Study Title

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

Study Chairs
Mitchell Horwitz, MD
Duke University Medical Center

Guillermo F. Sanz, MD PhD
Hospital Universitario y Politecnico La Fe

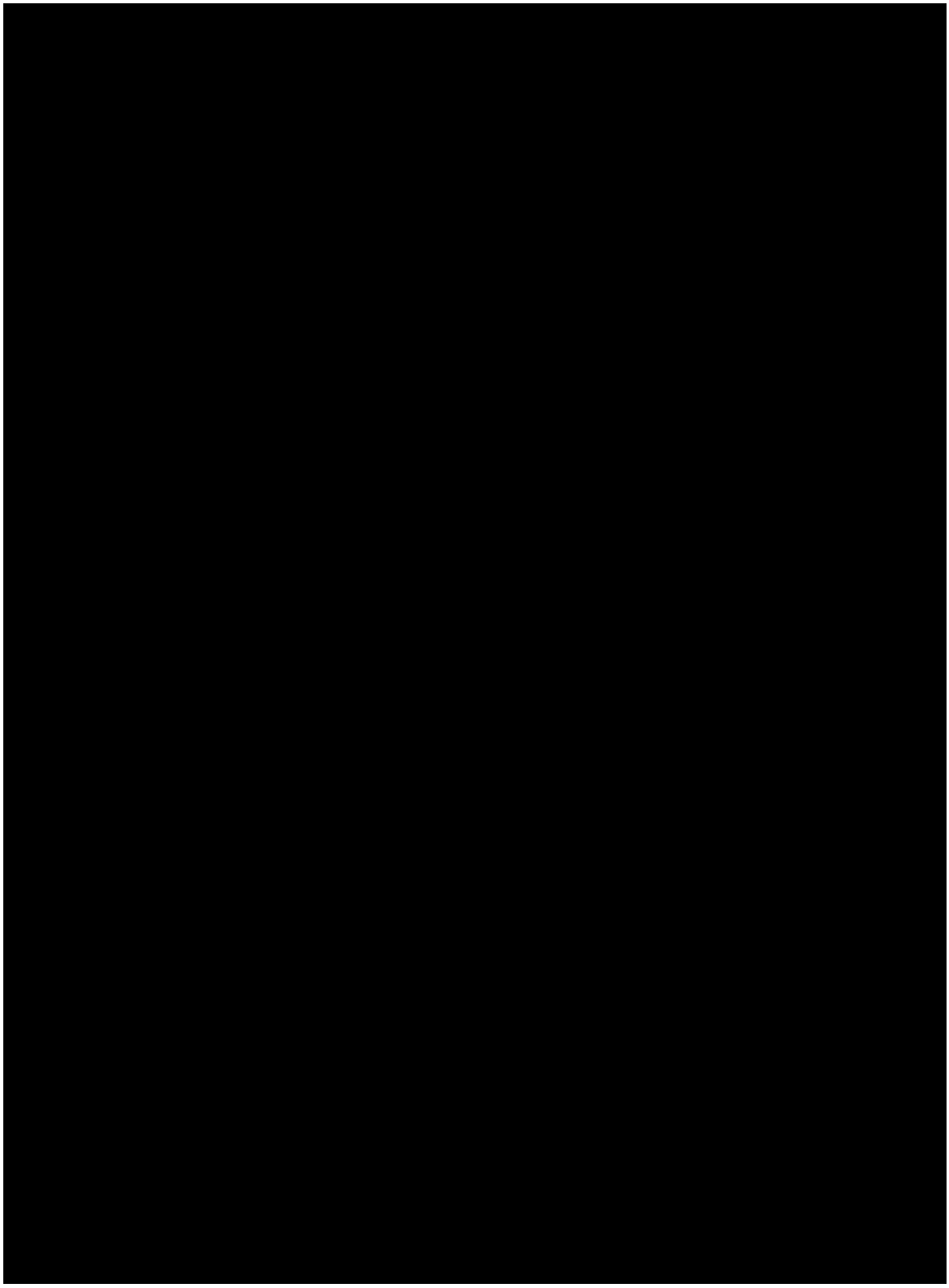
Clinical Phase	Phase I/II
Product:	NiCord®
IND Number:	14459
EudraCT Number:	2014-000074-19

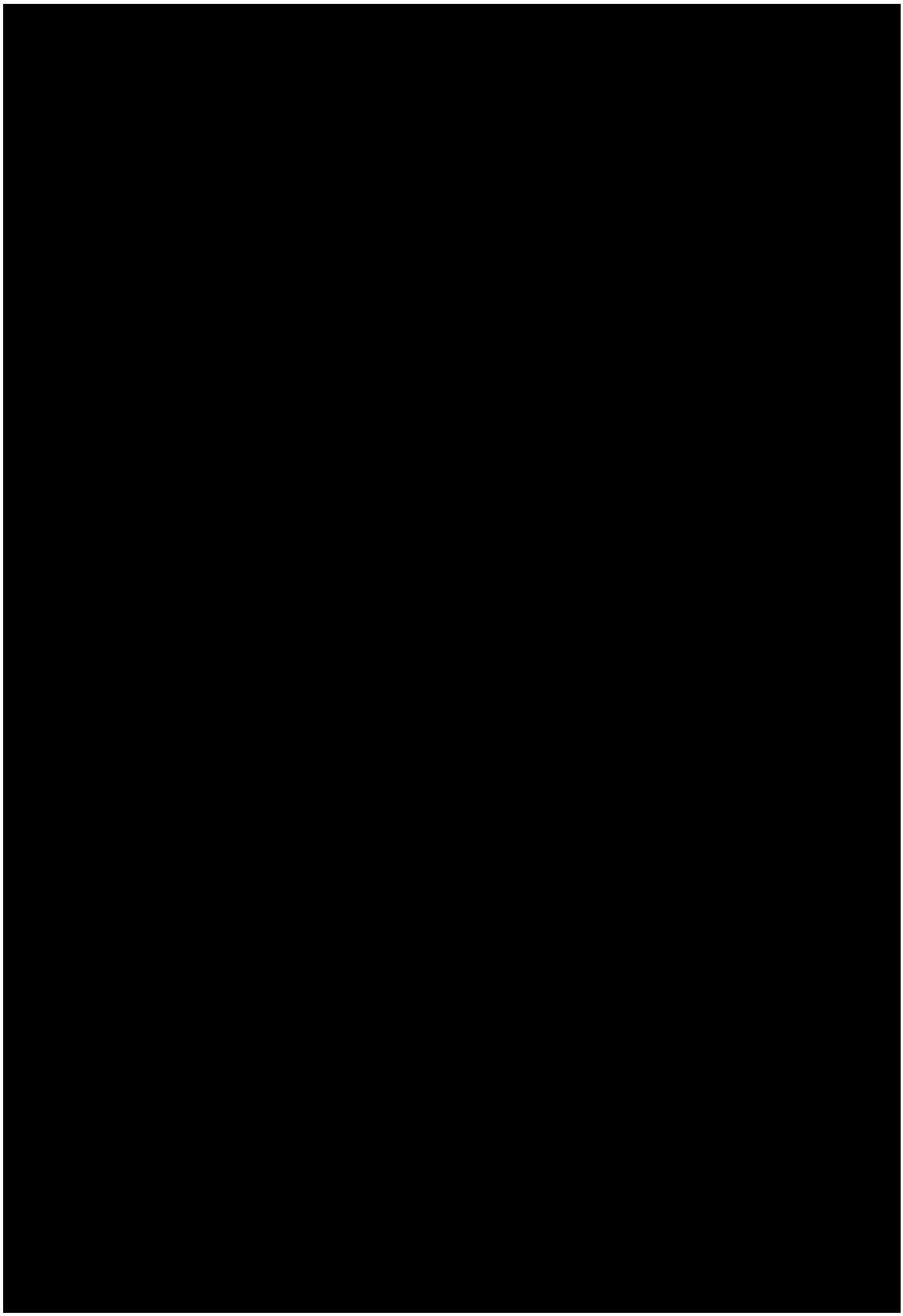
Sponsor
Gamida Cell Ltd.
PO Box 34670
Jerusalem 91340
Israel
Tel: 972-2-6595666
Fax: 972-2-6595616

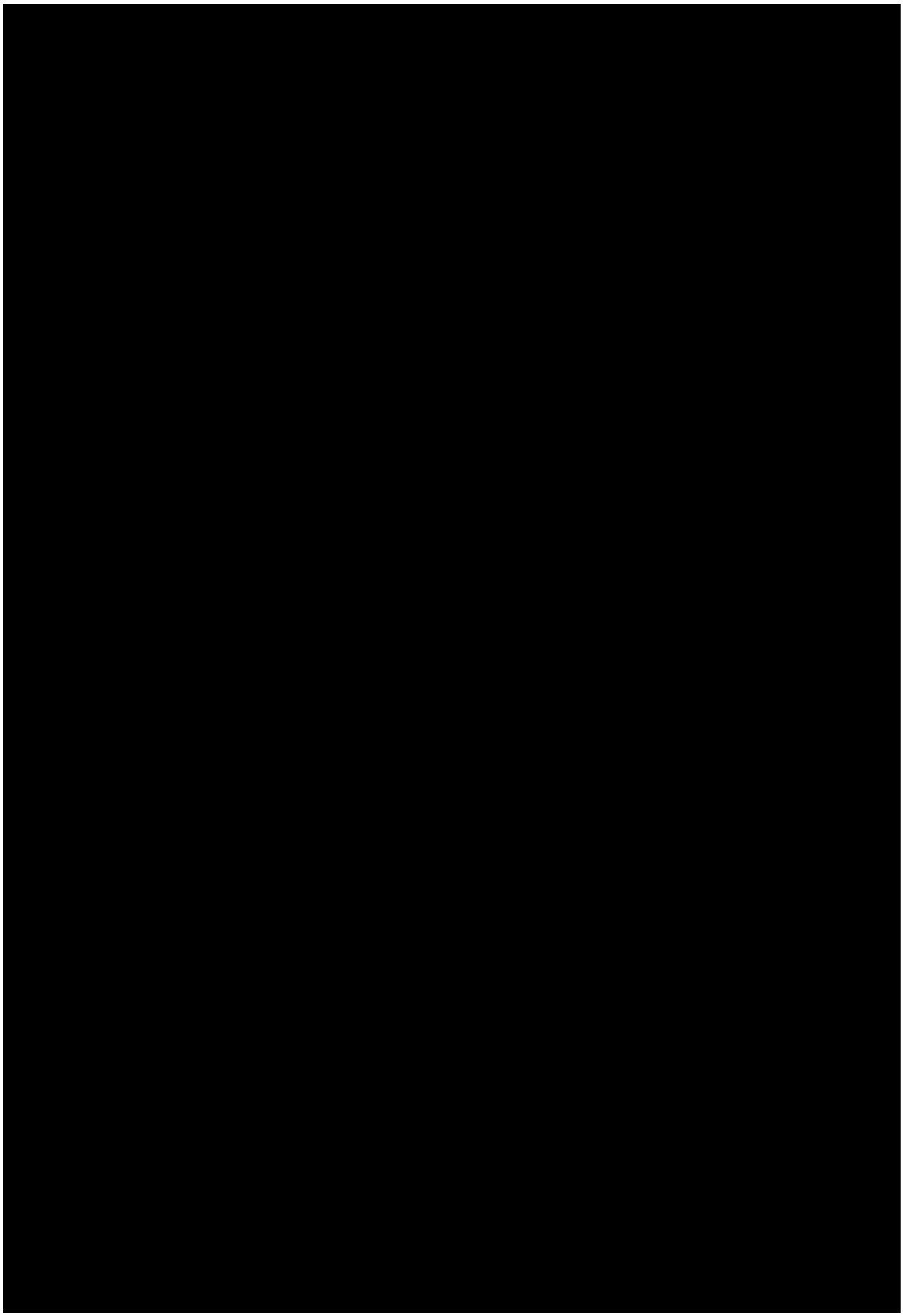
Director, Medical Affairs	Einat Galamidi Cohen, M.D.
Protocol No.	GC P#03.01.020
Amendment #	V
Dated	August 24, 2015

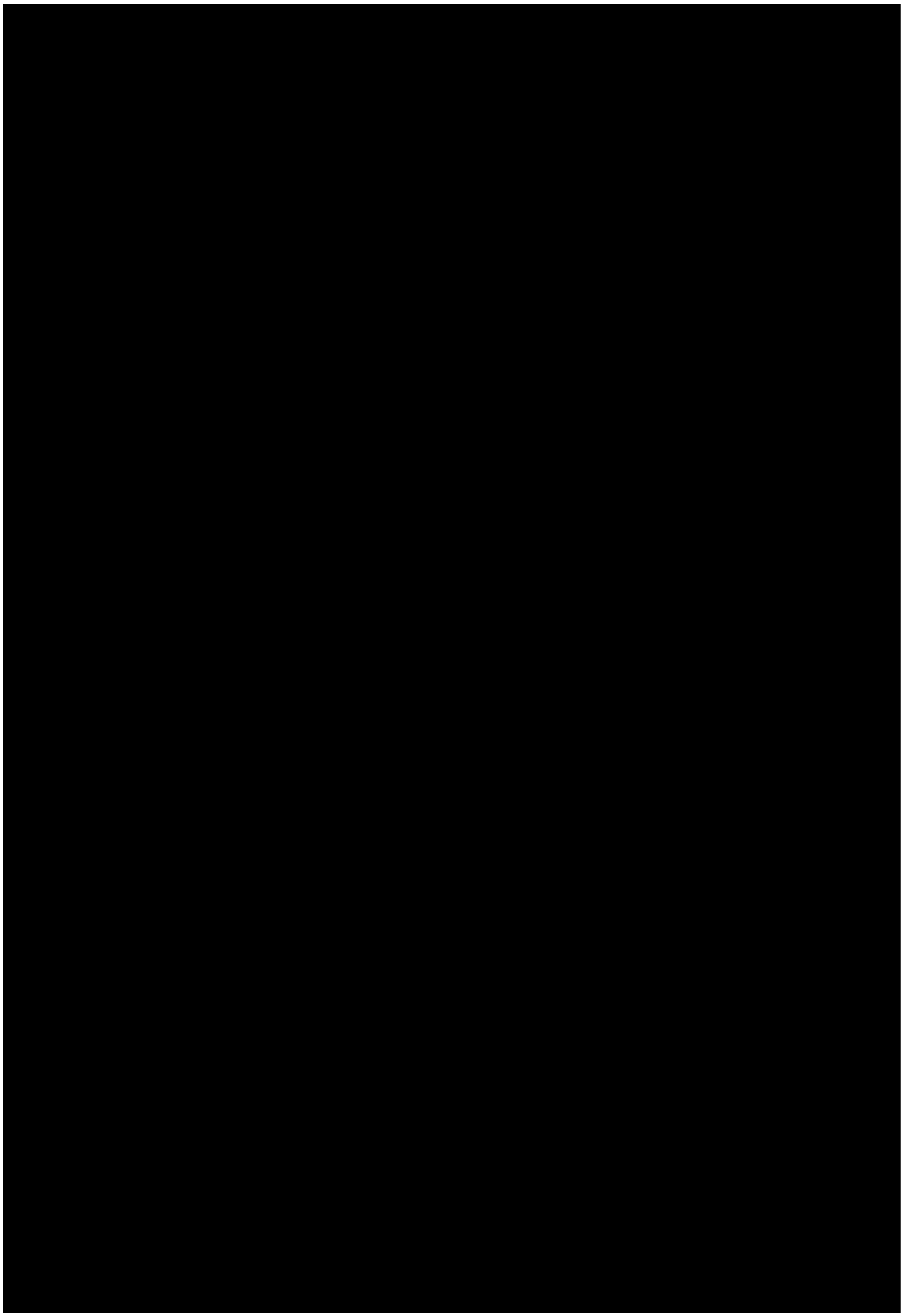
This clinical study will be conducted in accordance with the Sponsor's Standard Operating Procedures (SOPs), this protocol, current Good Clinical Practice (GCP), the Declaration of Helsinki, the provisions of International Conference on Harmonization (ICH) Guidelines and all local applicable laws and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

