination
- Vital Signs: temperature, blood pressure, pulse, respiratory rate and oxygen saturation 30, 60 minutes and at 2, 4 and 24 hours post transplantation of the NiCord® NF infusion
- CBC, blood chemistry
- Assessment of acute toxicity:
  - Part 1: From the start of the Unmanipulated CBU infusion up through 24 hours post infusion of the NiCord® NF
  - Part 2: From the start of NiCord® CF infusion up through 24 hours post infusion of the NiCord® NF
- Cardiac one lead monitor is optional; however, ECG twice a day will be mandatory in case of acute toxicity
- AEs Reporting
- G-CSF will be administered beginning on day +1
- Record RBC and platelet transfusions

7.10. Scheduled Treatment Visits (As Detailed in Table 4)

7.10.1. Scheduled Visits on Day 7/ Days (±3) 14, 21, 28, 35, 42, 70/ Day (±14) 100/ Day (±21) 180

The following assessments are mandatory:

- AEs and concomitant medications will be recorded in the patient's medical record
- Vital Signs (note, pulse oximetry not required after the Day 42 visit)
- Physical examination (days 28, 70, 100, and 180) including cardiac and pulmonary monitoring
- Karnofsky/ Lansky performance status score (days 28, 70, 100, and 180)
- CBC with WBC differential (differential not required if WBC<0.2), blood chemistry (serum creatinine, total bilirubin, alkaline phosphatase, AST, ALT and magnesium, at a minimum)
- CMV PCR weekly at the protocol specified visits up through Day 42 and then at day 70and day 100or more frequently as clinically indicated

- Hb-electrophoresis: Hb F, Hb S, Hb A2 (day 180 unless host reconstitution has occurred)
- Pulmonary Function Tests including Carbon Monoxide Diffusing Capacity (DLCOc), FEV1, and FVC if the patient is able to perform, and oxygen saturation (days 100 and 180)
- 12 lead ECG (days 100 and 180)
- Echocardiography for left ventricular ejection fraction (LVEF), left ventricular shortening fraction and presence or absence of tricuspid regurgitation. If present, measure jet velocity as a measure of pulmonary hypertension (days 100 and 180)
- Cyclosporine levels as per institutional guidelines to ensure blood levels are within target range
- Peripheral blood collection for chimerism (days 7, 14, 21, 28, 42, 70, 100 and 180 only). Whole blood and lineage specific (CD3 and either CD15 or CD33) chimerism will be performed. Optionally, red cell chimerism will be assessed after day 180 when RBC transfusion independence has been achieved for a minimum of 2 months.
- Immunophenotyping – Lymphocyte subsets: CD3, CD4, CD8, CD19, CD16/56 (days 100 & 180), additional immunophenotyping as per site practice
- Immunoglobulin levels (IgG, IgA, IgM) (days 100 & 180)
- Blood sample for T-cell Receptor Excision Circles (TREC) (days 100 & 180)
- GvHD assessment:
  - Acute: Weekly up to 100 days (inclusive) and at 180 day visit, or more frequently as clinically indicated. Acute GvHD will be assessed according to the Consensus Conference on Acute GvHD grading (Appendix A).
  - Chronic: day 100 and day 180 visits or more frequently as clinically indicated. GvHD will be assessed and classified as limited or extensive, according to standard criteria (Appendix A) on days 100 and 180 post-transplant, or more frequently as clinically indicated
- GvHD prophylaxis as specified in section 6.4
- Infection prophylaxis as specified in section 6.6.7
- Hospitalization recording
- Record RBC and platelet transfusions through Day 180

7.10.2. 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:

- Chimerism studies, viral/bacterial cultures including PCR analysis for Herpes viruses (including CMV and HHV6). Assessment should be performed between day 21 and 42 for primary graft failure

Treatment of Graft Failure: If the patient meets the definition of primary or secondary graft failure, they will be treated at the discretion of the treating physician.

7.10.3. Early Discontinuation of Follow-up

Reasons for withdrawal of the patient prior to Day 180 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 did not start the treatment. **(Patients will be defined as screening failures when withdrawn from the study before receiving the NiCord® infusion). For early termination patients that withdraw/are withdrawn from the study post transplant, any assessments due at the time of withdraw (according to Table 4) are requested.**

Patients who experience graft failure or autologous recovery post transplant will continue to be followed for survival. No other study related assessments are required for these subjects after the date of graft failure or autologous recovery.

7.10.4. Criteria for Early Termination/Discontinuation

Patients who are prematurely discontinued 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 first year following treatment. This will allow us to continue to gather clinical information on patients who subsequently withdraw from 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
- Non-compliance (per investigator judgment)
- Lost to follow-up
- AE

7.11. Unscheduled Visit

An unscheduled visit may be performed at any time during the study at the patient's request, or as deemed necessary by the Investigator. The date and reason for the unscheduled visit will be recorded in the patient medical record. Vital signs, AEs and concomitant medications will be assessed.

7.12. Post-study Follow-up

Clinical outcomes including secondary graft failure, chronic GvHD, cardiac and pulmonary function tests, chimerism, Hb-electropheresis, incidence of life-threatening infections, immune reconstitution, routine labs, vital signs, physical exam, performance scale, and survival status (including causes of death), will be collected from the center at six months post study completion (1 year post transplantation), as per site practice. Other than life threatening infections and events resulting in death, SAE reporting is not required during post-study follow-up. Data from the post-study follow-up period will be used in the post-study analysis of one year post transplant outcomes.

7.13. Data Reporting

7.13.1. Criteria for Forms Submission

[redacted]

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 3.5.

8.2. CBU Supply

All CBUs should be procured from public banks that meet local applicable regulations. If the optimal unit(s) for the patient was determined ineligible or with unusual findings 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 at Gamida Cell manufacturing site by personnel that have been trained and qualified by the Sponsor according to the Sponsor's SOPs.

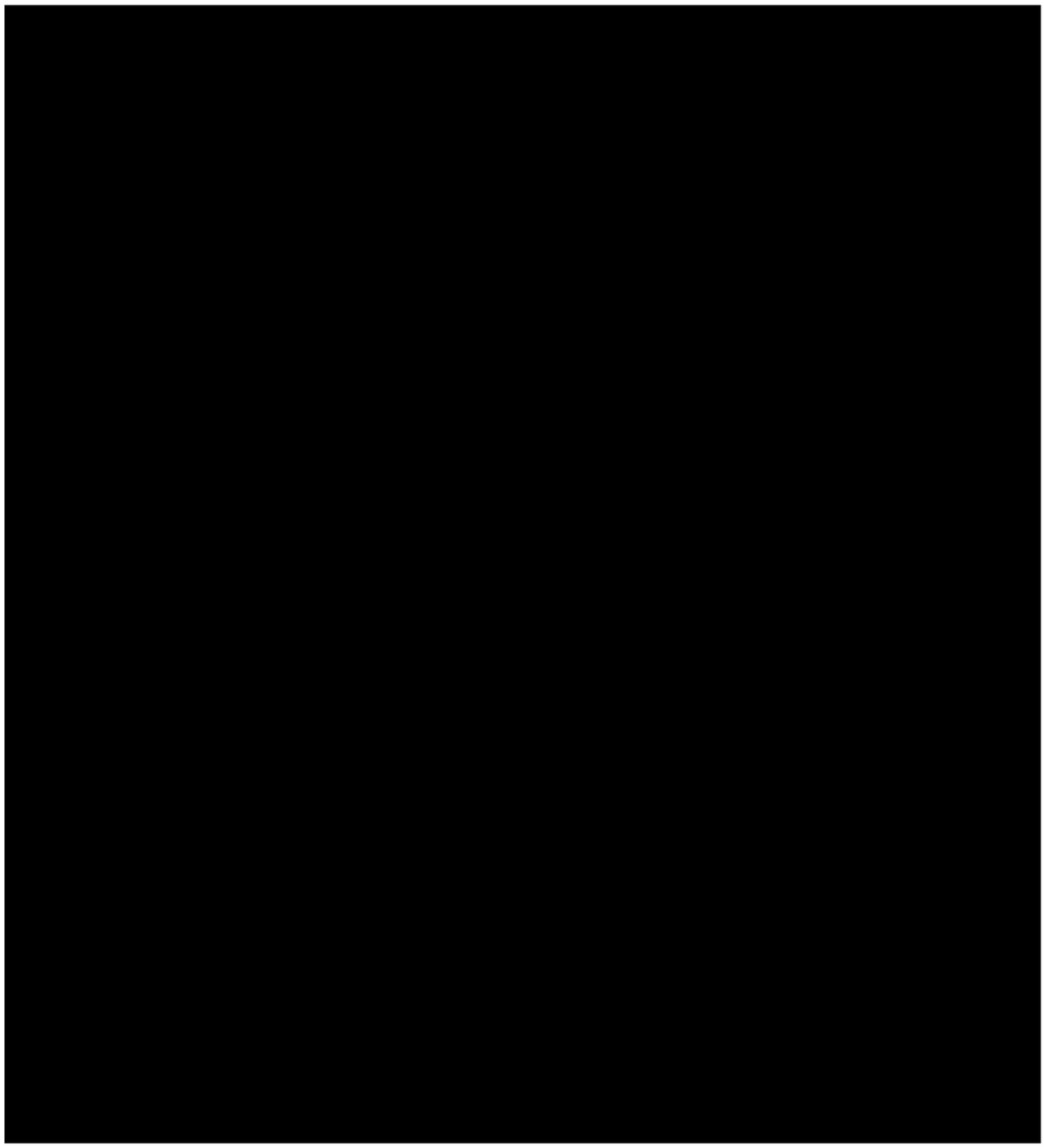
NiCord® is manufactured in a production site, inside a laminar flow hood (class 100, ISO 5) within a room that has been qualified as a Class 10,000 (ISO 7), in compliance with the production instructions and procedures as provided by the Sponsor.