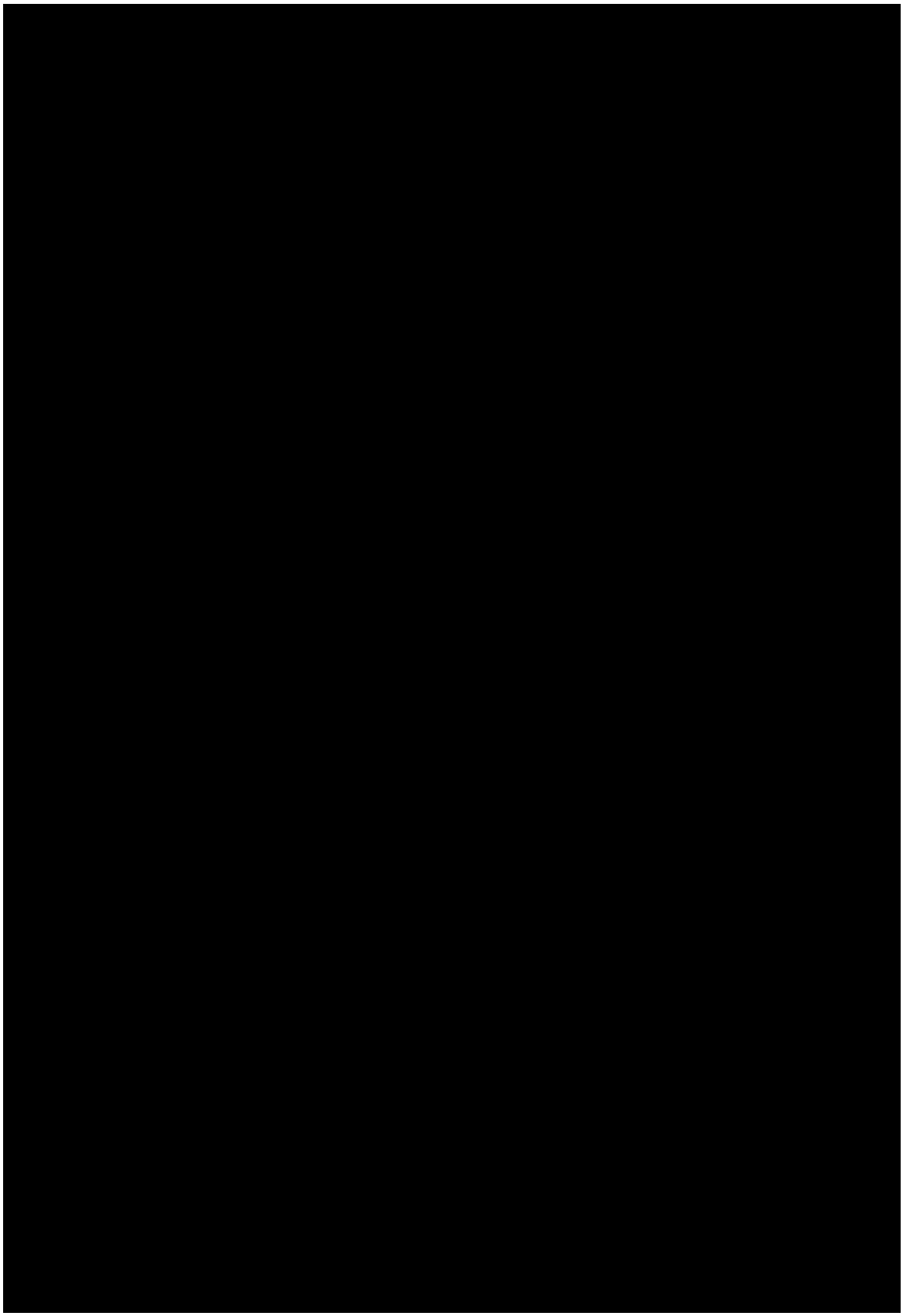
Table of Contents

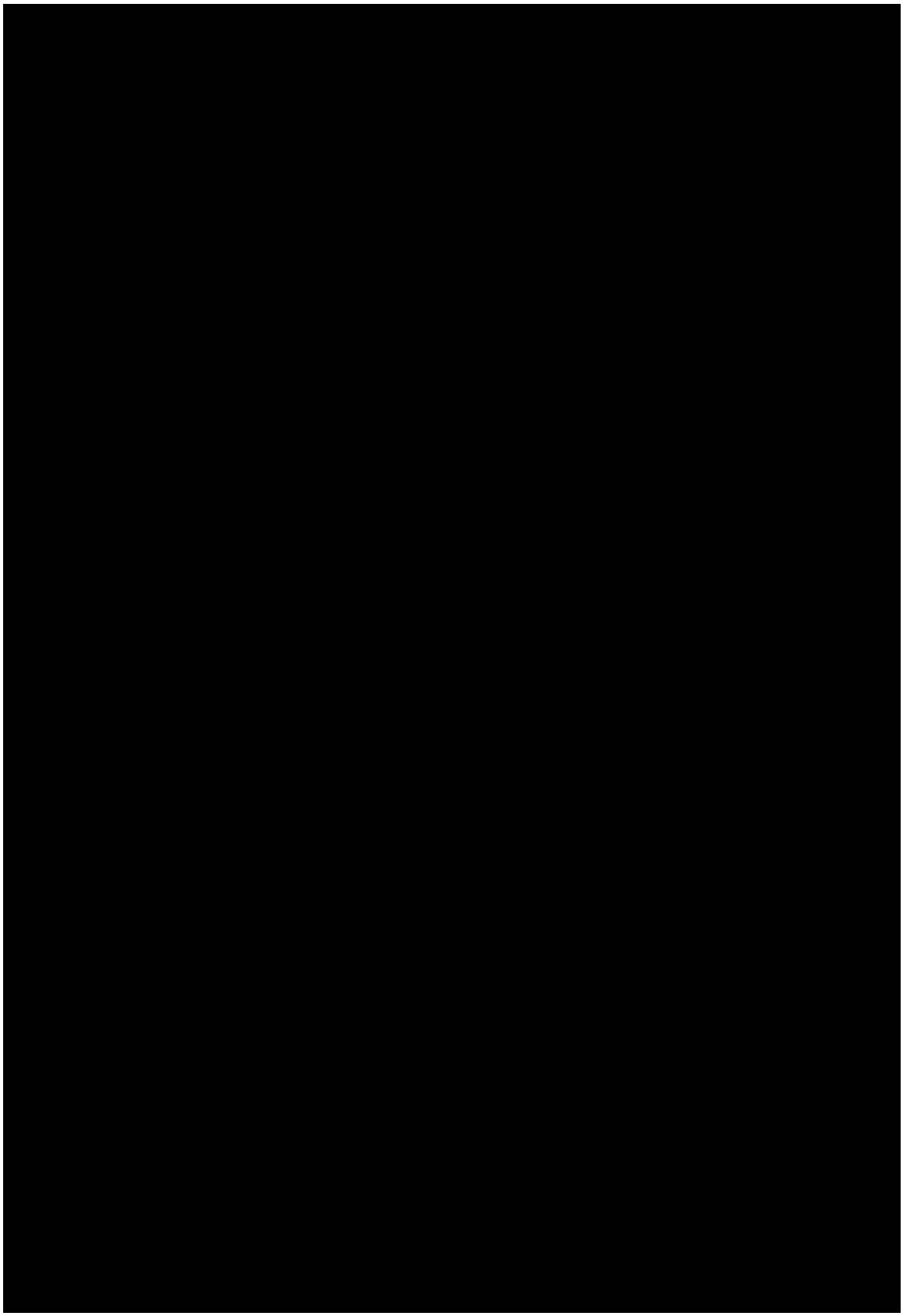


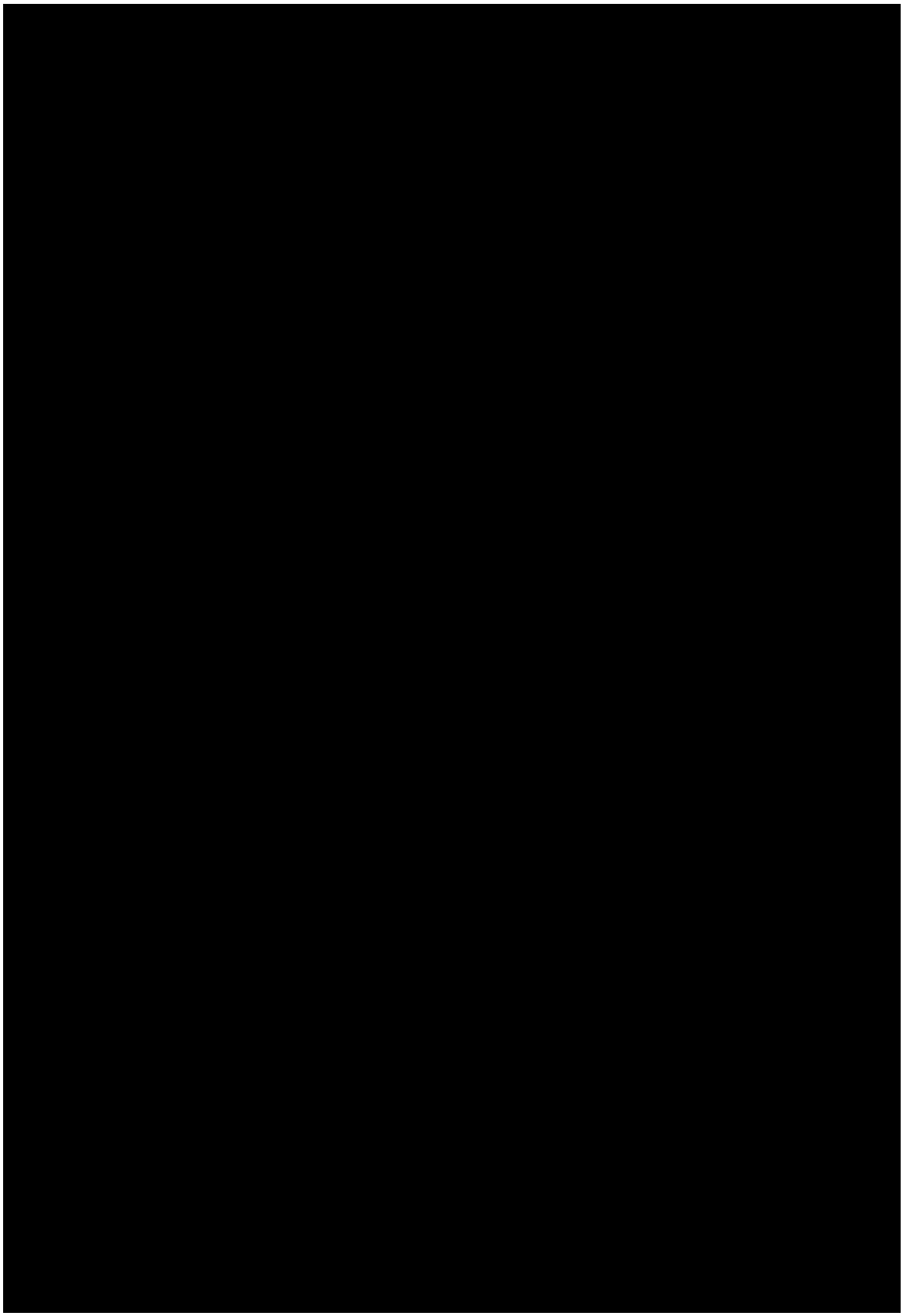


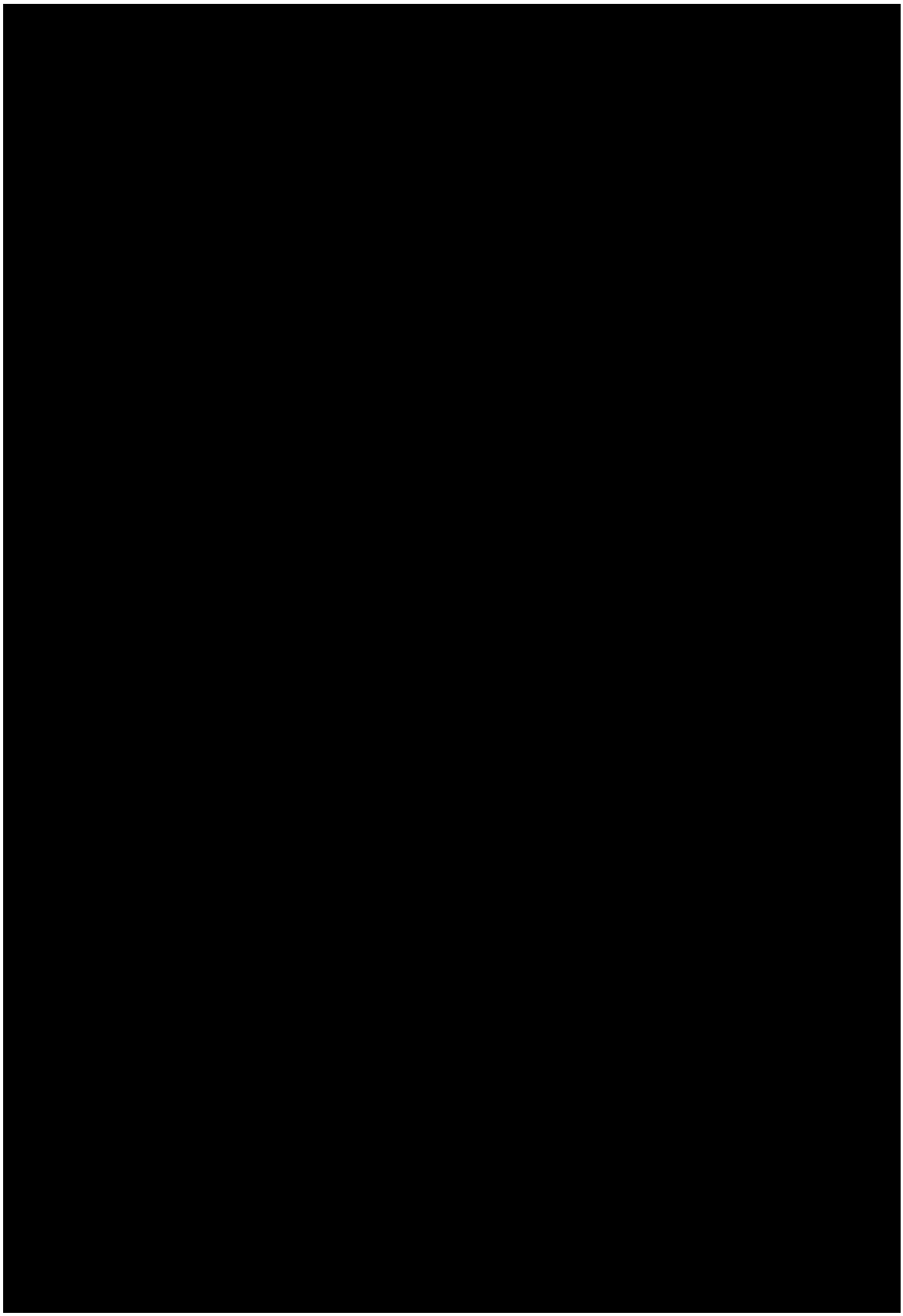












SPONSOR PROTOCOL APPROVAL PAGE

Protocol Title: 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

Clinical Phase Phase I/II

Protocol Number: GC P#03.01.020

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 Adolescent and Adult Patients with Hematological Malignancies