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.

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.



[redacted]

Table 7: Final Process Quality Control Tests for the NiCord® CF/NF Thawing/Infusion Solution

Test	Acceptance Criteria
Appearance	Clear solution, free of foreign particles
Safety Tests	
Sterility – bacteria	No growth
Sterility – yeast and molds	No growth
Endotoxin content (EU/ml)	≤0.5

8.3.1. Out of Specification Results

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

[redacted]

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

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

[redacted]

8.3.1.2. NiCord® NF OOS

[redacted]

8.4. Handling of Cord Blood Unit

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

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

8.5. Shipment

NiCord® CF and NF will be kept frozen at the production site until release, and then will be shipped together with all available CBU segments/samples to the clinical site 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 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 Sponsors procedures. The checks performed will be documented in a special form according to the Manufacturer's SOP. When a shipment is received, the Investigator/Coordinator 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.

9.1.2. Infusion Reaction

Part 1: Any adverse event that begins or worsens (i.e., increases in grade) between the start of the first CBU infusion and 24 hours after the end of the second CBU infusion.

Part 2: Any adverse event that begins or worsens (i.e., increases in grade) between the start of the NiCord® infusion and 24 hours after the end of the 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 fulfils one or more of the following criteria:

- Results in death
- Is life-threatening

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

  NOTE: The term disability is defined as a substantial disruption of the ability to conduct normal life functions. 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.
- Is a congenital anomaly/birth defect

Important medical events that do not meet any of the criteria above should be considered serious when, based upon appropriate medical judgment, they jeopardize the patient or subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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 drug and adverse event.

The Investigator must make the determination of relationship to the study product for each AE/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 and/or Product Information for marketed products in the determination of his/her assessment.

9.1.5. Causality

The Investigator must make the determination of causal relationship to the study product for each AE/SAE. The Investigator should decide whether, in his or her medical judgment there is a reasonable possibility that the event may have been caused by the study product. 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.

9.1.6. Expectation

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

9.1.7. Toxicity Grading

All AEs will be graded using NCI's CTCAE Version 4.03. An AE that is assessed as grade three (i.e., "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 severe. 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

[redacted]

- Grade 3-5 infusion reactions
- Part 1: Non-engraftment at 42 days post NiCord® cultured cell and unmanipulated CBU infusion
- Part 2: Non-engraftment at 42 days post NiCord® infusion
- All serious, unexpected, suspected adverse reactions as defined in 21 CFR312.32

After initial notification within 24 hours, a detailed summary of the events above is 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 SAEs that do not meet the criteria for expedited reporting should also be reported within 24 hours of the transplant team's knowledge of the event. Other non serious AEs should be recorded in the database as outlined in Appendix B.

Clinical centers are expected to report AEs to their IRB according to their own institutional guidelines.

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 are 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.

- All infections post transplant will be reported on an infection form.
- Graft versus Host Disease (GvHD) will be reported on GvHD forms.
- Common events post transplant (summarized in Appendix C) will be reported on the Toxicity 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.
- Serious Adverse Events post transplant will be reported on SAE summary forms
- 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.

Serious Adverse Events

At all times during the transplant and post transplant follow-up phase, SAEs will be reported on SAE summary forms. These events may require reporting on other forms as well (e.g., Death form when applicable). **SAEs must be reported within 24hrs of the transplant team's knowledge of the event.**

[redacted]

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.

[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. Clinical Laboratory Evaluations

All laboratory measurements will be evaluated for abnormalities. 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.

9.5. Pregnancy

Investigators must inform all female subjects of child-bearing potential that it is currently unknown whether NiCord® poses any risk to an unborn child, and should instruct subjects to use appropriate methods of contraception. Subjects should also be instructed to inform the investigator immediately should they become pregnant during the study. The investigator should counsel the subject, discuss the risks of continuing with the pregnancy and the possible effects on the fetus. The investigator should also recommend that the subject be closely monitored by her personal physician until conclusion of the pregnancy, and once concluded, that both the subject and her infant be carefully monitored throughout the puerperium. Breast feeding is not recommended as there is no data regarding the safety of a nursing child either during or following NiCord® administration to the mother. All AEs will be communicated to the investigator by the subject.

Pregnancy will not be considered as 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.

9.6. Patient Withdrawal from Study Procedures due to Adverse Events

Any patient can be removed from the study at any time if the subject experiences an AE or SAE, which, in the in the judgment of the Investigator, justifies withdrawal due to its severity, nature or requirements for treatment, regardless of the causal relationship to the study product. Full details of withdrawal criteria are provided in section 5.4.

9.7. Medical Monitor Review

[redacted]

- Grade 3-5 infusion reactions
- Part 1: Non-engraftment at 42 days post NiCord® cultured cell and unmanipulated CBU infusion
- Part 2: Non-engraftment at 42 days post NiCord® infusion
- All serious adverse events as defined in 21 CFR312.32

[redacted]

9.8. Sponsor Obligations

Any concerns regarding the type or frequency of an 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 of the study.

9.9. FDA Reporting

The Sponsor is responsible for reporting all unexpected fatal or life-threatening suspected adverse reactions to the FDA by telephone or fax according to FDA guidelines no later than seven calendar days after knowledge of the event. All grade 3-5 infusion reactions, non-engraftment at 42 days post NiCord® cultured cell and unmanipulated CBU infusion (Part 1), non-engraftment at 42 days post NiCord® infusion (Part 2), and all serious, unexpected, suspected adverse reactions are reported to the FDA by the Sponsor via a written report within fifteen days of receipt of the information (21 CFR 312.32).

10. STATISTICAL METHODOLOGY

The study is designed as a pilot study to evaluate the safety and efficacy of transplantation of NiCord® with or without an unmanipulated cord blood unit to patients with Hemoglobinopathies following myeloablative therapy.

Safety and efficacy data from all participating patients will be reviewed periodically by an independent Data Monitoring Committee (DMC). Interim analyses will be conducted to check for safety with regard to serious acute toxicity, neutrophil engraftment by day 42, and transplant related mortality at 100 days.

Eligible patients who underwent all study screening procedures, completed the conditioning treatment and were infused with NiCord® will be included in the statistical analyses. Summary data and listings of the patients who were excluded from efficacy and safety analyses will be appended to the clinical trial report in order to enable an assessment of the nature of the missing data.

Final analysis will be performed when the planned 15 evaluable patients who received NiCord® and unmanipulated cord blood have been assessed 180 days after transplant and the planned 5 evaluable patients who received NiCord® without unmanipulated cord blood have been assessed 180 days after transplant. If enrollment in Part 1 or Part 2 is closed before the maximum number of evaluable patients have been transplanted, the final analysis for each part will be performed after the last evaluable patient has been assessed after transplant. The final analysis for Part 2 will include a secondary analysis in which Part 1 and Part 2 patients are evaluated together, however, the results of the separate analyses will be shown with the combined analysis.

Interim analyses may be conducted as the study is on-going at the Sponsor's discretion. There will be no adjustment to control the overall Type I error.

10.1. Patients & Analysis Cohorts

The following data analysis sets are defined for the final analysis of this study:
Part 1 and Part 2 Primary (ITT) Data Analysis Sets consist of all patients who have entered the study under Part 1 or Part 2 of the protocol and have received a transplant of CB cells. These cohorts will serve as the principal cohorts for the primary analysis to be conducted at the completion of the study.

In addition, an interim analysis for the DMC was conducted on the interim ITT data analysis set that included the first 6 patients who enrolled in Part 1 and were evaluated for acute toxicity, neutrophil engraftment and percent donor derived engraftment/chimerism (of either NiCord®, unmanipulated CBU or both) by day 42 and 100-day transplant related mortality. Similarly, an interim analysis for the DMC will be conducted on the interim ITT data analysis set that includes the first 3 patients who enroll in Part 2 and have been evaluated for acute toxicity, neutrophil engraftment and percent donor derived engraftment/chimerism by day 42 and 100-day transplant related mortality

10.1.1. Per Protocol (PP) Data Analysis Set

The two Per Protocol Data Analysis Sets will include all patients enrolled in Part 1 or Part 2, respectively, who actually received NiCord® with or without the unmanipulated CBU and who, in addition, met all of the following criteria:

a) Did not receive any stem cells up to day 28 except for the NiCord® and, if in Part 1, the unmanipulated CBU (e.g., second unmanipulated CBU)
b) Did not die prior to day 14

c) Received myeloablative conditioning therapy according to or similar to that specified in the protocol
d) Did not seriously contravene the eligibility criteria specified in section 5.2
e) Did not receive a NiCord® transplant that was outside FPQC limits, as specified in section 8.3

Patients satisfying the above criteria will be termed "evaluable". All study endpoints will be assessed in the PP cohorts.

10.1.2. Withdrawals from the Trial

- Patients who enter the study but do not receive a transplant of CB cells (screening failures) will not be included in the main statistical analysis and will be replaced.
- 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 first year following treatment. This will allow us to continue to gather clinical information on patients who subsequently withdraw from active participation without withdrawal of the informed consent, and to include them in the analyses of all clinical endpoints

10.2. Sample Size

Up to 15 evaluable patients will be entered into the study for Part 1 and up to 5 evaluable patients will be entered into the study for Part 2. If patients are entered and are subsequently found not to have satisfied all the per protocol criteria (as specified in section 10.1.1), then further patients will be recruited. These sample sizes were chosen for this pilot study informally and were not calculated to meet any specific considerations of statistical power. It is however, rather typical of the size that is used in similar pilot studies. The number is large enough to provide reasonable experience with the practical issues involved in administering the treatment and small enough to allow a reasonably rapid progression to the next phase of the research, should the treatment appear both safe and promising.

10.3. Interim Analysis & Early Stopping

The data emerging from this study will be reviewed by an independent DMC. This committee reviewed the accumulated data after 6 patients entered Part 1 of the study and were assessed at day 100 following the transplant.

A subsequent DMC review will occur after 3 patients have entered Part 2 of the study and have been assessed at Day 100 following the transplant. At this review, the DMC will monitor safety data and in particular the detailed chimerism and engraftment data of the first 3 patients transplanted with NiCord® as a single expanded graft, including:

- Any occurrence of primary or secondary graft failure
- Any substantial decrease in donor chimerism (especially myeloid chimerism), or evidence of impending graft failure.

Particular consideration will be given to cases of graft failure which can be attributed to post-transplant complications such as HHV6 infection, CMV infection, severe GvHD, prolonged ganciclovir usage, or other medicine-related, e.g., MMF, Cidofovir, etc.

The committee will make recommendations to the Sponsor regarding early stopping or study modification.

Early safety assessment guidelines will be used to monitor the following events, and alert the DMC.
If an alert occurs, accrual to the study will be halted. The DMC will consider the data in depth and make recommendations to the sponsor. It is understood that DMC recommendations to the sponsor are not binding and that the sponsor is the sole party responsible for final decisions regarding termination or continuation of the trial.

10.3.1. Part 1 Guidelines

The following events will prompt consideration of early stopping or modification of the protocol for Part 1.

10.3.1.1. Serious (Grade 4+5) Acute Toxicities

If ≥2 out of the first 7 or ≥3 out of the first 14 patients experience grade 4 or 5 acute toxicity

10.3.1.2. Neutrophil Engraftment

If ≥3 of the first 5 patients, ≥4 out of the first 8 patients, or ≥5 of the first 11 patients or ≥6 of the first 14 patients fail to achieve neutrophil engraftment by day 42 (from either NiCord®, the unmanipulated CBU or both), as defined in Section 4.3.2. Additionally, early consideration will be given by the DMC if 2 out of the first 2 patients fail to engraft.

10.3.1.3. Secondary Graft Failure

If ≥3 of the first 5 patients, ≥4 out of the first 8 patients, or ≥5 of the first 11 patients or ≥6 of the first 14 patients experience secondary graft failure, as defined in Section 4.3.2.

10.3.1.4. Transplant Related Mortality At 100 Days

If ≥3 out of the first 5 patients, ≥4 out of the first 8 patients, or ≥5 out of the first 11 patients or ≥6 of the first 14 patients die before 100 days from treatment-related causes.

In the case of an early stopping event, study recruitment may be renewed based on both the recommendation and rationale of the DMC and local IRB approval.

Statistical Notes: The above guidelines are formulated so that an alert will occur if the posterior probability is sufficiently high that the chance of an event exceeds a given threshold.

Acute Toxicity: posterior probability that chance of grade 4 or 5 toxicity is greater than 5% exceeds 0.95. Prior distribution: beta (0.05, 0.95).

Neutrophil Engraftment: posterior probability that chance of no neutrophil engraftment by day 42 is greater than 20% exceeds 0.95. Prior distribution: beta (0.2, 0.8).

Secondary Graft Failure: posterior probability that chance of secondary graft failure is greater than 20% exceeds 0.95. Prior distribution: beta (0.2, 0.8).

Transplant Related Mortality: posterior probability that chance of transplant related mortality within 100 days of transplant is greater than 20% exceeds 0.95. Prior distribution: beta (0.2, 0.8).

10.3.2. Part 2 Guidelines

The following events will prompt consideration of early stopping or modification of the protocol for Part 2, using the same statistical considerations as provided in Part 1.

10.3.2.1. Serious (Grade 4+5) Acute Toxicities
If 1 out of the first 1, or ≥2 out of the first 5 patients experience grade 4 or 5 acute toxicity

10.3.2.2. Neutrophil Engraftment
If 2 of the first 2 patients, or ≥3 of the first 5 patients fail to achieve neutrophil engraftment by day 42 as defined in Section 4.3.2. Additionally, early consideration will be given by the DMC if the first patient in Part 2 fails to engraft.

10.3.2.3. Secondary Graft Failure
If 2 of the first 2 patients, or ≥3 of the first 5 patients experience secondary graft failure, as defined in Section 4.3.2.

10.3.2.4. Transplant Related Mortality At 100 Days
If 2 of the first 2 patients, or ≥3 of the first 5 patients die before 100 days from treatment-related causes.

10.4. Statistical Analysis
Patients enrolled in Part 1 and Part 2 will be analyzed separately. Data listings will be provided for Part 2 results, given the small sample size. A secondary analysis will analyze the data from Part 1 and Part 2 patients combined, however, the results from the separate analyses will also be presented with the combined results.