Clinical Phase Phase I/II

Protocol Number: GC P#03.01.020

1. INVESTIGATOR'S AGREEMENT

I have carefully read the foregoing protocol including all appendices and agree that it contains all the necessary information for conducting the study safely.
I will conduct this study in strict accordance with this protocol and according to the current GCP regulations and will attempt to complete the study within the time designated.

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

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

_____
Principal Investigator's Name

_____
Signature

_____
Date

_____
Institution

2. STUDY SYNOPSIS

Protocol Number
GC P# 03.01.020

Protocol Title
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

Number of Centers and Planned Geographical Distribution
Multicenter, multinational

Clinical Phase
Phase I/II

Investigational Product

NiCord® is a cryopreserved stem/progenitor cell based product [redacted] kept frozen until they are infused on the day of transplantation.

Study Duration

Total study duration per patient is approximately 400 days from the signing of informed consent to the last visit one year following transplantation. An accrual period of 28 months is estimated to obtain 40 evaluable patients. The trial ends when the last patient completes their last visit.

Study Objectives

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

Primary Objectives

- Assess the cumulative incidence of patients with NiCord®-derived neutrophil engraftment at 42 days following transplantation.
- Assess the incidence of secondary graft failure at 180 days following transplantation of NiCord®

Secondary Objectives

- Time from infusion to neutrophil engraftment
- Time from infusion to platelet engraftment
- Incidence of platelet engraftment at 100 days
- Proportion of non-relapse mortality at 100 days
- Incidence of acute GvHD grade II-IV and III-IV at 100 days
- Incidence of chronic GvHD (limited or extensive) at 180 days and 1 year
- Incidence of secondary graft failure at 1 year following transplantation of NiCord®
- Overall survival at 180 days and 1 year
- Safety and tolerability of NiCord® transplantation

Exploratory Objectives

- Immune reconstitution at 70, 100, 180, and 365 days

Study Hypothesis

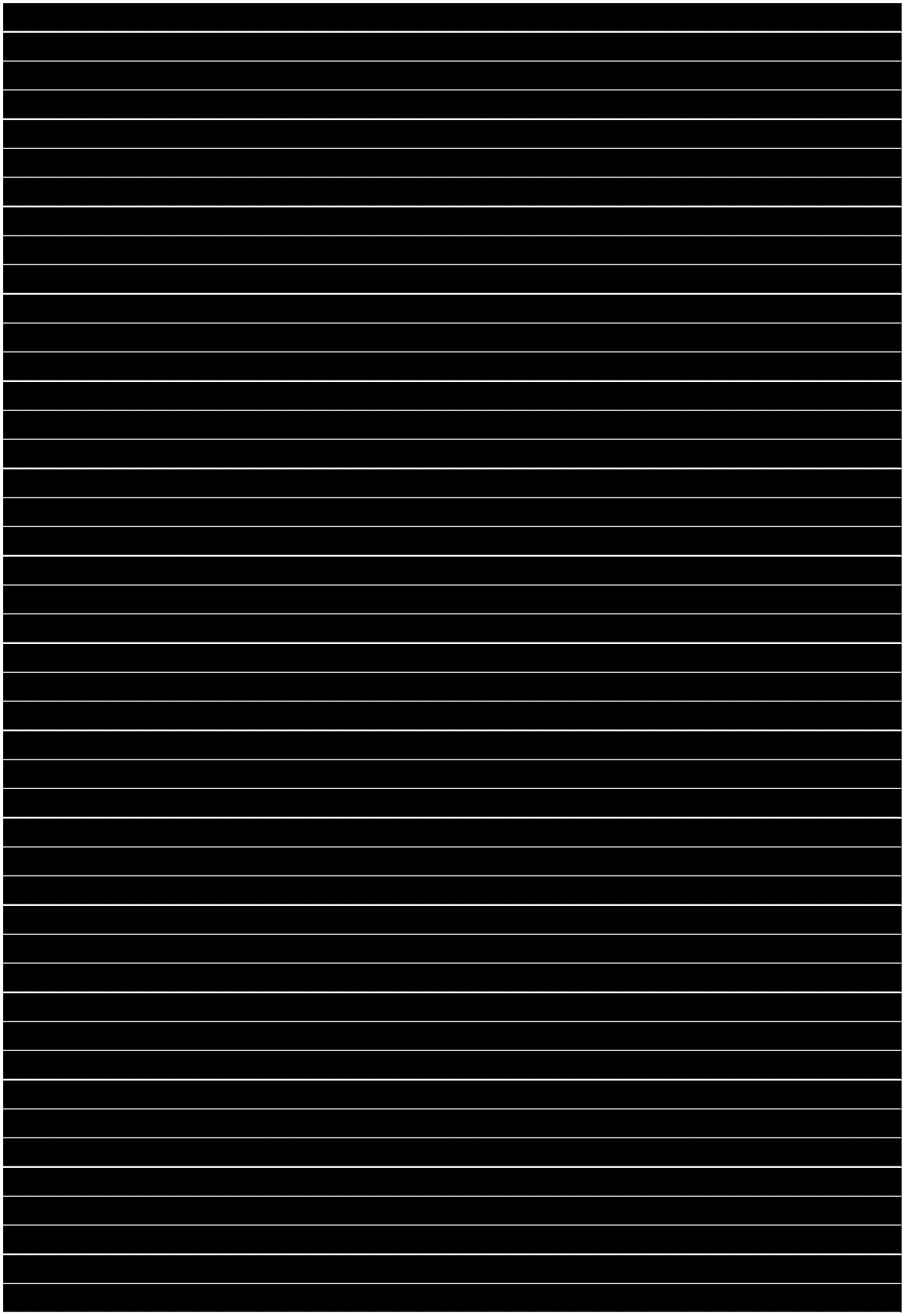
Transplantation of NiCord® following myeloablative conditioning in patients with hematological malignancies will provide sustained engraftment.

Study Design

This is an open-label, non-randomized, interventional, single group assignment study of NiCord® in adolescent and adult patients suffering from hematological malignancies.

Once an optimally matched CBU has been identified and the patient (or legal guardian) signed the informed consent (IC), the patient will be screened for the study.

[redacted]



[redacted]

Number of Patients

40 evaluable patients, up to a maximum of 50 treated patients.

Inclusion Criteria

1. Patients must be 12-65 years of age
2. Patients with one of the following hematologic malignancies:

[redacted]

[redacted]

- [redacted]

3. [redacted]

4. [redacted]

[redacted]

[redacted]

5. [redacted]

6. [redacted]

Exclusion Criteria

[redacted]

9. [redacted]

10. [redacted]

[redacted]

Statistical Considerations

The sample size for the study was not determined by statistical power considerations. Descriptive statistics will be applied to the results of all data from primary and secondary assessment.

Primary End-point and Principal Analysis:

Neutrophil engraftment is defined as achieving an absolute neutrophil count (ANC) greater than or equal to 0.5 x 10^9/L on 3 consecutive measurements on different days with donor chimerism ($\leq$ 10% host cells by peripheral blood chimerism) within 42 days of transplant. The day of neutrophil engraftment is designated as the first of the 3 consecutive measurements.

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

Interim Analysis and Safety Assessment Guidelines:

The data emerging from this study will be reviewed by an independent DMC. This committee will review the accumulated data after 3 patients have entered the study and have been assessed at day 100 following the transplant. A 4th patient may be transplanted prior to DMC review. At this initial review, the DMC will monitor in particular: any occurrence of primary or secondary graft failure, as well as any substantial decrease in donor chimerism (especially myeloid chimerism), or evidence of impending graft failure,

as well as all study data in general. A subsequent DMC review will occur after 3 patients receive the cryopreserved NiCord product and have been assessed at day 100 following transplant. Recruitment may continue during the follow-up of the third cryopreserved NiCord recipient. The committee will make recommendations to the Sponsor regarding early stopping or study modification.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

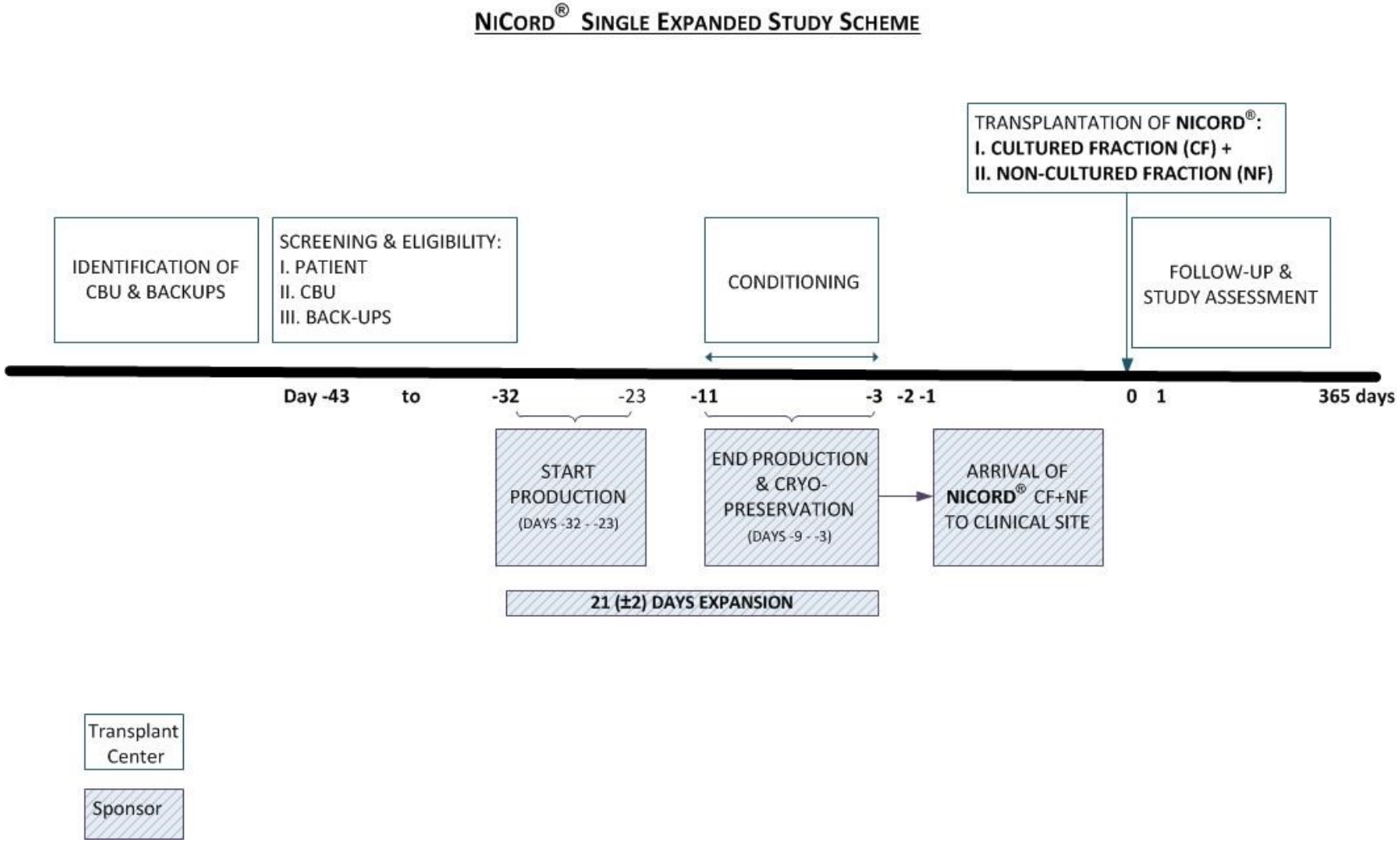
[redacted]

[redacted]

In addition to monitoring the overall study events, the above stopping guidelines will also be applied to each of the individual conditioning regimens separately. Therefore, if one of the guidelines is met with respect to patients transplanted following a specific conditioning regimen, but not with respect to the overall study enrollment, then further use of that conditioning regimen will be prohibited until the DMC reviews the data and provides recommendations to the Sponsor regarding further use or modification of the conditioning regimen.

[redacted]

Figure 1: Study Scheme



3. INTRODUCTION

3.1. Overview

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

Despite the development of large international volunteer donor registries, less than 50% of unrelated donor searches result in identification and availability of a suitably matched donor graft. Donor searches for recipients of non-Northern-European descent result in even lower success. Umbilical cord blood (UCB) is an alternative stem cell source for hematopoietic stem cell transplantations (HSCT) and is clinically in use for the treatment of diverse life-threatening diseases, such as hematological malignancies or genetic blood disorders. UCB grafts have been used in over 20,000 stem cell transplant recipients and provide an alternative source of stem cells in cases where a matched related or unrelated stem cell donor are unavailable. There are numerous advantages to UCB as a transplantable graft source. These include the ease of procurement, the absence of risk to the donor, the reduced risk of transmissible infections, and the availability for immediate use, potentially reducing a long wait and risk of disease progression - particularly important for patients with acute leukemia[Wagner 2009[2]; Aljitawi 2012[3]]. However, a major drawback of UCB is the low stem cell dose available for transplantation, compared to mobilized peripheral blood (PB) or bone marrow[Aljitaw 2012[3]]. This low stem cell dose can compromise the chances of engraftment and contributes to delayed kinetics of neutrophil and platelet recovery (Yamazaki, Kuwana et al. 2006[4]). The delay in graft function may negatively impact transplant outcome [Brunstein, Gutman et al. 2010 [5] ; Ramirez, Brunstein et al. 2010[6]] and prolong the duration of hospitalization and costly supportive care measures.