10.4.1. Primary Endpoints

10.4.1.1. Acute Toxicity
The proportion of patients with grade 4 or 5 toxicity will be estimated together with 95% confidence limits based on the binomial distribution. The proportion with toxicity grades 1, 2, and 3 will also be estimated.

10.4.1.2. Neutrophil Engraftment
To assess the incidence of neutrophil engraftment post transplant, a cumulative incidence curve will be computed along with a 95% confidence interval at 42 days post-transplant. Death, autologous recovery, and second transplant prior to engraftment will be considered as a competing risk.

10.4.2. Secondary Endpoints & Analysis
Planned secondary endpoints are defined in Section 4 and will be analyzed as follows:

10.4.2.1. Transplant Related Mortality
To assess the incidence of transplant related mortality, a cumulative incidence curve of death occurring in a subject not preceded by autologous recovery will be computed along with a 95% confidence interval at 100 days post-transplant. Autologous recovery will be considered as a competing risk.

10.4.2.2. Event-free Survival
The proportion of patients with event-free survival at 100 days post transplant will be estimated along with a 95% confidence interval using the Kaplan-Meier method. Death, autologous recovery, primary or secondary graft failure will be considered events for this endpoint.

10.4.2.3. Overall Survival
The proportion of patients alive at 180 days post transplant will be estimated using the Kaplan-Meier method.

10.4.3. Exploratory Endpoints & Analyses

The list of exploratory endpoints and their pre-planned analyses is as follows:

10.4.3.1. Incidence of Donor Cell Chimerism

The incidence of patients achieving donor chimerism (< 90% host cells), from either NiCord® or the unmanipulated CBU if transplanted in Part 1, at day 100 will be estimated. Death, autologous recovery, and graft failure will be considered competing risks for this endpoint.

10.4.3.2. Percentage Donor Chimerism in Whole Blood, CD3+ and Myeloid (CD15+ or CD33+) Fractions

The chimerism proportions of the unmanipulated CBU and NiCord® will be measured on days 7, 14, 21, 28, 42, 70, 100 and 180 post transplant in patients with neutrophil engraftment before target day. The distribution of these portions (median, quartiles) will be estimated at each time point. Patients who do not have neutrophil engraftment will be excluded from this analysis. Patients who have secondary graft failure, autologous recovery, or who die before target day (14, 21, 28, 42, 70, 100 and 180 respectively) will be excluded from this analysis after the event. The contribution of NiCord® alone will be estimated as will the total donor (NiCord® + unmanipulated CBU) contribution.

10.4.3.3. Time from Transplantation to Neutrophil Engraftment

Median time to neutrophil (>500/uL) engraftment will be estimated among those in whom engraftment is achieved.

10.4.3.4. Time from Transplantation to Platelet Engraftment

Median time to platelet (>50K/uL) engraftment will be estimated among those in whom engraftment is achieved.

10.4.3.5. Platelet Engraftment (>50k/uL) at 180 Days

To assess the incidence of platelet engraftment (>50k/uL) post transplant a cumulative incidence curve will be computed along with a 95% confidence interval at 180 days post-transplant. Death, autologous recovery, and second transplant prior to engraftment will be considered as a competing risk.

10.4.3.6. Acute GvHD Grade II-IV and III-IV

The cumulative incidence of patients who experience these events will be computed along with a 95% confidence interval at day 100. Death, autologous recovery, graft failure and second transplant will be counted as competing risks in the estimation.

10.4.3.7. Chronic GvHD (Limited or Extensive)

The cumulative incidence of patients who experience this event will be computed along with a 95% confidence interval at day 180. Death, autologous recovery, graft failure and second transplant will be counted as competing risks in the estimation.

10.4.3.8. Regimen-related Toxicity

The cumulative incidence of patients who experience regimen-related toxicity by day 180 will be estimated.

10.4.3.9. Life-threatening or Fatal Infections

The cumulative incidence of patients who experience life-threatening or fatal infections by day 180 will be estimated. Death will be counted as competing risk in the estimation

10.4.3.10. Immune Reconstitution

The distributions of total immunoglobulin levels at days 100 and 180 (mean, standard deviation, median, quartiles) will be estimated. The distributions of the numbers and proportions of different lymphocyte subpopulations at days 100 and 180 (mean, standard deviation, median, quartiles) will also be estimated. The distributions of T-cell excision circles at days 100 and 180 (mean, standard deviation, median, quartiles) will also be estimated. Patients who have graft failure, who have autologous reconstitution, or who die before target day (100 or 180 respectively) will be excluded from this analysis after the event.

10.4.4. Post Study Analysis

The following secondary, and exploratory endpoints will also be analyzed as noted in sections 10.4.2 and 10.4.3 above, however the timepoint of the analysis will be at 1 year post transplant; event-free survival, overall survival, percentage donor chimerism, incidence of chronic GvHD, incidence of life-threatening and fatal infections, and immune reconstitution.

10.5. Safety Assessment

10.5.1. Adverse Experiences

The incidence and frequency of adverse experiences will be presented by System Organ Class and preferred terminology according to MedDRA dictionary and to NCI toxicity criteria. AEs will also be presented by System Organ Class, High Level Term and preferred terminology. Serious adverse experiences will be listed and discussed on a case-by-case basis.

10.6. 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.

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 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.

<u>Direct access to source data - documents</u>

- 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.

11.6. Confidentiality

Individual names of participants will be masked by participating centers and all patients will be assigned a patient identifier code. The link between the patient's identity and the ID code will be kept securely at the center. Only the ID code will be used to identify the patient when submitting study data. Patient identity will not be revealed in any presentations or publications resulting from this study.

APPENDIX A. GVHD CLASSIFICATION

Acute GvHD Definition

Acute GvHD will be assessed at every visit from transplantation (day 0) until end of study or more frequently as clinically indicated. GvHD will be classified according to the Consensus Conference on Acute GvHD grading:[115]

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 the clinical judgment the investigator feels it should be classified as acute rather than chronic.

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

Chronic GvHD Definition

Chronic GvHD will be assessed from day 100 until day 180 or more frequently as clinically indicated. Chronic GvHD will be classified as limited or extensive according to the following criteria.

Criteria for Extent of Involvement in Chronic Graft-versus-Host Disease	
Involvement	Clinical Criteria
Limited	Localized skin involvement, liver dysfunction, or both.
Extensive	Generalized skin involvement OR Localized skin involvement or liver dysfunction plus any one of the following: Chronic aggressive hepatitis, bridging necrosis, cirrhosis. Eye involvement (result on Schirmer test: <5 mm). Involvement of mucosalivary glands. Mucosal involvement (on lip biopsy). Involvement of other target organs.

Chronic GvHD will also be classified as mild, moderate, or severe, according to the National Institute of Health consensus grading criteria[51].

APPENDIX B. SAFETY DATA REPORTING

≤ 24 hours post infusion

Protocol Specified[a]	Unspecified[b]
• Grade 3-5 -- Record name & grade on Infusion form -- Submit SAE summary forms -- Expedited report • Grade 1-2* -- Capture name & grade only on Infusion form	• Grade 3-5 -- Submit SAE summary forms -- Expedited report • Grade 1-2* -- Submit AD1

Prior to infusion or > 24 hours post infusion

Non engraftment @ 42 days post tx	Protocol Specified[a]	Unspecified[b]
-- Submit SAE summary forms -- Expedited report	• Grade 3-5* -- Capture name and grade only on visit summary forms[c] • Grade 1-2* -- Not reported	• SAE -- Submit SAE summary forms -- If associated w/ NiCord® and un-expected then expedited report • Grade 3 non SAE -- Submit AD1 • Grade 1-2 non SAE -- Not reported

* If SAE, submit SAE summary forms. If SAE associated with NiCord®, then submit expedited report

[a] Protocol specified events and database reporting location are listed in Appendix C of this document

[b] Unspecified events are events that are not listed as protocol specified events

[c] Visit Summary Forms include: "Transplant Toxicity", "Acute GvHD", and "Follow-up GvHD" The following forms are also required when applicable:

- Hospitalization Form, Death Form, Infection Form required if applicable

APPENDIX C. PROTOCOL SPECIFIED ADVERSE EVENTS

≤ 24 hours post CBU or NiCord® infusion

Event	Database Location*
Allergic reaction/ Hypersensitivity	Infusion Form
Anaphylaxis	Infusion Form
Diarrhea	Infusion Form
Dyspnea	Infusion Form
Fever	Infusion Form
Hemoglobinuria	Infusion Form
Hypertension	Infusion Form
Hypotension	Infusion Form
Hypoxia	Infusion Form
Infection	Infusion Form and Infection Form
Nausea	Infusion Form
Rigors, Chills	Infusion Form
Sinus bradycardia	Infusion Form
Sinus tachycardia	Infusion Form
Vomiting	Infusion Form
*Grade 3-5 events also require SAE summary forms.	