The transplant community has been actively engaged in developing methods to address the cell dose issue in cord blood transplantation (CBT), which is most acute in adolescent and adult recipients. Several approaches were developed, including dual umbilical cord blood transplantation (DCBT) and *ex vivo* expansion of UCB stem cells. Although to date no prospective clinical trials on the efficacy of single cord versus double cord in adults have been published, the DCBT has become standard practice in CBT for recipients in whom a single CBU of adequate cell dose is unavailable.[Cottler-Fox [1], MacMillan, Weisdorf et al. 2009 [7]; Brunstein, Gutman et al. 2010[5]; Ramirez, Brunstein et al. 2010[6]; Stanevsky, Shimoni et al. 2010[8]] *Ex vivo* expansion is still an experimental approach. Published data of clinical studies evaluating this approach are discussed in section 3.2.

NiCord® is a stem/progenitor cell-based product composed of *ex vivo* expanded allogeneic cells from one entire unit of UCB. NiCord® was developed based on the finding that Nicotinamide (NAM), a form of vitamin B3, delays differentiation and increases functionality of *ex vivo* expanded hematopoietic progenitor cells. Pre-clinical *in*

vitro and *in vivo* studies performed by the Sponsor demonstrated that *ex vivo* expansion of $CD34^+$ cells in a NAM-containing culture system increases the fraction of early stem/progenitor cells within the expanded cell graft, and augments bone marrow homing and engraftment. Based on these results the Sponsor believes that NiCord® has the potential to enable broader application and improvement of clinical outcomes of UCB transplantation.

The chief aim of the proposed study is to evaluate the safety and efficacy of NiCord® transplantation in a single cord blood unit (CBU) study in patients with hematological malignancies.

Currently, NiCord® is being investigated in two pilot studies in a DCBT configuration, as described in Section 3.5 (the first study has been completed). In these pilot studies, the DCBT platform serves as a model to evaluate both the safety of use of a manipulated graft and enables the simultaneous tracking of the contribution of NiCord® to short- and long-term hematopoietic recovery and its relative contribution to the myeloid and lymphoid hematopoietic lineages reconstitution.

The study GC P#01.01.020 was launched in September 2010 and completed follow-up in February 2013. A total of eleven patients were enrolled and transplanted with NiCord®. The study GC P#02.01.020 was initiated in May 2012 and as of December 17, 2013, five patients have been transplanted with NiCord®. Both of these studies are evaluating the safety and efficacy of NiCord® transplantation in combination with a second, unmanipulated CBU in patients with hematological malignancies or sickle cell disease, respectively.

3.2. The Use of DCBT and Ex-Vivo Expansion to Overcome the Cell Dose Limitation in CBT

The following section provides a review of literature describing the advantages and disadvantages of the DCBT modality and published data describing the expansion technologies evaluated in DCBT studies.

The DCBT approach is now standard practice for adolescent and adult recipients for whom a single UCB of adequate size is unavailable. 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 UCB transplantation using a single adequately sized CBU[(Verneris, Brunstein et al. 2009[9]]. Transplant-Related Mortality (TRM) and overall survival appear to be comparable in single and double CBT modalities. The use of DCBT as a transplant modality has been shown to possibly reduce the risk of relapse in patients with less advanced leukemia[Stanevsky, Shimoni et al. 2010[8]; Sideri, Neokleous et al. 2011[10]]; however this may be associated with a slight increase in the risk of graft-versus-host disease (GvHD)[(Verneris, Brunstein et al. 2009[9]]. Viability of UCB stem cells is a prerequisite for successful engraftment. Adequate viability cannot be confirmed until the CBU is thawed on the day of transplantation. The DCBT approach increases the chance that a highly viable CBU is provided to the patient[Scaradavou, Smith et al. 2009[11]]. 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[Sideri, Neokleous et al. 2011[10]]. Thus the use of DCBT does not appear to improve the hematopoietic recovery following transplantation.

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.[Ramirez, Wagner et al. 2012[12]] The mechanism of single donor dominance is likely to be multi-factorial, involving intrinsic features of the CBUs such as homing properties and proliferative potential of the stem cells, graft-graft interactions mediated by T-cell interactions, as well as host-graft interactions. No reproducible association has been found between CBU characteristics such as median infused total nucleated cells (TNC), $CD34^+$, and $CD3^+$ cell doses and unit dominance[Majhail, Brunstein et al. 2006 [13]], therefore 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[Newell, Milano et al. 2012 [14]] 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*[Eldjerou, Chaudhury et al. 2010 [15]] and *in vitro*[Moretta, Andriolo et al. 2012 [16]] 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. The time needed for the predominant CBU to overcome the other CBU *in vivo* could depend on the degree of reciprocal alloantigen-specific cytotoxic potency of the two CBUs. 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[Moretta, Andriolo et al. 2012[16]].

Ex vivo expansion was suggested as a modality to increase the numbers and/or potency of cells in a single CBU and to enhance the efficacy and applicability of CBT[(Kelly, Parmar et al. 2010 [17]; Dahlberg[18], Delaney et al. 2011 [19]; Aljitawi 2012[3]] . This has prompted intensive research and development of novel and more potent expansion technologies.

DCBT serves as a model to evaluate novel graft manipulations[Wagner 2009 [2]] not only adding a measure of safety (with an unmanipulated CBU) but by permitting to track the contribution of the manipulated CBU to short- and long-term hematopoietic recovery[Ramirez, Wagner et al. 2012[12]]. Two studies reported so far describe the transplantation of *ex vivo* expanded cells from one CBU in combination with a second non-manipulated CBU[De Lima, Robinson et al. 2010 [20]; De Lima et al. 2012 [21]; Delaney, Heimfeld et al. 2010 [19]]. In their publications they show that the expanded cells contributed mainly to initial myeloid engraftment that occurred at a median time of about 15-16 days and platelet engraftment at a median of about 40-42 days. The expanded cells have been observed as early as one week post transplantation but were lost before or after engraftment, while the unmanipulated CBU took over in all of the recipients. A lack of *in vivo* persistence of the

expanded graft could either be due to loss of stem cell self-renewal capacity during culture or to an immune-mediated rejection as described above. It was therefore suggested that combining an *ex vivo* expanded CBU for early hematologic recovery with an unmanipulated CBU for long-term sustained hematopoiesis could be an optimal strategy to shorten the neutropenic phase following CBT.

3.3. 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[Srour, Abonour et al. 1999 [22]; Ando, Yahata et al. 2006 [23]; Drake, Khoury et al. 2011 [24]] . 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[Holmes, Yan et al. 2012 [25]].

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 both the literature described in section 3.2 and the preliminary results from the ongoing study as summarized below and detailed in section 3.5, the Sponsor aims to assess whether UCB transplantation of a single expanded CBU using the NiCord® technology is feasible and provides sustained donor-derived engraftment in adult patients with hematological malignancies following myeloablative therapy.

The clinical outcomes of patients with hematological malignancies transplanted with NiCord®, delivered as part of a DCBT approach, demonstrate that eight out of eleven patients engrafted with a myeloid predominance of the expanded CBU (NiCord®) and those eight patients achieved neutrophil and platelet engraftment at a median of 10.5 and 31.5 days post-transplantation, respectively (Table 2). Based on the last chimerism tests performed the expanded cells are shown to persist in all eight patients initially engrafted with NiCord® (Table 3). In five out of eight patients, both myeloid and lymphoid cells derived entirely from the NiCord® graft (Table 3). Immune reconstitution analysis of these 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) (Table 4). The pattern of immunologic reconstitution of all blood cell lineages appears to be comparable between patients who engrafted with NiCord® only and patients who engrafted with the unmanipulated unit only (Table 4). At a median follow-up of 364 days after transplantation (range 100-404), 9 of 11 transplanted patients are alive with no reported secondary graft failure.

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. The Sponsor believes 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. As detailed in section 3.6, the study has been designed to assess the use of NiCord® in a single CBT configuration while maintaining a careful monitoring of patient safety. Thus, prohibitive cell dose requirements will be applied, both to the CBU selection, and to the NiCord® product when administered as a single CBT. The primary endpoints focus on the risk of graft failure, both in the short and long term. Moreover, strict stopping rules are applied with regard to graft failure.

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 alternative graft for unrelated donor transplantation in patients who do not have a matched adult donor option, thereby addressing a critical unmet need in the treatment of hematologic 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 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.

3.4. Gamida Cell Expansion Technology

NiCord® is composed of CB-derived allogeneic stem and progenitor cells expanded ex vivo from an entire CBU with cytokines and nicotinamide, a form of the vitamin B3.

[redacted]

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

Engraftment is a multi-step process involving directed migration of the inoculated cells, homing to the BM, retention within the BM niche followed by self-renewal and differentiation. Engraftment efficacy following expansion is known to be low due to poor homing to the bone marrow compared to fresh CD34+ cells (Szilvassy 1999[26]; Ahmed, Ings et al. 2004[27]; Foguenne 2005[28]) or reduced self-renewal owing to enhanced differentiation in culture.

Therefore, the goal of the ex vivo expansion of hematopoietic progenitor cells (HPC) is to increase their numbers while maintaining their self-renewal capacity and their ability to home to the bone marrow (BM) and efficiently reconstitute hematopoiesis. Exposure of HPC to different combinations of cytokines promotes their exit from the G0 phase of the cell cycle and enables extensive proliferation. Nonetheless, in vitro proliferation is tightly coupled with commitment to differentiation, and reduced self-renewal (Von Drygalski, Alespeiti et al. 2004[29]). Exposure to early-acting cytokines (SCF, TPO, FLT3 and IL6) induces robust in vitro expansion of CD34+ cells, but expansion of engraftable progenitors is modest (Xu and Reems 2001[30]). This discrepancy could be explained, at least in part, by an acquired defect in the BM homing capacity of HPC expanded ex vivo (Szilvassy 1999[26]; Szilvassy, Meyerrose et al. 2000[31]), which is primarily attributed to their active cycling (Takatoku, Sellers et al. 2001[32]) accompanied by alterations in adhesion and chemokine receptor expression or functionality (Ahmed, Ings et al. 2004 [27]). Strategies to augment the BM homing and engraftment efficacy are particularly important to increase clinical applicability of ex vivo expanded CD34+ cells (Hofmeister 2007[33]).

Gamida Cell extensive studies discovered that NAM delays differentiation and increases the engraftment efficacy of cord-blood derived, purified CD133+ cells cultured with a combination of 4-cytokines (FLT3, SCF, TPO and IL6) for 19-23 days. In the presence of NAM the fraction of CD34+CD38- early progenitor cells increases and the fraction of differentiated myelomonocitic cells (CD14+, CD11b+, CD11c+) decreases over cytokines alone treated cultures. CD34+ cells cultured with NAM displayed increased migration towards SDF-1 and home to the bone marrow (24hr post infusion) with higher efficacy than cells cultured with cytokines only or non-cultured cells (Peled 2012[34]).

[redacted]

[redacted]

NAM serves as a precursor of nicotinamide adenine dinucleotide (NAD+) (Berger, Ramirez-Hernandez et al. 2004[35]). On the other hand, NAM is a potent inhibitor of enzymes that require NAD+ for their activity(Banasik, Komura et al. 1992[36]; Corda and Di Girolamo 2003[37]), such as mono-ADPribosyltransferases (mARTs), poly-ADP-ribose polymerases (PARPs) and CD38, cADPR/NADase (Krebs, Adriouch et al. 2005[38]). Having multiple effects on numerous cells, NAM is implicated in regulation of cell adhesion, polarity, migration, proliferation and differentiation (Glowacki, Braren et al. 2002[39]). NAM was shown to modulate the fate of embryonic stem cells (Papaccio, Ammendola et al. 1999[40]) and of primary non-hematopoietic cells

(Papaccio, Ammendola et al. 1999; Sato, Mitaka et al. 1999[41]; Miura and Kameda 2005[42]). On hematopoietic cell lines it has dual effects; on the one hand it inhibits HL-60 cell differentiation mediated by retinoic acid, (Munshi, Graeffet al. 2002[43]) and on the other hand it directly drives HL-60 cell differentiation (Iwata, Ogata et al. 2003[44]).

NAM has also been demonstrated as a strong noncompetitive inhibitor of SIRT1, the NAD-dependent class III histone deacetylase (Denu 2005[45]). In lower eukaryotes, Sir2 (the mammalian SIRT1 homolog) has been strongly implicated in the modulation of replicative lifespan and promotion of longevity while NAM strongly inhibits silencing and shortens replicative life span (Bitterman, Anderson et al. 2002[46]).

In contrast to its function in lower eukaryotes, SIRT1 function in higher eukaryotes is still debatable (Vaca, Berna et al. 2003[47]). A growing body of evidence suggests SIRT1 to inhibit proliferation and to promote differentiation of mammalian cells, and NAM, through inhibition of SIRT1, to inhibit their differentiation (Blander, Bhimavarapu et al. 2008[48]; Kim, Ahn et al. 2009[49]). Our studies show that EX-527, a specific inhibitor of SIRT1 catalytic activity, inhibits differentiation of culture expanded CD34+ cells similar to NAM. NAM positional isomers, NAM-related molecules or NAM non-related PARP and mARTs inhibitors did not inhibit differentiation, suggesting SIRT1 as the primary target of NAM-modulating differentiation of cultured CD34+ cells (Peled 2012).

3.5. Clinical Experience

Currently NiCord® is being investigated in two pilot studies in a DCBT configuration, as summarized in Table 1 below.

Table 1: Overview of Ongoing Clinical Studies of NiCord®

Protocol Number (ClinicalTrials.gov Number)	Study Title	Study Status	Institution / Principal Investigator
GC P#01.01.020 (NCT01221857[a])	Allogeneic Stem Cell Transplantation of NiCord®, Umbilical Cord Blood-Derived *Ex Vivo* Expanded Stem and Progenitor Cells, in Combination With a Second, Unmanipulated Cord Blood Unit in Patients With Hematological Malignancies	Complete	Duke University Health System/ 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#02.01.020 (NCT01590628[b])	Allogeneic Stem Cell Transplantation of NiCord®, Umbilical Cord Blood-Derived *Ex Vivo* Expanded Stem and Progenitor Cells, in Combination with a Second, Unmanipulated Cord Blood Unit in Patients with Sickle Cell Disease	Ongoing	Duke University Health System/ Dr. Joanne Kurtzberg Cohen Children's Medical Center of New York/ Dr. Joel Brochstein

http://clinicaltrials.gov/ct2/show/NCT01221857?term=nicord&rank=1.
http://clinicaltrials.gov/ct2/show/NCT01590628?term=NCT01590628&rank=1.

The subsequent sections describe the clinical studies mentioned above. The preliminary clinical data provided in Tables 2-5 are updated as of December 17, 2013.

3.5.1. Study GC P#01.01.020

A pilot study (GC P#01.01.020), entitled: "Allogeneic Stem Cell Transplantation of NiCord®, Umbilical Cord Blood-derived *Ex Vivo* Expanded Stem and Progenitor Cells, in Combination with a Second, Unmanipulated Cord Blood Unit in Patients with Hematological Malignancies" has been completed at Duke University Medical Center, NC, USA and Loyola University Cardinal Bernardin Cancer Center, IL, USA. The study evaluated the transplantation of NiCord® in combination with an unmanipulated CBU, for the hematopoietic support of subjects with hematological malignancies receiving high-dose chemotherapy.

As of December 17, 2013, eleven adult subjects with hematological malignancies have received myeloablative therapy followed by the transplantation of an unmanipulated CBU and NiCord®. The conditioning regimen consisted of total body irradiation (TBI) 1350 cGy fractionated to nine doses and fludarabine 160 mg/m^2. Two patients also received cyclophosphamide 120 mg/kg.

Study results show a 16-186 fold enrichment in the numbers of CD34$^+$ cells infused following expansion, compared to the CD34$^+$ cell dose in the CBU post-thaw. Ten out of eleven patients transplanted with NiCord® have experienced donor hematopoietic engraftment. In all eleven patients (including the non-engrafting patient), day seven PB chimerism demonstrated predominance of the NiCord® expanded CBU. Eight patients have engrafted with a myeloid predominance of the expanded CBU (NiCord®). As of December 17, 2013, based on last chimerism follow-up of 42-365 days after transplantation, the expanded cells are shown to persist in all eight patients that were initially engrafted with the expanded CBU (Table 3). These eight patients achieved neutrophil engraftment at a median of 10.5 days after transplantation (range 7-18 days), and platelet engraftment at a median of 31.5 days after transplantation (range 26-41 days, one patient did not achieve platelet engraftment at time of death 47 days post transplant). Within the eight patients engrafted with a myeloid predominance of the expanded CBU; one patient engrafted with myeloid cells from both NiCord® and the unmanipulated CBU and CD3 cells from the unmanipulated CBU, two patients engrafted with myeloid cells

from NiCord® only and CD3 cells from both NiCord® and the unmanipulated CBU, five patients engrafted with NiCord® alone.

Based on the last chimerism (total PB, myeloid-CD15 and lymphoid-CD3) follow-up at days 42 to 365 post-transplantation, the expanded cells persist in all patients that initially engrafted with NiCord® (Table 3). In addition to myeloid recovery, the patients who are fully engrafted with the expanded CBU also demonstrate robust recovery of lymphoid cell lineages: T cells (CD3, CD4 and CD8), B cells (CD19), and NK cells (CD56/16) from NiCord®, as shown in Table 4.

Two patients engrafted with a predominance of the unmanipulated CBU (Table 3). These patients achieved neutrophil engraftment at 18-26 days after transplantation, and platelet engraftment at 36-49 days (Table 2). One patient failed to achieve engraftment 42 days after transplantation (Table 2), and received a second stem cell transplant from a haploidentical donor.

As of December 17, 2013, 9 of 11 transplanted patients are alive at follow-up of 42 to 404 days post transplant with no reported relapse or secondary graft failure. One patient died of pneumonia at 47 days post transplant and one patient died of relapse at 196 days post transplant.

Subjects were monitored closely prior to, during, and for 24 hours post-transplantation. As of December 17, 2013, two patients were reported to have experienced Grade 3 hypertension events and one patient reported a Grade 3 hematuria on the day of transplantation. All three events were resolved with no residual effects. Acute GvHD grade II was observed in five subjects (Table 2).

In addition to the eleven patients described above, one patient received only the unmanipulated CBU due to a positive Gram stain result obtained from the NiCord® CF during release testing. NiCord® CF and NF were not infused to the patient and were discarded. NiCord® CF was tested for complete sterility (14 and 21 days) and the results of all the sterility tests were negative. The patient achieved hematopoietic recovery following infusion of the unmanipulated unit and is alive at 386 days post-transplantation. This case was reported to the FDA in the annual report.

The patient data were reviewed twice by the DSMB as per protocol, after the first three and six patients completed 100 days follow-up, with a subsequent recommendation to continue study accrual and transplantations.

3.5.2. Study GC P#02.01.020

The study GC P#02.01.020 entitled: “Allogeneic Stem Cell Transplantation of NiCord®, Umbilical Cord Blood-derived *Ex Vivo* Expanded Stem and Progenitor Cells, in Combination with a Second, Unmanipulated Cord Blood Unit in Patients with Sickle Cell Disease” is ongoing at Duke University Medical Center, NC, USA and Cohen Children’s Medical Center of New York. The study is evaluating the transplantation of NiCord® in combination with an unmanipulated CBU, for hematopoietic support of subjects with Sickle Cell Disease (SCD). The study was launched in May 2012. The first patient was

transplanted on October 31, 2012 and as of December 17, 2013, five patients have been transplanted with NiCord® in a double cord blood configuration.

Table 2: Data from NiCord® Study (GC P#01.01.020) - Patient Follow-up

Patient Number	Disease Stage/Age	Myeloid Engrafted CBU	WBC at Day 7 (/mm^3)	Engraftment Day		Acute GvHD Grade (II-IV)	Last Study Follow Up Post Transplant[a]
				ANC >500	Platelet >20,000		
1	AML (CR1)/61	NiCord® + Unmanipulated CBU	200	14	33	aGvHD-II (Day 60)	376
2	MDS (Int-2)/43	NiCord®	300	11	30	No aGvHD	372
3	MDS (Int-2)/59	NiCord®	500	10	30	No aGvHD	348
6	AML (CR2)/45	NiCord®	400	10	30	No aGvHD	393
7	HL/21	NiCord®	1100	7	26	aGvHD-II (Day 60)	355
9	AML (CR1)/45	NiCord®	100	14	41	aGvHD-II (Day 80)	196[c]
10	AML (PR)/59	NiCord®	500	18	-	No aGvHD	47[d]
11	ALL (CR1)/45	NiCord®	900	7	33	aGvHD-II (Day 60)	333
4	AML (CR2)/41	Unmanipulated CBU	100	18	36	No aGvHD	364
5	AML (CR1)/57	Unmanipulated CBU	100	26	49	aGvHD-II (Day 35)	404
8	NHL/46	Engraftment failure	900[b]	-	-	-	100

[a] Last follow-up, as of 13 December, 2013

[b] Total blood chimerism at day 7: NiCord® 95%, unmanipulated CBU 2%

[c] Patient Died at 196 days post transplant

[d] Patient Died at 47 days post transplant

Table 3: Data from NiCord® Study (GC P#01.01.020) - Chimerism of NiCord® and Unmanipulated CBU

Patient Number	Disease Stage/Age	Myeloid Engrafted CBU	Chimerism of NiCord® and Unmanipulated CBU				
			Total Blood Chimerism at Engraftment Day		Last Follow-up Chimerism		
			NiCord® (%)	Unmanipulated CBU (%)	At Day	NiCord® (%)	Unmanipulated CBU (%)
1	AML(CR1)/61	NiCord® + Unmanipulated CBU	79	21	365	TBC[a] - ND CD15 - 42 CD3 - 2	TBC - ND CD15 - 58 CD3 – 78
2	MDS (Int-2)/43	NiCord®	100	0	365	TBC - 98 CD15 - 98 CD3 - 98	TBC - 2 CD15 -2 CD3 -2
3	MDS (Int-2)/59	NiCord®	95	5	365[b]	TBC - 92 CD15 - 98 CD3 - 97	TBC - 2 CD15 - 2 CD3 – 2
6	AML (CR2)/45	NiCord®	98	1	365	TBC - 98 CD15 - 98 CD3 - 81	TBC - 2 CD15 - 2 CD3 – 2
7	HL/21	NiCord®	98	2	365	TBC - 84 CD15 - 98 CD3 - 24	TBC - 16 CD15 - 2 CD3 – 76
9	AML (CR1)/45	NiCord®	87	7	180	TBC - ND CD15 - 72 CD3 - 40	TBC - ND CD15 - 2 CD3 – 2
10	AML (PR)/59	NiCord®	100	0	42	TBC - 100 CD15 - ND CD3 - ND	TBC - 0 CD15 - ND CD3 – ND
11	ALL (CR1)/45	NiCord®	98	2	365	TBC - 98 CD15 - 98 CD3 - 98	TBC - 1 CD15 - 1 CD3 – 2
4	AML (CR2)/41	Unmanipulated CBU	2	98	365[b]	TBC - 2 CD15 - 2 CD3 - 2	TBC - 98 CD15 - 98 CD3 – 98
5	AML (CR1)/57	Unmanipulated CBU	2	98	365[b]	TBC - 2 CD15 – 2 CD3 – 2	TBC - 98 CD15 – 98 CD3 – 98

[a] Total Blood Chimerism [b] TBC is day 365, CD3/15 are day 180.

[redacted]

[redacted]

[redacted]

3.6. Overall Risk Benefit

NiCord® is an allogeneic graft for HSCT composed of CB-derived stem and progenitor cells expanded ex vivo from an entire CBU with cytokines and nicotinamide, as well as non-cultured CD133- cells. NiCord is intended for the treatment of patients who are medically indicated for allogeneic hematopoietic stem cell transplantation following preparative conditioning, including high risk hematological malignancies. Non-clinical studies have demonstrated that culturing CD133+ cells with NAM delays differentiation and increases engraftment efficacy.

UCB is an easily procured stem cell source for allogeneic HSCT, with high availability for patients of different ethnic backgrounds. However, its use is limited by the low stem cell dose, compromising robust and timely hematopoietic recovery, leading to increased morbidity and mortality post transplantation. Several technologies are attempting to improve the kinetics of engraftment following UCBT, by using dual CBT, whereby one of the CBUs undergoes ex-vivo manipulation or expansion. Such technologies may shorten the time to neutrophil engraftment, however the long-term durable hematopoietic recovery is provided by the second, unmanipulated CBU.

The first study of NiCord® (GC P#01.01.020) has demonstrated that infusion of NiCord® together with a second unmanipulated CBU was well tolerated. Engraftment of NiCord® cells in eight of eleven patients provided rapid short term neutrophil and platelet recovery as well as stable, long term multilineage hematopoiesis. No NiCord® recipients developed grade III or IV acute GvHD. Five of the eleven who received the NiCord® study product developed grade II acute GvHD. Two patients died during the study period (AML relapse and pneumonia). Neither death was considered related to NiCord®.

As in all cases of allogeneic HSCT, the overall risks of cord blood administration following a cytotoxic preparative regimen can be serious and fatal. The potential risks associated with cord blood include early death, infusion reactions, GvHD and graft failure. The deaths and other adverse events experienced by NiCord® recipients in study GC P#01.01.020 are common effects of allogeneic stem cell transplantation following myeloablative therapy.

The current study aims to evaluate the ability of NiCord® to safely and durably engraft, when given as a sole stem cell source. Thus the primary endpoints assess the safety of NiCord® infusion, NiCord®-derived neutrophil engraftment, and secondary graft failure. The secondary endpoints assess non-relapse mortality and overall survival up to one year post transplantation, as well as the time to engraftment, and the incidence of GvHD.

3.7. Rationale For Study Design & Dosages

3.7.1. Study Population

As reviewed above, the study will include adult and adolescent patients with hematological malignancies for whom myeloablative SCT is currently a recommended and potentially lifesaving treatment. [redacted] the study will [redacted] enroll

patients who do not have an adequate suitably matched and readily available stem cell donor.

3.7.2. CBU Cell Dose

The CBU intended for expansion is required to contain a pre-cryopreserved (post-processing), total CD34+ cell count of at least $8x10^6$, as well as a pre-cryopreserved (post-processing) total nucleated cell count of at least $1.8x10^9$, and a total nucleated cell dose of at least$1.8x10^7$ TNC/kg body weight, a dose predicted to be sufficient in size to provide robust and sustained engraftment, based on the current clinical experience with NiCord® (study GC P#01.01.020 - see Table 5). [redacted]

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

3.7.3. Selection of CBUs

Decisions on the selection of CBUs are never arbitrary, but rather are based on specific histocompatibility data, cell dose, availability, and in some cases the source of the CBU. However, there is no clear consensus or evidence-based algorithm as to the hierarchy of these factors. Thus, some physicians believe cell dose is of greatest importance, some examine CD34+ dose, and others prioritize HLA matching. For this reason, the protocol does not specify prioritization rules when more than one eligible CBU is identified.

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

3.7.4. Study Endpoints

In order to assess the safety of administration of NiCord® as a single expanded UCB unit, the primary endpoints were chosen to be the cumulative incidence of patients with NiCord®-derived neutrophil engraftment at 42 days following transplantation, and the incidence of secondary graft failure at 180 days following transplantation of NiCord®.

The two primary endpoints together provide the assessment of successful and sustained engraftment achieved by NiCord® transplantation.

4. STUDY OBJECTIVES, HYPOTHESIS & STUDY ENDPOINTS

4.1. Objectives

Primary Objectives

- Assess the cumulative incidence of patients with NiCord®-derived neutrophil engraftment at 42 days following transplantation.
- Assess the incidence of secondary graft failure at 180 days following transplantation of NiCord®

Secondary Objectives

- Time from infusion to neutrophil engraftment
- Time from infusion to platelet engraftment
- Incidence of platelet engraftment at 100 days
- Proportion of non-relapse mortality at 100 days
- Incidence of acute GvHD grade II-IV and III-IV at 100 days
- Incidence of chronic GvHD (limited or extensive) at 180 days and 1 year
- Incidence of secondary graft failure at 1 year following transplantation of NiCord®
- Overall survival at 180 days and 1 year
- Safety and tolerability of NiCord® transplantation

Exploratory Objectives

- Immune reconstitution at 70, 100, 180, and 365 days

Study Hypothesis

Transplantation of NiCord® following myeloablative conditioning in patients with hematological malignancies will provide sustained engraftment.

4.2. Definition Of Study Endpoints

4.2.1. Neutrophil Engraftment

Neutrophil engraftment is defined as achieving an absolute neutrophil count (ANC) greater than or equal to 0.5 x 10^9/L on 3 consecutive measurements on different days with donor chimerism (≤ 10% host cells by peripheral blood chimerism using RFLP or microsatellite) by day 42 inclusive. The first day of the three measurements will be designated the day of neutrophil engraftment.