>24 hours post NiCord® infusion with or without unmanipulated CBU up to 100 days post transplant

Event	Database Location*
Acute chest syndrome	Transplant Toxicity
Alkaline phosphatase increased	Transplant Toxicity
ALT increased	Transplant Toxicity
Avascular necrosis	Transplant Toxicity
Bilirubin increased	Acute GvHD Form**
Capillary leak syndrome	Transplant Toxicity
Cardiac Arrhythmia	Transplant Toxicity
Creatinine increased	Transplant Toxicity
Diarrhea	Acute GvHD Form**
Dyspnea	Transplant Toxicity
Fever	Transplant Toxicity
Hemorrhage	Transplant Toxicity
HUS/TTP/Microangiopathy	Transplant Toxicity
Hypertension	Transplant Toxicity
Hypotension	Transplant Toxicity
Hypoxia	Transplant Toxicity
Infection	Infection Form
Intracranial Hemorrhage	Transplant Toxicity
Left ventricular systolic dysfunction	Transplant Toxicity
Maculopapular rash/ Erythroderma	Acute GvHD Form**
Nausea/ Vomiting/ Anorexia	Acute GvHD Form**
Non-infective cystitis	Transplant Toxicity
Oral Mucositis	Transplant Toxicity

Event	Database Location*
Pericardial Effusion	Transplant Toxicity
Pulmonary hypertension	Transplant Toxicity
Restrictive cardiomyopathy	Transplant Toxicity
Rigors, Chills	Transplant Toxicity
RPLS- Reversible Posterior Leukoencephalopathy Syndrome	Transplant Toxicity
Seizure	Transplant Toxicity
Somnolence	Transplant Toxicity
Stroke	Transplant Toxicity
Thrombocytopenia	Transplant Toxicity***
*Grade 1-2 events are not reported. SAEs also require SAE summary forms. **Note that events on the Acute GvHD form are not graded using the CTCAE *** Note that all post transplant related Thrombocytopenia events (grade 0-4) will be captured on the Transplant Toxicity form only, and will not require AE reporting unless associated with an SAE.	

101-180 days post transplant

Event	Database Location*
Acute chest syndrome	Transplant Toxicity
Alkaline phosphatase increased	Transplant Toxicity
ALT increased	Transplant Toxicity
Avascular necrosis	Transplant Toxicity
Bilirubin increased	Follow-up GvHD**
Capillary leak syndrome	Transplant Toxicity
Cardiac Arrhythmia	Transplant Toxicity
Creatinine increased	Transplant Toxicity
Diarrhea	Follow-up GvHD**
Dry eye	Follow-up GvHD**
Dysphagia	Follow-up GvHD**
Dyspnea	Transplant Toxicity and Follow-up GvHD**
Forced expiratory volume decreased	Follow-up GvHD**
Fever	Transplant Toxicity
Hemorrhage	Transplant Toxicity
HUS/TTP/Microangiopathy	Transplant Toxicity
Hypertension	Transplant Toxicity
Hypotension	Transplant Toxicity
Hypoxia	Transplant Toxicity and Follow-up GvHD **
Infection	Infection Form
Intracranial Hemorrhage	Transplant Toxicity
Left ventricular systolic dysfunction	Transplant Toxicity
Malabsorption	Follow-up GvHD**
Myositis	Follow-up GvHD**
Nausea/ Vomiting/ Anorexia	Follow-up GvHD**
Non-infective cystitis	Transplant Toxicity (
Oral Mucositis	Transplant Toxicity and Follow-up GvHD** (
Pericardial Effusion	Transplant Toxicity
Pulmonary Fibrosis	Follow-up GvHD**

Event	Database Location*
Pulmonary hypertension	Transplant Toxicity
Rash	Follow-up GvHD**
Restrictive cardiomyopathy	Transplant Toxicity
Rigors, Chills	Transplant Toxicity
RPLS- Reversible Posterior Leukoencephalopathy Syndrome	Transplant Toxicity
Seizure	Transplant Toxicity
Somnolence	Transplant Toxicity
Stroke	Transplant Toxicity
Thrombocytopenia	Transplant Toxicity***
Vaginal inflammation	Follow-up GvHD**
*Grade 1-2 events are not reported. SAEs also require adverse event forms SAE summary forms. **Note that events on the Follow-up GvHD) form are not graded using the CTCAE *** Note that all post transplant related Thrombocytopenia events (grade 0-4) will be captured on the Transplant Toxicity form only, and will not require AE reporting unless associated with an SAE.	

APPENDIX D. COMMON TERMINOLOGY CRITERA FOR ADVERSE EVENTS V4.03 (CTCAE)

Document available upon request.

APPENDIX E. DRUG LABELS

Documents available upon request

REFERENCES

[1] Rees DC, Williams TN, Gladwin MT. (2010). "Sickle-cell disease." The Lancet 376:2018-2031.

[2] Herrick JB. (1910). "Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia." Archives of Internal Medicine 6:517-521.

[3] Pauling L, Itano HA, Singer SJ, Wells IC. (1949). "Sickle Cell Anemia, a Molecular Disease" Science 110:543-548.

[4] Ingram VM. (1957). "Gene Mutations in Human Hæmoglobin: the Chemical Difference Between Normal and Sickle Cell Hæmoglobin" Nature 180:326-328.

[5] Friedrich MJ. (2011). "Advances Reshaping Sickle Cell Therapy." JAMA: The Journal of the American Medical Association 305:239-242.

[6] Miller ST, Sleeper LA, Pegelow CH, et al. (2000). "Prediction of Adverse Outcomes in Children with Sickle Cell Disease." New England Journal of Medicine 342:83-89.

[7] Gladwin MT, Sachdev V, Jison ML, et al. (2004). "Pulmonary Hypertension as a Risk Factor for Death in Patients with Sickle Cell Disease." N Engl J Med 350:886-895.

[8] Panepinto JA, O'Mahar KM, DeBaun MR, Loberiza FR, Scott JP. (2005). "Health-related quality of life in children with sickle cell disease: child and parent perception." British Journal of Haematology 130:437-444.

[9] Platt OS, Brambilla DJ, Rosse WF, et al. (1994). "Mortality In Sickle Cell Disease -- Life Expectancy and Risk Factors for Early Death." N Engl J Med 330:1639-1644.

[10] Diggs LM. (1973). Anatomic lesions in sickle cell disease. In: Abramson H, Bertles J, DL W, eds. Sickle cell disease: diagnosis, management, education, and research. St. Louis: C.V.Mosby; 189-229.

[11] Vichinsky E. (2002). "New therapies in sickle cell disease." The Lancet 360:629-631.

[12] Adams RJ, McKie VC, Hsu L, et al. (1998). "Prevention of a First Stroke by Transfusions in Children with Sickle Cell Anemia and Abnormal Results on Transcranial Doppler Ultrasonography." New England Journal of Medicine 339:5-11.

[13] Pegelow CH, Adams RJ, McKie V, et al. (1995). "Risk of recurrent stroke in patients with sickle cell disease treated with erythrocyte transfusions." The Journal of Pediatrics 126:896-899.

[14] Scothorn DJ, Price C, Schwartz D, et al. (2002). "Risk of recurrent stroke in children with sickle cell disease receiving blood transfusion therapy for at least five years after initial stroke." The Journal of Pediatrics 140:348-354.