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

- Backup CBU transplantation within 5 days of NiCord® transplantation due to NiCord® bioassays outside of the specification limits will not be sufficient evidence of 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 neutrophil engraftment, followed by severe neutropenia (<0.5 x 10^9/L for three or more consecutive laboratory values on separate days) with marrow cellularity <5%, without subsequent improvement occurring either spontaneously or after growth factor treatment. Infusion of an additional stem cell product after documented neutrophil engraftment will be considered secondary graft failure.

4.2.2. Platelet Engraftment

Platelet engraftment is defined as the first day of a minimum of 3 consecutive measurements on different days such that the patient has achieved a platelet count >20x10^9/L and >50x10^9/L with no platelet transfusions in the preceding 7 days (count day of engraftment as one of the preceding 7 days). The first day of the three measurements will be designated the day of platelet engraftment.

4.2.3. Non-Relapse Mortality

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

4.2.4. 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 year 1 and classified as limited or extensive according to Appendix A.

4.2.5. Immune Reconstitution

Immune reconstitution will be assessed on days 70, 100, 180, 365. 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 on days 100, 180 and 365.

4.2.6. Safety and Tolerability of NiCord® Transplantation

The safety and tolerability of NiCord® transplantation will be evaluated by the nature, incidence and frequency of adverse experiences and an estimation of the relationship to NiCord®, as well as infections and laboratory data follow-up, with special emphasis on safety of cell therapy, including the detection of infusion reactions, transmission of infections, new malignancies and autoimmune diseases.

4.2.7. Other Definitions

4.2.7.1. Response Criteria for Acute Leukemia

- Bone Marrow Myeloblasts < 5% by morphologic assessment;
- No circulating leukemic myeloblasts;
- Neutrophil count ≥ 1,000/μL;
- Absence of previous cytogenetic or molecular abnormality identified prior to transplantation in the bone marrow aspirate.

4.2.7.2. Response Criteria for CML

- Bone Marrow Myeloblasts < 5% by morphologic assessment;
- No circulating leukemic myeloblasts;

4.2.7.3. Response Criteria for Lymphoma

Response criteria for lymphoma are described in Table 6 below

Table 4: Response Definitions for Lymphoma

Table 2. Response Definitions for Clinical Trials				
Response	**Definition**	**Nodal Masses**	**Spleen, Liver**	**Bone Marrow**
CR	**Disappearance of all evidence of disease**	**(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative** **(b) Variably FDG-avid or PET negative; regression to normal size on CT**	**Not palpable, nodules disappeared**	**Infiltrate cleared on repeat biopsy: If indeterminate by morphology, immunohistochemistry should be negative**
PR	**Regression of measurable disease and no new sites**	**≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes** **(a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site** **(b) Variably FDG-avid or PET negative; regression on CT**	**≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen**	**Irrelevant if positive prior to therapy; cell type should be specified**
SD	**Failure to attain CR/PR or PD**	**(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET** **(b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT**		
Relapse disease or PD	**Any new lesion or increase by ≥50% of previously involved sites from nadir**	**Appearance of a new lesion(s) > 1.5 cm in any axis, ≥50% increase in SPD of more than one node or ≥50% increase in longest diameter of a previously identified node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy**	**>50% increase from nadir in the SPD of any previous lesions**	**New or recurrent involvement**
Abbreviations: CR, complete remission; FDG [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.				

From Cheson, B.D. et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 5:579-586, 2007.

4.2.7.4 Relapse and Residual Disease

Relapse of malignancy - testing for recurrent malignancy in the blood, marrow or other sites will be used to assess relapse after transplantation. For the purpose of this study, relapse is defined by either morphological or cytogenetic evidence of AML, ALL, CML, MDS consistent with pre-transplant features or radiologic evidence (including the recurrence of fluoro-deoxyglucose [FDG]-avid lesions on PET scan) of progressive lymphoma. When in doubt, the diagnosis of recurrent or progressive lymphoma should be documented by tissue biopsy.

Minimal residual disease - minimal residual disease is defined by the sole evidence of malignant cells by flow cytometry, or fluorescent in situ hybridization (FISH), or Southern blot or Western blot, or polymerase chain reaction (PCR), or other techniques, in the absence of morphological or cytogenetic evidence of disease in blood or marrow. Since the frequency of testing for minimal residual disease is highly variable among centers, and the sensitivity is highly variable among laboratory techniques, evidence of minimal residual disease alone will not be sufficient to meet the definition of relapse in the context of this trial. However, minimal residual disease that progresses will be considered as relapse and the date of relapse will be the date of detection of minimal residual disease that prompted an intervention by the treating physician.

Acute Leukemia - Relapse will be defined as any of the following:

- > 5% blasts in the marrow, not attributed to other causes (e.g., bone marrow regeneration)
- The appearance of new dysplastic changes within the bone marrow.
- Reappearance of leukemic blasts in the peripheral blood.
- Reappearance of previous cytogenetic or molecular marker of disease present prior to transplantation.
- The development of extramedullary leukemia or leukemic cells in the cerebral spinal fluid.
- Institution of any therapy to treat relapsed disease, including withdrawal of immunosuppressive therapy or DLI, will be considered evidence of relapse regardless of whether the criteria described above are met.

Chronic Myelogenous Leukemia (CML) –

Hematologic relapse will be diagnosed when:

1. Immature hematopoietic cells are persistently documented in the peripheral blood; or,
2. There is myeloid hyperplasia in the bone marrow in the presence of cytogenetic relapse.

Cytogenetic relapse will be diagnosed when:

1. 50% of the metaphases exhibit the characteristic 9;22 translocation with at least ten metaphases analyzed; or,
2. At least one metaphase exhibits the 9;22 translocation on each of two separate consecutive examinations at least one month apart, regardless of number of metaphases analyzed.

MDS - Relapse will be defined as any of the following:

- Satisfying above criteria for evolution into acute leukemia; or,
- Reappearance of pre-transplant morphologic abnormalities, detected in two consecutive bone marrow specimens taken at least one month apart; or,
- Reappearance of pre-transplant cytogenetic abnormality in at least one metaphase on each of two separate consecutive examinations at least one month apart, regardless of the number of metaphases analyzed.
- Institution of any therapy to treat relapsed disease, including withdrawal of immunosuppressive therapy or DLI, will be considered evidence of relapse regardless of whether the criteria described above are met.

Lymphoma - Relapse will be diagnosed when one or more of the following criteria apply:

- Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

- At least a 50% increase from nadir in the sum of the product diameters (SPD) of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥ 50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.

  Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (<.1.5 cm in its long axis by CT).

- Institution of any therapy to treat persistent, progressive or relapsed disease, including withdrawal of immunosuppressive therapy or DLI, will be considered evidence of relapse/progression regardless of whether the criteria described above are met.

4.2.7.5 CML Stages

Chronic phase is defined as:

- Stable, not hematologic remission: blasts present in marrow and/or peripheral blood, but disease does not qualify as accelerated or blast phase
- Hematological remission: no blast cells or precursor cells in the blood or marrow
- Partial cytogenetic remission: Ph+ metaphases >0% but < 35%
- Complete cytogenetic remission: absence of Ph+ metaphases

Accelerated phase is defined as:

- WBC difficult to control (> 50 x 10^9/L despite therapy)
- Rapid doubling of WBC (< 5 days)
- Anemia or thrombocytopenia unresponsive to standard treatment
- Persistent thrombocytosis (> 1000 x 10^9/L)
- Cytogenetic abnormalities in addition to Ph+
- Increasing splenomegaly
- Marrow fibrosis

Blasts Crisis is defined as:

- > 5% blasts in the marrow, not attributed to other causes (e.g., bone marrow regeneration)

5. STUDY POPULATION

5.1. Number Of Patients

The sample size is 40 evaluable patients, up to a maximum of 50 treated patients, who received NiCord® and who, in addition, met all of the following criteria:

- Did not receive any stem cells up to day 28 except for NiCord®
- Did not die prior to day 21
- Received myeloablative 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 can 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.

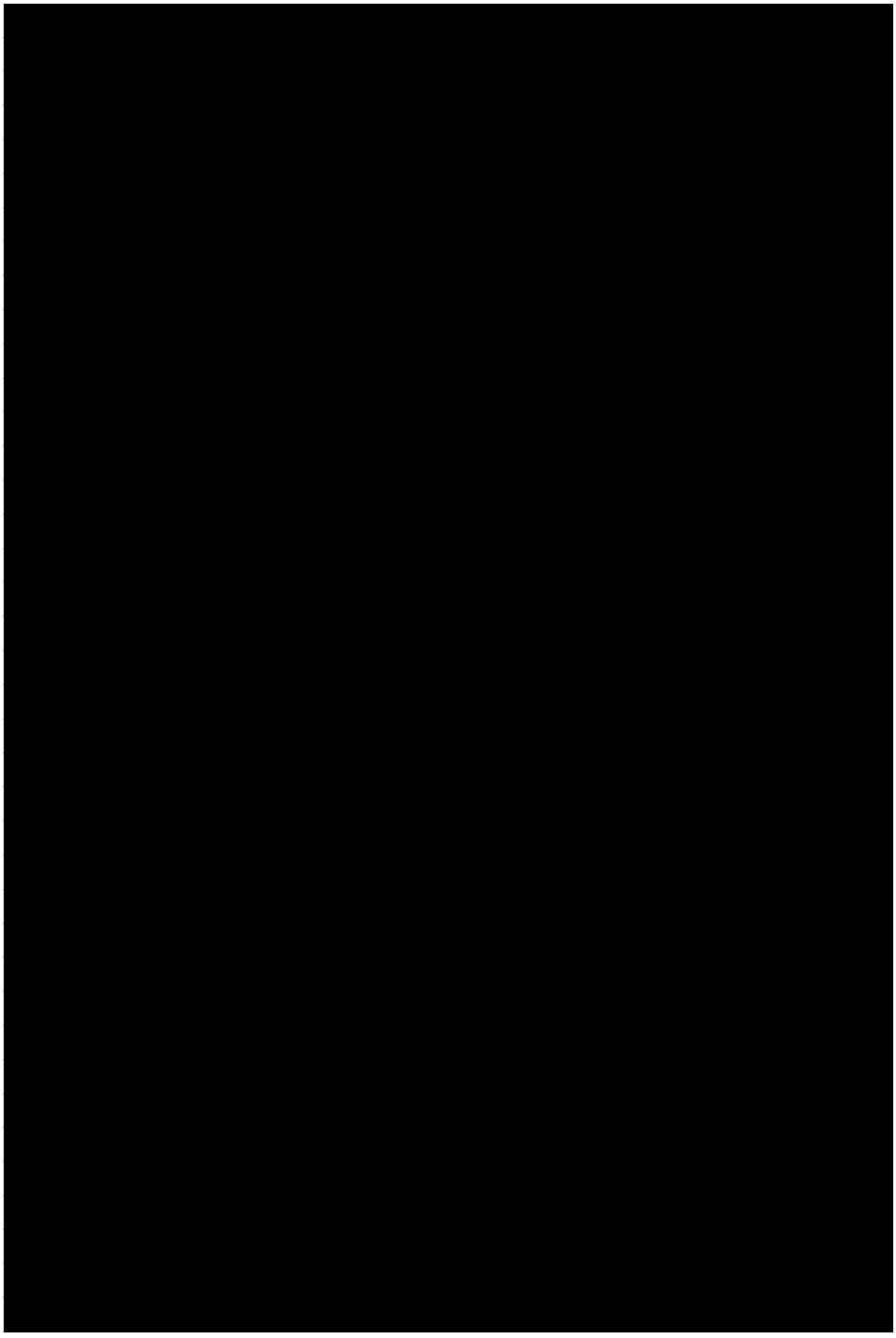
Patients will be defined as screening failures when withdrawn from the study before receiving NiCord® or as early termination/discontinuation, if dropout occurs after transplantation of the NiCord®. Screening failures can be replaced.

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 365 days following transplantation and to capture this information in the CRF.

5.2. Eligibility Criteria

5.3. Inclusion Criteria

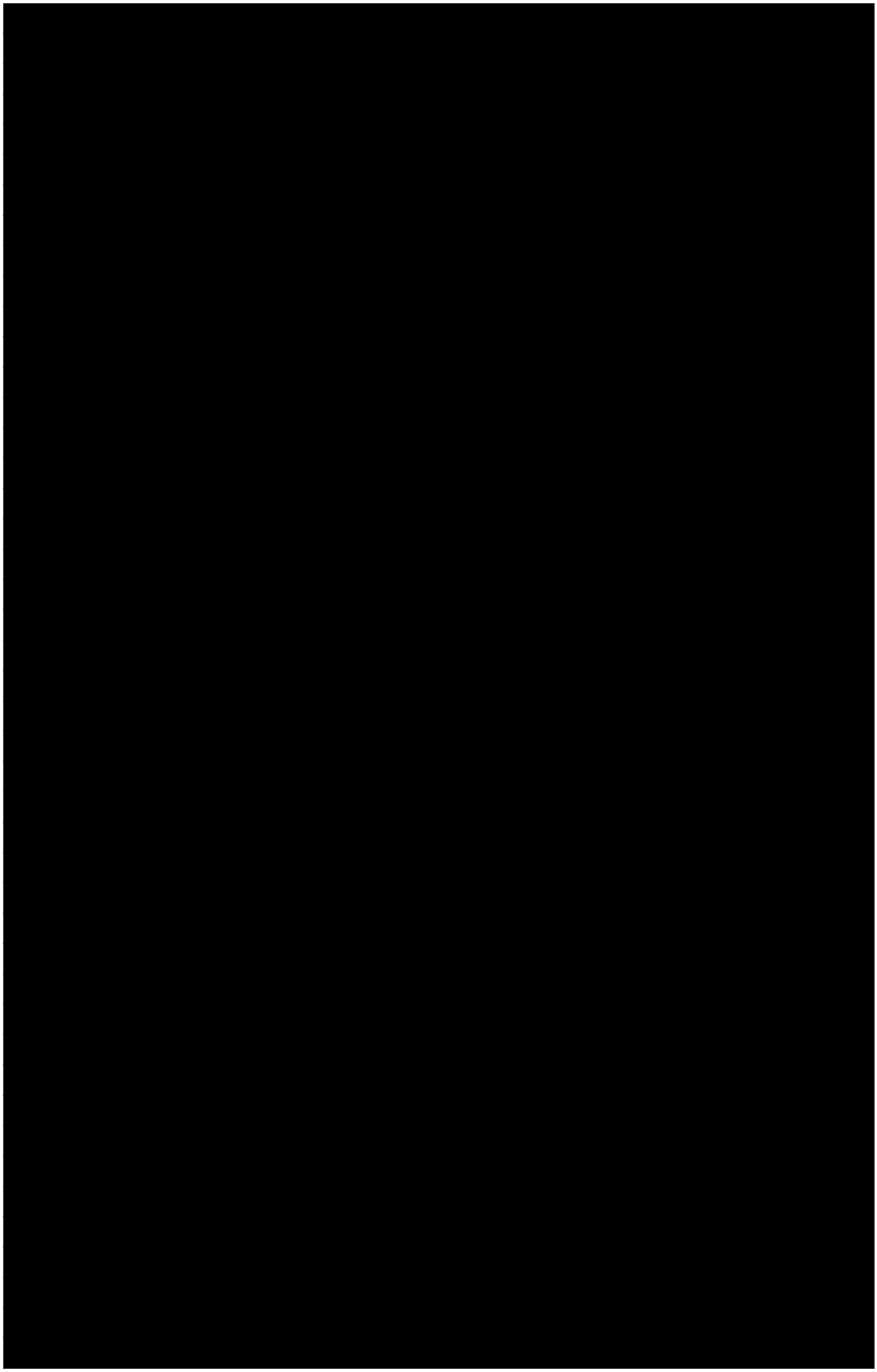
1. Patients must be 12-65 years of age
2. Patients with one of the following hematologic malignancies:



[redacted]

Exclusion Criteria

1. [redacted]



Graft Selection

- If more than one unit meets the minimum cell dose and HLA match requirements, the best available unit per investigator discretion should be selected for expansion.
- CBUs should be procured from public banks that meet local applicable regulations. If the chosen unit for the patient is determined ineligible or with unusual findings as per regulation, the unit may be used under the urgent medical need provision
- The unit selected for expansion should be typed twice (i.e. initial typing and confirmatory typing). Confirmatory typing should be in a laboratory that is ASHI/EFI accredited and must come from an attached segment

Backup Grafts

- In case NiCord® fails to meet the required specifications, the backup CBU will be transplanted as detailed in section 8.3. The clinical site will notify the CBB and the backup CBU will be shipped and transplanted.

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.

All chemotherapy and radiotherapy courses administered to the patient, as prior treatment for his/her hematological malignancy, will be recorded in the CRF (including treatment regimen, number of cycles, and dates). Sites should obtain this information from the referring physician for source verification.

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)
- The use of Bactrim is discouraged on or after day -2 until the time of engraftment as it may delay engraftment, and is reserved only for cases where it is assessed to be essential and superior to all alternative medications
- Investigational agents, unless previously approved by the sponsor

6.3 Conditioning Regimen

All patients will receive one of the conditioning regimens shown in Table 7 below. Each transplant center must commit to use the same conditioning regimen for all patients transplanted at their center. In unique cases where the use of a different conditioning regimen is deemed to be in the patient's best interest, approval from the study chairs must be obtained prior to use of the different regimen.

Table 7: Conditioning Regimens

Regimen A:

Treatment \ Study Day	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0
TBI 1350 cGy in 8 or 9 fractions			x2 or x1 or x0	x2	x2	x2	x0 or x1 or x2				REST	Infusion of NiCord®
Fludarabine# 40 mg/m^2 IV							x	x	x	x		
Cyclophosphamide 60mg/Kg# IV (optional*)									x	x		
Thiotepa 5mg/kg IV (optional*)	x	x										

#Adjusted ideal body weight for adult patients

*Either Cyclophosphamide or Thiotepa (not both) may be added to the TBI/Flu preparative regimen at the discretion of the managing physician, with consideration given to nature of the underlying malignancy (cytogenetics and/or minimal residual disease), patient risk status (extent of prior therapies and/or comorbidities), and, increased risk of graft failure in chemotherapy naïve patients. Cyclophosphamide or Thiotepa addition is recommended for patients with CML.

Regimen B:

Treatment \ Study Day	-7	-6	-5	-4	-3	-2	-1	0
Thiotepa# 5mg/kg IV	x	x				REST	REST	Infusion of NiCord®
Busulfan# 3.2 mg/kg IV			x	x	x			
Fludarabine# 50 mg/m^2 IV over 1 hour			x	x	x			

#Adjusted ideal body weight for adult patients

Regimen C*:

Treatment \ Study Day	-5	-4	-3	-2	-1	0
Clofarabine 30mg/m^2	x	x	x	x	REST	Infusion of NiCord®
Fludarabine 10mg/m^2	x	x	x	x		

Busulfan: weight based dosing[#$]	x	x	x	x		

*Clofarabine infused for 1 hour followed by Fludarabine infused for 1 hour, followed by Busulfan infused for 3 hours.

[#]Dosing according to Bartelink et al,[50]

[$]Cumulative target AUC (Area Under the Curve) = 90mg*h/L. Bu levels after 1st dose will be measured at 5min, 1h, 2h and 4h after end of Bu infusion

6.3.1 Radiotherapy (Regimen A)

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

Total dose will be 1350 cGy in 8 or 9 fractions over 4 or 5 days. Two fractions on the same day will be given at a minimum of 6 hours apart from beam on to beam on.

Risks and Toxicities:

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

6.3.2 Fludarabine Administration (Regimens A, B, and C)

Regimen A: Fludarabine 40 mg/m2/day will be administered as a 60 minute IV infusion on days -5 through -2.

Regimen B: Fludarabine 50 mg/m2/day will be administered as a 60 minute IV infusion on days -5 through -3.

Regimen C: Fludarabine 10 mg/m^2/day will be administered as a 60 minute IV infusion on days -5 through -2. Fludarabine will be given after 1h infusion of Clofarabine.

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 Cyclophosphamide (CY) Administration (Regimen A)

Cyclophosphamide will be added to the preparative regimen at the discretion of the managing physician. Reasons for the addition of cyclophosphamide include high-risk features of underlying malignancy (cytogenetics and/or minimal residual disease), patient risk status (extent of prior therapies and/or comorbidities), and increased risk of graft failure in chemotherapy naïve patients. Cyclophosphamide addition is recommended for patients with CML.

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

Cyclophosphamide 60 mg/Kg/day as per adjusted ideal body weight will be administered as per institutional practice.

Doses and schedule for uroprotective agents (i.e. Mesna) should follow local institutional guidelines. For patients weighing more than 125% of their IBW, cyclophosphamide will be dosed based on the adjusted ideal body weight (AIBW).

The following are dose adjustment formulas:

- **Ideal Body Weight (IBW) formulas:**
  - Males IBW = 50 kg+2.3 kg/inch over 5 feet (or 50 kg + 0.91kg/cm over 152.4cm)
  - Females IBW = 45.5 kg+2.3 kg/inch over 5 feet (or 45.5 kg + 0.91kg/cm over 152.4cm)
- **Adjusted Ideal Body Weight (AIBW) formula:**
  - AIBW = IBW+[(0.25)x(ABW-IBW)]

6.3.4 Thiotepa Administration (Regimen A and B)

Regimen A: Thiotepa 5 mg/kg/day will be administered as a 4 hour IV infusion on days -11 and -10. Thiotepa will be dosed as per adjusted ideal body weight (as described in section 6.3.3 for cyclophosphamide).

Regimen B: Thiotepa 5 mg/kg/day will be administered as a 4 hour IV infusion on days -7 and -6. Thiotepa will be dosed as per adjusted ideal body weight (as described in section 6.3.3 for cyclophosphamide).

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

6.3.5 Busulfan Administration (Regimen B and C)

Regimen B: Busulfan 3.2 mg/kg/day will be administered as a 3 hour IV infusion (or in four separate 2 hour IV infusions every six hours) on days -5 through -3. Busulfan will be dosed as per adjusted ideal body weight (as described in section 6.3.3 for cyclophosphamide). Refer to Appendix E, 'Drug Labels', for risks and toxicities of Busulfan administration.

Regimen C: Busulfan (weight-based dosing according to Bartelink et al [50]) will be administered over 3 hours IV infusion (or in four separate 2 hour IV infusions every six hours) on days -5 through -3 (after clofarabine and fludarabine). Busulfan dose will be adjusted (if necessary) on the second day to achieve a cumulative Busulfan exposure (AUC) after 4 days of 90 mg*h/L ($\pm$5 mg*h/L).

6.3.6 Clofarabine Administration (Regimen C)

Clofarabine 30mg/m^2 will be administered as a 1 hour IV infusion on days -5 through -2. For patients receiving Regimen C, Clofarabine will be infused first, followed by

Fludarabine, in turn followed by Busulfan. Refer to Appendix E, 'Drug Labels', for risks and toxicities of Clofarabine administration.

6.4 GvHD Prophylaxis Medications

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

Calcineurin inhibitor (Tacrolimus or Cyclosporine)

Each transplant center must commit to use the same calcineurin inhibitor (Tacrolimus or Cyclosporine) for all patients transplanted at their center. In unique cases where the use of a different calcineurin inhibitor is deemed to be in the patient's best interest, approval from the study chairs must be obtained prior to use of the different calcineurin inhibitor.

Tacrolimus or Cyclosporine from day -3 through day +150 Target tacrolimus trough blood levels of 5-15 ng/ml. If administering via continuous IV infusion, 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 target cyclosporine trough levels of 150-300 ng/mL by TDX method (or equivalent level for other CSA testing methods). In the event of toxicity, dosing may be adjusted per institutional standard practice. Calcineurin inhibitor taper may begin at day +150 at the discretion of the managing physician, with the goal for discontinuation at day 180-200. Refer to Appendix E, 'Drug Labels', for risks and toxicities of tacrolimus administration.

Mycophenolate Mofetil (MMF)

Mycophenolate Mofetil (MMF) 1 g TID IV or PO (15 mg/kg IV TID if patient weighs <50 kg) beginning day -3 to at least day +60. In the event of toxicity, dosing may be adjusted per institutional standard practice. Refer to Appendix E, 'Drug Labels', for risks and toxicities of mycophenolate mofetil administration.

6.5 Acute & Chronic GvHD Treatment

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

6.6 Venous Access

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

6.7 Infusion Support

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

- Diphenhydramine 50 mg IVP (or 0.5 mg/kg up to a maximum of 50 mg)
- Hydrocortisone 50 mg IVP (or 0.5 mg/kg up to a maximum of 50 mg)

- Acetaminophen 650 mg PO (or 10 mg/kg up to a maximum of 650 mg)

Methylprednisolone should not be used in conjunction with standard delivery of NiCord to the patient. Management of infusion reactions during and post transplant is at the discretion of the managing physician.

6.8 Supportive Cytokine Therapy

G-CSF (e.g. Filgrastim, Neupogen, Granix) therapy will be started on day +1 at a dose of 5 µg/kg/day (rounded to nearest vial size) given IV or SC and continuing at least until the ANC is >1,000/µl x 2 consecutive days as per site practice.

6.9 Blood Products

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

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

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

6.10 Engraftment Syndrome

Engraftment syndrome is a clinical diagnosis. The most frequently reported manifestations are transient fever, rash, and respiratory symptoms not attributable to infection or GVHD. The pathophysiology is poorly understood, but is thought to be multifactorial mediated by cellular, complement and cytokine components.

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

6.11 Infection Prophylaxis and Surveillance

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

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

6.11.1 Anti-viral Prophylaxis

Acyclovir 400 mg (or 250mg/m^2) PO BID is recommended for anti-viral prophylaxis with conditioning through the duration of neutropenia and then at 800 mg PO BID (or 60–90 mg/kg/day PO divided in 2–3 doses for patients <40kg, up to a maximum of 800mg BID) until 1 year 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.

6.11.2 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.

6.11.3 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.

6.11.4 Fungal Prophylaxis

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

6.11.5 CMV Surveillance

All recipients must be tested weekly for CMV using the PCR method after the start of the conditioning regimen until Day 42±3 and then at day 70±5 and day 100±7 or more frequently as clinically indicated. Antiviral therapy for CMV reactivation should commence preemptively if CMV testing reveals a high or rising viral load. If CMV reactivation occurs at or before engraftment, foscarnet is recommended to prevent marrow suppression.

6.11.6 HHV6 Surveillance

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

6.11.7 EBV Surveillance

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

6.11.8 Adenovirus Intervention Guideline

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

6.11.9 Intravenous Immune Globulin

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

6.11.10 Identification of Infectious Agents - Recommendations

6.11.10.1 Blood Cultures

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

6.11.10.2 Blood Culture Procedure

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

6.11.10.3 Additional Identification Procedures

The following procedures are recommended in patients with suspected infection:

- Chest X-ray
- Sinus CT in patients with suspected sinusitis
- Diarrhea: Clostridium difficile toxin PCR to be determined once in patients with clinical suspicion. Viral diagnostics (rotavirus, adenovirus, norovirus, astrovirus) in patients with clinical suspicion of infectious cause.
- Urine culture in patients with suspected infection of indwelling catheter
- CSF culture in patients with suspected meningitis

- Skin lesions: biopsy or aspirate, for culture, Gram stain, GMS and cytology.
- Pulmonary source of infection: sputum culture in patients with productive cough. Consider viral diagnostics using viral throat swab, especially in season: Influenza A and B, RSV, Coronavirus, Rhinovirus, Bocavirus, Para-influenza, Human metapneumovirus and mycoplasm. BAL in patients with chest HRCT abnormalities.

6.11.11 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, they will be treated per institutional practice and will be recorded in the source documents and in the e-CRF. As standard treatment practices differ between institutions, will evolve over time, and vary by patient circumstances, we do not prescribe a specific approach to treatment. Rather, it is the responsibility of the treating physician to manage infections according to their institutional best practices.

6.11.12 Discharge Instructions and Follow-up

Patients and their treating physicians should be provided clear instructions at discharge that emphasize the importance of continued follow-up as per study protocol, including early reporting of infectious symptoms, medical treatments received and any other medical events to their clinical center. The transplant center should attempt weekly contact with patients through day 70 to ask about infectious symptoms and any other medical events or treatments. Transplant centers will continue with monthly contact from day 70 to the completion of follow-up.

6.12 Nutrition

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

6.13 Guidelines for Infusing a Second Stem Cell Product

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

6.14 Investigational Agents

Unless approved by the Sponsor, investigational agents should be withheld.

6.15 Other Medications

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

All concomitant medications and blood products administered, from time of signature on the IC 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. All concomitant medications from time of transplant through ANC engraftment (or 42 days post transplant for non-engrafters) will be reported on the e-CRF.