[15] Hulbert ML, McKinstry RC, Lacey JL, et al. (2011). "Silent cerebral infarcts occur despite regular blood transfusion therapy after first strokes in children with sickle cell disease." Blood 117:772-779.

[16] Charache S, Terrin ML, Moore RD, et al. (1995). "Effect of Hydroxyurea on the Frequency of Painful Crises in Sickle Cell Anemia." New England Journal of Medicine 332:1317-1322.

[17] Walters MC, Patience M, Leisenring W, et al. (1996). "Barriers to bone marrow transplantation for sickle cell anemia." Biol Blood Marrow Transplant 2:100-104.

[18] Vermylen C, Cornu G, Ferster A, et al. (1998). "Haematopoietic stem cell transplantation for sickle cell anaemia: the first 50 patients transplanted in Belgium." Bone Marrow Transplant 22:1-6.

[19] Bernaudin F, Socie G, Kuentz M, et al. (2007). "Long-term results of related myeloablative stem-cell transplantation to cure sickle cell disease." Blood 110:2749-2756.

[20] Locatelli F, Rocha V, Reed W, et al. (2003). "Related umbilical cord blood transplantation in patients with thalassemia and sickle cell disease." Blood 101:2137-2143.

[21] Walters MC, Storb R, Patience M, et al. (2000). "Impact of bone marrow transplantation for symptomatic sickle cell disease: an interim report. Multicenter investigation of bone marrow transplantation for sickle cell disease." Blood 95:1918-1924.

[22] Hsieh, M. M., C. D. Fitzhugh and J. F. Tisdale (2011). "Allogeneic hematopoietic stem cell transplantation for sickle cell disease: the time is now." Blood 118(5): 1197-1207.

[23] Ruggeri, A., M. Eapen, A. Scaravadou, M. S. Cairo, M. Bhatia, J. Kurtzberg, J. R. Wingard, A. Fasth, L. Lo Nigro, M. Ayas, D. Purtill, K. Boudjedir, W. Chaves, M. C. Walters, J. Wagner, E. Gluckman and V. Rocha (2011). "Umbilical cord blood transplantation for children with thalassemia and sickle cell disease." Biol Blood Marrow Transplant 17(9): 1375-1382.

[24] Rund D, Rachmilewitz E. Beta-thalassemia. N Engl J Med. 2005; 353:1135-46.

[25] Thomas ED, Buckner CD, Sanders JE, et al. Marrow transplantation for thalassaemia. Lancet 1982; 2:227-229.

[26] Lucarelli G, Galimberti M, Polchi P, et al. Bone marrow transplantation in patients with thalassemia. N Eng J Med 1990; 322:417-421.

[27] Giardini C, Lucarelli G. Bone marrow transplantation for beta-thalassemia. Hematol Oncol Clin North Am, 1999; 13:1059-1064.

[28] Locatelli F, De Stefano P. New insights into haematopoietic stem cell transplantation for patients with haemoglobinopathies. British Journal of Haematology, 2004; 125:3-11.

[29] Lucarelli G, Clift RA, Galimberti M, et al. Bone marrow transplantation in adult thalassemic patients. Blood 1999; 93, 1164-1167.

[30] Storb RF, Lucarelli G, McSweeney PA, Childs RW. Hematopoietic cell transplantation for benign hematological disorders and solid tumors. Hematology (Am Soc Hematol Educ Program). 2003; 372-97.

[31] Lucarelli G, Clift RA, Galimberti M, et al. Marrow transplantation for patients with thalassemia: results in class 3 patients. Blood 1996; 87:2082-2088.

[32] Sodani P, Gaziev D; Polchi P, et al. A new approach for bone marrow transplantation in class 3 thalassemic patients aged less than 17 years. Blood 2004; 104: 1201-3.

[33] Ghavamzadeh A, Nasseri P, Eshraghian MR, et al. Prognostic factors in bone marrow transplantation for beta thalassemia major: experiences from Iran. Bone Marrow Transplant 1998; 22:1167-1169.

[34] Lawson SE, Roberts IA, Amrolia P, Dokal I, Szydlo R, Darbyshire PJ. () Bone marrow transplantation for beta-thalassaemia major: the UK experience in two paediatric centres. Br J Haematol 2003; 120:289-295.

[35] Andreani M., Manna M, Lucarelli G, et al. Persistence of mixed chimerism in patients transplanted for the treatment of thalassemia. Blood 1996; 87:3494-3499.

[36] Locatelli F, Bruno B, Zecca M, et al. Cyclosporine A and short-term methotrexate versus cyclosporine A as graft versus host disease prophylaxis in patients with severe aplastic anemia given allogeneic bone marrow transplantation from HLA-identical sibling: results of a GITMO/EBMT randomized trial. Blood 2000; 96:1690-1697.

[37] Sykes M, Eisenthal A, Sachs DH. Mechanism of protection from graft-versus-host disease in murine mixed allogeneic chimeras. Development of a null cell population suppressive of cell-mediated lympholysis responses and derived from the syngeneic bone marrow component. J Immunol 1988; 140:2903-2911.

[38] Slavin S, Nagler A, Naparstek E, et al. Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. Blood 1998; 91:756-763.

[39] Hongeng S, Chuansumrit A, Hathirat P, Rerkamnuaychoke B, Chaisiripoomkere W, Jootar S. Full chimerism in nonmyeloablative stem cell transplantation in a beta-thalassemia major patient (class 3 Lucarelli). Bone Marrow Transplant 2002; 30:409-410.

[40] Iannone R, Casella JF, Fuchs, EJ, et al. Results of minimally toxic nonmyeloablative transplantation in patients with sickle cell anemia and beta-thalassemia. Biol Blood and Marrow Transplant 2003; 9:519-28.

[41] Ende M, Ende N. (1918). "Hematopoietic transplantation by means of fetal (cord) blood. A new method." Va Med Mon 99:276-280.

[42] Broxmeyer HE, Douglas GW, Hangoc G, et al. (1989). "Human Umbilical Cord Blood as a Potential Source of Transplantable Hematopoietic Stem/Progenitor Cells." PNAS 86:3828-3832.

[43] Gluckman E, Rocha V. (2005). "History of the clinical use of umbilical cord blood hematopoietic cells." Cytotherapy 7:219-227.

[44] Frassoni F, Podesta M, Maccario R, et al. (2003). "Cord blood transplantation provides better reconstitution of hematopoietic reservoir compared with bone marrow transplantation." Blood 102:1138-1141.

[45] Barker, J. N., D. J. Weisdorf, T. E. DeFor, B. R. Blazar, P. B. McGlave, J. S. Miller, C. M. Verfaillie and J. E. Wagner (2005). "Transplantation of 2 partially HLA-matched umbilical cord blood units to enhance engraftment in adults with hematologic malignancy." Blood 105(3): 1343-1347.

[46] Laughlin, M. J., J. Barker, B. Bambach, O. N. Koc, D. A. Rizzieri, J. E. Wagner, S. L. Gerson, H. M. Lazarus, M. Cairo, C. E. Stevens, P. Rubinstein and J. Kurtzberg (2001). "Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donors." N Engl J Med 344(24): 1815-1822.

[47] Scaradavou, A., C. G. Brunstein, M. Eapen, J. Le-Rademacher, J. N. Barker, N. Chao, C. Cutler, C. Delaney, F. Kan, L. Isola, C. Karanes, M. J. Laughlin, J. E. Wagner and E. J. Shpall (2013). "Double unit grafts successfully extend the application of umbilical cord blood transplantation in adults with acute leukemia." Blood 121(5): 752-758.

[48] Verneris, M. R., C. G. Brunstein, J. Barker, M. L. MacMillan, T. DeFor, D. H. McKenna, M. J. Burke, B. R. Blazar, J. S. Miller, P. B. McGlave, D. J. Weisdorf and J. E. Wagner (2009). "Relapse risk after umbilical cord blood transplantation: enhanced graft-versus-leukemia effect in recipients of 2 units." Blood 114(19): 4293-4299.

[49] Wagner, J., Eapen, M., Carter, S.L., Haut, P.R., Peres, E., Schultz, K.R., Thompson, J., Wall, D.A., Kurtzberg, J. (2012). No Survival Advantage After Double Umbilical Cord Blood (UCB) Compared to Single UCB Transplant in Children with Hematological Malignancy: Results of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN 0501) Randomized Trial. ASH. Atlanta.

[50] Sideri, A., N. Neokleous, P. B. De La Grange, B. Guerton, M. C. Le Bousse Kerdilles, G. Uzan, C. Peste-Tsilimidos and E. Gluckman (2011). "An overview of the progress on double umbilical cord blood transplantation." Haematologica 96(8): 1213-1220.

[51] Ramirez, P., J. E. Wagner, T. E. Defor, B. R. Blazar, M. R. Verneris, J. S. Miller, D. H. McKenna, D. J. Weisdorf, P. B. McGlave and C. G. Brunstein (2012). "Factors predicting single-unit predominance after double umbilical cord blood transplantation." Bone Marrow Transplant 47(6): 799-803.

[52] Newell, L. F., F. Milano, I. B. Nicoud, S. Pereira, T. A. Gooley, S. Heimfeld and C. Delaney (2012). "Early CD3 Peripheral Blood Chimerism Predicts the Long-Term Engrafting Unit Following Myeloablative Double-Cord Blood Transplantation." Biol Blood Marrow Transplant.

[53] Eldjerou, L. K., S. Chaudhury, A. Baisre-de Leon, M. He, M. E. Arcila, G. Heller, R. J. O'Reilly, J. N. Barker and M. A. Moore (2010). "An in vivo model of double-unit cord blood transplantation that correlates with clinical engraftment." Blood 116(19): 3999-4006.

[54] Moretta, A., G. Andriolo, D. Lisini, M. Martinetti, A. Pasi, P. Rebulla, D. Soligo, R. Giordano, L. Lazzari and R. Maccario (2012). "In Vitro Evaluation of Graft-versus-Graft Alloreactivity as a Tool to Identify the Predominant Cord Blood Unit before Double Cord Blood Transplantation." Biol Blood Marrow Transplant 18(7): 1108-1118.

[55] Gluckman E, Ruggeri A, Volt F, Cunha R, Boudjedir K, Rocha V. (2011). "Milestones in umbilical cord blood transplantation." British Journal of Haematology 154:441-447.

[56] Barker, J. N., D. J. Weisdorf, et al. (2005). "Transplantation of 2 partially HLA-matched umbilical cord blood units to enhance engraftment in adults with hematologic malignancy." Blood 105(3): 1343-1347.

[57] McKenna DH, Brunstein CG. (2011). "Umbilical cord blood: current status and future directions." Vox Sanguinis 100:150-162.

[58] Ballen, K. K., T. R. Spitzer, et al. (2007). "Double unrelated reduced-intensity umbilical cord blood transplantation in adults." Biol Blood Marrow Transplant 13(1): 82-89.

[59] Kanda J, Rizzieri DA, Gasparetto C, et al. (2011). "Adult Dual Umbilical Cord Blood Transplantation Using Myeloablative Total Body Irradiation (1350 cGy) and Fludarabine Conditioning." Biology of Blood and Marrow Transplantation 17:867-874.

[60] Wagner, J., Eapen, M., Carter, S.L., Haut, P.R., Peres, E., Schultz, K.R., Thompson, J., Wall, D.A., Kurtzberg, J., No Survival Advantage After Double Umbilical Cord Blood (UCB) Compared to Single UCB Transplant in Children with Hematological Malignancy: Results of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN 0501) Randomized Trial, in ASH. 2012: Atlanta.

[61] Piacibello, W., F. Sanavio, et al. (1998). "Differential growth factor requirement of primitive cord blood hematopoietic stem cell for self-renewal and amplification vs proliferation and differentiation." Leukemia 12(5): 718-727.

[62] Vavrova, J., S. Filip, et al. (1999). "Ex vivo expansion CD34+/AC133+-selected autologous peripheral blood progenitor cells (PBPC) in high-risk breast cancer patients receiving intensive chemotherapy." Hematol Cell Ther 41(3): 105-112.

[63] Filip, S., J. Vavrova, et al. (2000). "Myeloid differentiation and maturation of SCF+IL-3+IL-11 expanded AC133+/CD34+ cells selected from high-risk breast cancer patients." Neoplasma 47(2): 73-80.

[64] Lazzari, L., S. Lucchi, et al. (2001). "Comparison of different serum-free media for ex vivo expansion of HPCs from cord blood using thrombopoietin, Flt-3 ligand, IL-6, and IL-11." Transfusion 41(5): 718-719.

[65] Lazzari, L., S. Lucchi, et al. (2001). "Long-term expansion and maintenance of cord blood haematopoietic stem cells using thrombopoietin, Flt3-ligand, interleukin (IL)-6 and IL-11 in a serum-free and stroma-free culture system." Br J Haematol 112(2): 397-404.

[66] Yao, C. L., I. M. Chu, et al. (2004). "A systematic strategy to optimize ex vivo expansion medium for human hematopoietic stem cells derived from umbilical cord blood mononuclear cells." Exp Hematol 32(8): 720-727.

[67] Mohamed, A. A., A. M. Ibrahim, et al. (2006). "Ex vivo expansion of stem cells: defining optimum conditions using various cytokines." Lab Hematol 12(2): 86-93.

[68] Young, J. C., S. Wu, et al. (2004). "Inhibitors of histone deacetylases promote hematopoietic stem cell self-renewal." Cytotherapy 6(4): 328-336.

[69] Sato, N., L. Meijer, et al. (2004). "Maintenance of pluripotency in human and mouse embryonic stem cells through activation of Wnt signaling by a pharmacological GSK-3-specific inhibitor." Nat Med 10(1): 55-63.

[70] Delaney, C., S. Heimfeld, et al. (2010). "Notch-mediated expansion of human cord blood progenitor cells capable of rapid myeloid reconstitution." Nat Med 16(2): 232-236.

[71] Delaney, C., B. Varnum-Finney, et al. (2005). "Dose-dependent effects of the Notch ligand Delta1 on ex vivo differentiation and in vivo marrow repopulating ability of cord blood cells." Blood 106: 2693-2699.

[72] de Lima, M., et al., Cord-blood engraftment with ex vivo mesenchymal-cell coculture. N Engl J Med, 2012. 367(24): p. 2305-15.

[73] Delaney, C., et al., Notch-mediated expansion of human cord blood progenitor cells capable of rapid myeloid reconstitution. Nature Medicine, 2010. 16(2): p. 232-6.

[74] Peled, T., E. Landau, et al. (2002). "Cellular copper content modulates differentiation and self-renewal in cultures of cord blood-derived CD34+ cells." Br J Haematol 116(3): 655-661.

[75] Peled, T., Mandel, J., Goudsmid, R.N., Lador, C., Hasson, N., Harati, D., Austin, M., and A. Hasson, Fibach, E., Shpall, E.J., Nagler, A. (2004). "Pre-clinical

development of cord blood-derived progenitor cell graft expanded ex vivo with cytokines and the polyamine copper chelator tetraethylenepentamine." Cytotherapy 6(4): 344-355.

[76] Peled, T., E. Landau, et al. (2004). "Linear polyamine copper chelator tetraethylenepentamine augments long-term ex vivo expansion of cord blood-derived CD34(+) cells and increases their engraftment potential in NOD/SCID mice." Exp Hematol 32(6): 547-555.

[77] Stiff, P.J., Montesinos, P., Peled, T., et. al., StemEx®(Copper Chelation Based) Ex Vivo Expanded Umbilical Cord Blood Stem Cell Transplantation (UCBT) Accelerates Engraftment and Improves 100 Day Survival In Myeloablated Patients Compared To a Registry Cohort Undergoing Double Unit UCBT: Results Of a Multicenter Study Of 101 Patients With Hematologic Malignancies, in ASH. 2013: New Orleans.

[78] Lapidot, T., Dar, A., Kollet, O. (2005). "How do stem cells find their way home?" Blood 106(6): 1901-1910.

[79] Szilvassy, S. J., Bass, M. J., Van Zant, G., Grimes, B. (1999). "Organ-selective homing defines engraftment kinetics of murine hematopoietic stem cells and is compromised by Ex vivo expansion." Blood 93(5): 1557-1566.

[80] Ahmed, F., S. J. Ings, et al. (2004). "Impaired bone marrow homing of cytokine-activated CD34+ cells in the NOD/SCID model." Blood 103(6): 2079-2087.

[81] Foguenne, J., Huygen, S., Greimers, R., Beguin, Y., Gothot, A. (2005). "Modulation of homing properties of primitive progenitor cells generated by ex vivo expansion." Haematologica 90(4): 445-451.

[82] Von Drygalski, A., G. Alespeiti, et al. (2004). "Murine bone marrow cells cultured ex vivo in the presence of multiple cytokine combinations lose radioprotective and long-term engraftment potential." Stem Cells Dev 13(1): 101-111.

[83] Xu, R. and J. A. Reems (2001). "Umbilical cord blood progeny cells that retain a CD34+ phenotype after ex vivo expansion have less engraftment potential than unexpanded CD34+ cells." Transfusion 41(2): 213-218.

[84] Szilvassy, S. J., Bass, M. J., Van Zant, G., Grimes, B. (1999). "Organ-selective homing defines engraftment kinetics of murine hematopoietic stem cells and is compromised by Ex vivo expansion." Blood 93(5): 1557-1566.

[85] Szilvassy, S. J., T. E. Meyerrose, et al. (2000). "Effects of cell cycle activation on the short-term engraftment properties of ex vivo expanded murine hematopoietic cells." Blood 95(9): 2829-2837.

[86] Takatoku, M., S. Sellers, et al. (2001). "Avoidance of stimulation improves engraftment of cultured and retrovirally transduced hematopoietic cells in primates." J Clin Invest 108(3): 447-455.

[87] Ahmed, F., S. J. Ings, et al. (2004). "Impaired bone marrow homing of cytokine-activated CD34+ cells in the NOD/SCID model." Blood 103(6): 2079-2087.

[88] Hofmeister, C. C., Zhang, J., Knight, K. L., Le, P., Stiff, P. J. (2007). "Ex vivo expansion of umbilical cord blood stem cells for transplantation: growing knowledge from the hematopoietic niche." Bone Marrow Transplant 39(1): 11-23.

[89] Berger, F., M. H. Ramirez-Hernandez, et al. (2004). "The new life of a centenarian: signalling functions of NAD(P)." Trends Biochem Sci 29(3): 111-118.

[90] Banasik, M., H. Komura, et al. (1992). "Specific inhibitors of poly(ADP-ribose) synthetase and mono(ADP-ribosyl)transferase." J Biol Chem 267(3): 1569-1575.

[91] Corda, D. and M. Di Girolamo (2003). "Functional aspects of protein mono-ADP-ribosylation." Embo J 22(9): 1953-1958.

[92] Krebs, C., S. Adriouch, et al. (2005). "CD38 controls ADP-ribosyltransferase-2-catalyzed ADP-ribosylation of T cell surface proteins." J Immunol 174(6): 3298-3305.

[93] Glowacki, G., R. Braren, et al. (2002). "The family of toxin-related ecto-ADP-ribosyltransferases in humans and the mouse." Protein Sci 11(7): 1657-1670.

[94] Papaccio, G., E. Ammendola, et al. (1999). "Nicotinamide decreases MHC class II but not MHC class I expression and increases intercellular adhesion molecule-1 structures in non-obese diabetic mouse pancreas." J Endocrinol 160(3): 389-400.

[95] Papaccio, G., E. Ammendola, et al. (1999). "Nicotinamide decreases MHC class II but not MHC class I expression and increases intercellular adhesion molecule-1 structures in non-obese diabetic mouse pancreas." J Endocrinol 160(3): 389-400.

[96] Sato, F., T. Mitaka, et al. (1999). "Effects of nicotinamide-related agents on the growth of primary rat hepatocytes and formation of small hepatocyte colonies." Liver 19(6): 481-488.

[97] Miura, M. and Y. Kameda (2005). "Nicotinamide promotes long-term survival and extensive neurite outgrowth in ultimobranchial C cells cultured from chick embryos." J Comp Neurol 492(3): 334-348.

[98] Munshi, C. B., R. Graeff, et al. (2002). "Evidence for a Causal Role of CD38 Expression in Granulocytic Differentiation of Human HL-60 Cells." J Biol Chem 277(51): 49453-49458.

[99] Iwata, K., S. Ogata, et al. (2003). "Induction of differentiation in human promyelocytic leukemia HL-60 cell line by niacin-related compounds." Biosci Biotechnol Biochem 67(5): 1132-1135.

[100] Denu, J. M. (2005). "Vitamin B3 and sirtuin function." Trends Biochem Sci 30(9): 479-483.

[101] Bitterman, K. J., R. M. Anderson, et al. (2002). "Inhibition of silencing and accelerated aging by nicotinamide, a putative negative regulator of yeast sir2 and human SIRT1." J Biol Chem 277(47): 45099-45107.

[102] Vaca, P., G. Berna, et al. (2003). "Nicotinamide induces both proliferation and differentiation of embryonic stem cells into insulin-producing cells." Transplant Proc 35(5): 2021-2023.

[103] Blander, G., A. Bhimavarapu, et al. (2008). "SIRT1 Promotes Differentiation of Normal Human Keratinocytes." J Invest Dermatol.

[104] Kim, M. J., K. Ahn, et al. (2009). "SIRT1 regulates tyrosine hydroxylase expression and differentiation of neuroblastoma cells via FOXO3a." FEBS Lett 583(7): 1183-1188.

[105] Peled T, et al. Nicotinamide, a SIRT1 inhibitor, inhibits differentiation and facilitates expansion of hematopoietic progenitor cells with enhanced bone marrow homing and engraftment. (2012) Exp Hematol. 40(4):342-55.

[106] Srour, E. F., R. Abonour, et al. (1999). "Ex vivo expansion of hematopoietic stem and progenitor cells: are we there yet?" J Hematother 8(2): 93-102.

[107] Ando, K., T. Yahata, et al. (2006). "Direct evidence for ex vivo expansion of human hematopoietic stem cells." Blood 107(8): 3371-3377.

[108] Drake, A. C., M. Khoury, et al. (2011). "Human CD34+ CD133+ hematopoietic stem cells cultured with growth factors including Angptl5 efficiently engraft adult NOD-SCID Il2rgamma-/- (NSG) mice." PLoS ONE 6(4): e18382.

[109] Holmes, T., F. Yan, et al. (2012). "Ex vivo expansion of cord blood progenitors impairs their short-term and long-term repopulating activity associated with transcriptional dysregulation of signalling networks." Cell Prolif 45(3): 266-278.

[110] Laughlin, M. J., J. Barker, et al. (2001). "Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donors." N Engl J Med 344(24): 1815-1822.

[111] Rocha, V., M. Labopin, et al. (2004). "Transplants of Umbilical-Cord Blood or Bone Marrow from Unrelated Donors in Adults with Acute Leukemia." N Engl J Med 351(22): 2276-2285.

[112] Barker, J. N., D. J. Weisdorf, et al. (2005). "Transplantation of 2 partially HLA-matched umbilical cord blood units to enhance engraftment in adults with hematologic malignancy." Blood 105(3): 1343-1347.

[113] Horwitz, M., Chao N., et al. Umbilical cord blood expansion with nicotinamide provides long-term multilineage engraftment. The Journal of Clinical Investigation. 2014 Jul; 124(7): 3121-3128

[114] Walters, M.C., Sullivan, K. M., et al. Neurologic complications after allogeneic marrow transplantation for sickle cell anemia. Blood. 1995 Feb; 85(4): 879-84

[115] Przepiorka, D., Weisdorf, D., et al. Meeting Report: Consensus Conference on Acute GvHD Grading. Bone Marrow Transplantation. 1995; 15: 825-828