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 8: Evaluations & Examinations Flow Sheet

	NiCord® Study for Single Fresh - Schedule of Assessments Summary														
	Baseline		Days Post-transplant												
	Phase 1: Screening Phase[4]	Phase 2: Conditioning Phase[1]	Phase 3: Transplantation and FU Phase												
Days	-43 to -12/-10/ -8/-6	-11/-9/ -7/-5 to -1	0	1	2-6	7	14±3	21±3	28±3	35±3	42±3	70 ±3	100 ±14	180 ±21	365 ±21
Identify UCB matching unit for expansion and backup CBU/s [2]	X														
Written Informed Consent[3]	X														
Eligibility Criteria[4]	X														
Confirm Eligibility within one week prior to conditioning	X														
CBU sent to the production site to arrive no later than two days before the start of manufacturing	X														
Medical History	X														
Infectious disease markers [5]	X														
Anti-HLA antibodies	X														
Cardiac: EKG, Echocardiography or MUGA scan for LVEF [6]	X														
Chest X-ray [6]	X														
Pulmonary Function Tests with DLCO, FEV1, FVC[6]	X														
Confirmatory HLA typing[7]	X														
CT scan chest, abdomen, pelvis (HD/NHL) [8]	X												X		X
BM aspiration/biopsy[8] (when clinically indicated) morphology In Leukemia/MDS: FACS; Cytogenetics; Molecular markers	X												X		X

Days	-43 to -12/-10/ -8/-6	-11/-9/ -7/-5 to -1	0	1	2-6	7	14±3	21±3	28±3	35±3	42±3	70± 3	100 ±14	180 ±21	365 ±21
Vital Signs[9]	X[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory [11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Historical and Concomitant medications[13]	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
Physical Examination	X	X							X			X	X	X	X
Complete urinalysis	X[12]														
Immunophenotyping Lymphocyte subsets[14]						X	X	X			X	X	X	X	X
MultiPlex Immuno Assays analyses[14]			X	X		X	X	X			X				
Immunoglobulins (IgG, IgA, IgM)	X											X	X	X	X
T-cell Receptor Excision Circles (TREC) and T cell receptor (TCR) beta within CD4+ & CD8+[14]	X												X	X	X
Peripheral blood baseline sample for Chimerism[15]	X														
Peripheral blood chimerism[16]						X	X	X	X		X	X	X	X	X
Conditioning regimen as per protocol		X													
NiCord® CF, NF, and infusion solutions shipped to transplant center prior to transplant		X													
NiCord® CF thawing and infusion			X												
NiCord® NF thawing and infusion			X												
Toxicity assessment 24 hours post infusion[17]			X	X											

[1] Start of conditioning varies by conditioning regimen chosen: Day -11/-9 for Regimen A, Day -7 for Regimen B, Day -5 for Regimen C

Days	-43 to -12/-10/ -8/-6	-11/-9/ -7/-5 to -1	0	1	2-6	7	14±3	21±3	28±3	35±3	42±3	70±3	100 ±14	180 ±21	365 ±21
Assess Acute GvHD [18]						X	X	X	X	X	X	X	X	X	X
Assess Chronic GvHD													X	X	X
CMV PCR		X				X	X	X	X	X	X	X	X		
EBV PCR		X						X				X	X		
HHV6 PCR weekly until ANC>500		X				X	X	X	X	X	X				
Infections			Infections collected post transplant until end of study												
Adverse events		From initiation of conditioning regimen until end of study													

[2] Before signing informed consent and according to CBUs matching criteria as detailed in Section 5.2 of the protocol.

[3] Signed consent is required prior to performing any protocol specific tests or procedures that are not part of the standard site practice.

[4] All eligibility criteria must be met prior to ordering the CBU for expansion. Unless otherwise indicated, screening and eligibility testing must be performed within three weeks prior to shipment of the CBU for expansion to the production facility.

[5] Infectious disease markers must include: CMV, Hepatitis panel (HepB sAg, HepB Core Ab, HepC Ab), herpes simplex virus, syphilis, HIV and HTLV I/II antibody, and varicella zoster.

[6] Tests from within 6 weeks of screening are acceptable.

[7] HLA -A,-B, -C, -DRB1 must be typed at high resolution and patient must also have ABO and Rh typing performed.

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

[9] Weight, temperature, blood pressure, pulse, respiratory rate as per site practice.

[10] Including height, weight and BSA.

[11] CBC performed daily from Day 0 until neutrophil engraftment. Differentials required if WBC >=0.2. Daily CBC and ANC counts must be uploaded to the eCRF on a weekly basis through neutrophil engraftment or day 42 post transplant for non-engrafters. Blood chemistries include (at a minimum): serum creatinine, total bilirubin, alkaline phosphatase, AST, ALT, and magnesium (at screening, day -1, day 0 and then at least twice weekly until Day 28, and weekly after Day 28 until 10 weeks post-transplant, 100 days, 6 months and 1 year post-transplant).

[12] As per site practice.

[13] Including total number of RBC and platelet units transfused until platelet recovery >50k

[14] Samples batch-shipped to University Medical Center Utrecht for analysis. At screening and on days 70, 100, 180, and 365 site will perform a basic T-cell subset analysis (CD3, CD4, CD8, CD19, CD56/16) locally in addition to collecting samples for batch shipment to University Medical Center Utrecht.

[15] Patient sample will be obtained prior to the initiation of the conditioning regimen; CBU sample will be shipped to the transplant center along with the NiCord product

[16] Measured by molecular methods, in whole blood and fractionated for lymphoid and myeloid components. Bone marrow chimerism is an acceptable alternative.

[17] (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)

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

7. DETAILED STUDY PLAN

7.1. Pre-Screening Activities: Search For Matching CBUs

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

[redacted]

[redacted]

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.

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

If more than one unit meets the minimum cell dose and HLA match requirements, all CBU documents for expansion eligible units should be sent to the Sponsor's study logistics manager (SLM) for eligibility review. At the request of the investigator, the SLM will send the CBU documents to the study chairs for a recommendation on the best available unit. Ultimately, the investigator chooses the best available units for expansion and backup from among all eligible units.

The unit selected for expansion must be typed twice (i.e. initial typing and confirmatory typing). Confirmatory typing should be in a lab that is ASHI/EFI accredited and must come from an attached segment.

7.2. Screening Assessments: (Three weeks prior to CBU shipment to the production facility) Acceptable CBUs (meeting CBU acceptance criteria as defined above) must be identified and available prior to patient's screening.

7.2.1. Informed Consent and Registration

A conference will be held with the patient and family to discuss this study and alternative treatments available for the treatment of the underlying disease. The conference will be conducted by the principal investigator or other designated physician.

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 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.

Patients will be registered [redacted]

7.2.2. Eligibility and Baseline Assessments

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

Patient's eligibility for the study will be assessed. The activities will be performed as detailed in Table 9 and will include:

- Baseline evaluation:
  - Medical history including primary and concomitant diseases. Concomitant medications will be recorded in the patient's medical record.
  - Patients' performance score by Karnofsky/Lansky scale
  - Physical examination and vital signs (including height, weight and BSA)
  - Laboratory: CBC with WBC differential, blood chemistry (serum creatinine, total bilirubin, alkaline phosphatase, AST, ALT, and magnesium *at a minimum*), serum beta HCG (females) (tests from the last week prior to screening are

acceptable); urinalysis including microscopic examinationAnti-HLA antibody testing
- Immunoglobulin levels (IgG, IgA, IgM)
- Lymphocyte subsets: CD3, CD4, CD8, CD19, CD16/56 and additional immunophenotyping as per site practice
- Collect blood samples for T-cell Receptor Excision Circles (TREC) and T cell receptor (TCR) beta within CD4+ & CD8+ for batch shipment to University Medical Center Utrecht
- Chest X-ray (tests from within 6 weeks prior to screening are acceptable).
- Bone Marrow morphology (aspiration/biopsy, when clinically indicated). To minimize findings of relapse during CBU expansion, bone marrow must be assessed within:
  - six weeks prior to CBU shipment to the production site for MDS patients who have never shown >20% blasts (leukemic transformation) in prior bone marrow biopsies and have <5% blasts in the most recent assessment, CML patients who have never experienced blast crisis, Lymphoma patients.
  - three weeks prior to CBU shipment to the production site for all other patients
  - For Leukemia or MDS: peripheral blood and BM morphology (aspiration/biopsy), FACS assay, cytogenetics and molecular markers
  - For NHL and HD: CT abdomen, pelvis & chest (tests from within 6 weeks prior to screening are acceptable)
- Serologic infectious disease markers for HIV 1/2 Ab, HTLV I/II Ab, HBsAg, HBcAb, HCV Ab, HSV Ab, VZV Ab, Syphilis (RPR), and CMV Screen (IgG or Total)
- Physiologic reserves assessment:
  - Pulmonary Function Tests including Carbon Monoxide Diffusing Capacity (DLCO), FEV1, FVC, and oxygen saturation (tests from within 6 weeks prior to screening are acceptable).
  - 12 lead ECG (tests from within 6 weeks prior to screening are acceptable)
  - Echocardiography or MUGA with left ventricular ejection fraction (LVEF) (tests from within 6 weeks prior to screening are acceptable).

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

- If more than one unit meets the eligibility criteria, all CBU documents for expansion eligible units should be sent to the Sponsor's study logistics manager (SLM) for eligibility review. At the request of the investigator, the SLM will send the CBU documents to the study chairs for a recommendation on the best available unit.
- Peripheral blood baseline sample for chimerism laboratory

All above mentioned activities must be completed prior to sending the CBU to the production site for expansion.

7.3. CBU Shipment & Receipt at the Production Site and Clinical Site

Once the Investigator has confirmed that the patient meets [redacted] Patients will retain the same study ID that was assigned during screening. The Sponsor's study logistics manager (SLM) and the CBBs or NMDP will be notified of the planned timeline for transplantation. Following confirmation of shipment timelines by the production site, the CBB will send the selected CBU for NiCord® expansion to the production site, to arrive no later than two days before the start of production. Qualified personnel at the production site will ensure that this is the requested CBU to be manipulated for the patient according to communication with the SLM and based on the CBU accompanying documentation [redacted]

7.4. Transplant Suitability Confirmation: (Prior to the start of conditioning)

Confirm that the patient is still suitable for transplant according to standard site practice. The site investigator, or designee, must sign a statement within 24 hours prior to the start of conditioning indicating that the patient remains suitable for transplant. Patients no longer suitable for transplant will be treated according to investigator's discretion and will be considered screen failures for this protocol.

Additional viral screening is suggested prior to administration of the conditioning regimen to confirm absence of infection. At the investigator's discretion, patients with fever or suspected minor infection should await resolution of symptoms before starting the conditioning regimen. If, as a result of delays in the transplant schedule, tests and evaluations are no longer within the acceptable timeframe for transplant suitability, these tests must be repeated prior to the start of conditioning.

7.5. Myeloablative Conditioning Day (-11/-9/-7/-5) to (-1)

The preparative & conditioning regimen will be administered as detailed in section 6.3. GvHD prophylaxis will be administered as detailed in Section 6.4. Patient monitoring during the conditioning phase (including physical examination, vital signs, CBC and blood chemistry) will be evaluated.

7.6. Transplantation Day (Day 0)

Safety Assessment

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

- Physical Examination including weight
- CBC, blood chemistry (serum creatinine, total bilirubin, alkaline phosphatase, AST, ALT and magnesium, at a minimum)
- Vital Signs: temperature, blood pressure, pulse, and respiratory rate

7.6.1. Preparation and Infusion of NiCord®

7.6.1.1. [redacted]

[redacted]

7.6.1.2. [redacted]

[redacted]

7.6.1.3. [redacted]

[redacted]

[redacted]

Evaluation and Treatment of IPQC/FPQC Safety Tests Failure

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

- Final results of day 14 sterility test performed on the CF
- [redacted]

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

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

Safety assessment including:

- Vital Signs
- Assessment of acute toxicity 24 hours post transplant
- AEs Reporting
- Filgrastim will be administered beginning on day +1
- Blood samples for MultiPlex Immuno Assays collected for batch-shipment to University Medical Center Utrecht (day 0)

7.7 Scheduled Treatment Visits (As Detailed In Table 8)

7.7.1. Scheduled Visits on Day 1, 2, 3, 4, 5, 6

The following assessments are mandatory:

- AEs and concomitant medications (including RBC and platelet transfusions) will be recorded
- Vital Signs
- 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)

- GvHD prophylaxis as specified in Section 6.4
- Infection prophylaxis as specified in Section 6.11
- Blood samples for MultiPlex Immuno Assays collected for batch-shipment to University Medical Center Utrecht (day 1)

7.7.2. Scheduled Visits on Day 7/ Days (±3) 14, 21, 28, 35, 42, 70/ Day (±14) 100/ Days (+21) 180, 365

The following assessments are mandatory:

- Information about AEs, hospitalizations, and concomitant medications (including RBC and platelet transfusions) will be recorded in the patient's medical record
- Vital Signs
- Physical examination (days 28, 70, 100, 180, and 365) including routine cardiac and pulmonary monitoring
- Karnofsky/Lansky performance status score (days 28, 70, 100, 180, and 365)
- 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 until day 100
- EBV PCR (monthly, or more frequently as clinically indicated, until day 100, or longer if patient is on immunosuppression)
- HHV6 DNA assessment by PCR weekly until ANC >500
- Peripheral blood collection for donor/host chimerism (days 7, 14, 21, 28, 42, 70, 100, 180, and 365 only). Bone marrow chimerism is an acceptable alternative to peripheral blood. Whole blood chimerism and lineage specific (CD3 and either CD15 or CD33) chimerism must be performed. In cases where NiCord® was transplanted with an additional CBU, chimerism testing will also delineate the donor source (donor1/donor2/host)
- Bone Marrow (aspirate/biopsy, when clinically indicated) for morphology (all) and for FACS, molecular markers and cytogenetics (if abnormal findings present at diagnosis for leukemia/MDS patients)-days 100 and 365 or other as per Investigator's discretion
- CT abdomen, pelvis, chest (lymphoma only) (day 100, 180, and 365 or other schedule as per Investigator's discretion)
- Blood samples for Immunophenotyping for batch shipment to University Medical Center Utrecht (days 7, 14, 21, 42, 70, 100, 180, and 365).

  - On days 70, 100, 180, and 365 site will assess T-cell subsets (CD3, CD4, CD8, CD19, CD56/16) locally as well as collecting samples for batch shipment to University Medical Center Utrecht

- Blood samples for MultiPlex Immuno Assays analyses sent to University Medical Center Utrecht (days 7, 14, 21, 42)
- Immunoglobulin levels (IgG, IgA, IgM) (days 70, 100, 180, and 365)
- Blood samples for T-cell Receptor Excision Circles (TREC) and T cell receptor (TCR) beta within CD4+ & CD8+ for batch shipment to University Medical Center Utrecht (days 100, 180, and 365)
- GvHD assessment:
  - Acute: At every visit post transplant, or more frequently as clinically indicated, Acute GvHD will be assessed according to the Consensus Conference on Acute GvHD grading (Appendix A)
  - Chronic: days 100,180, and 365 or more frequently as clinically indicated. Chronic GvHD will be assessed and classified as limited or extensive, according to standard criteria (Appendix A) and also classified as mild, moderate, or severe, according to the National Institute of Health consensus grading criteria[51].
- GvHD prophylaxis as specified in Section 6.4
- Infection prophylaxis as specified in Section 6.11

7.7.3. Evaluation and Treatment of Graft Failure

Evaluation of Graft Failure: should a patient suffer primary or secondary graft failure, an attempt will be made to determine the cause of failure. Evaluation will include:

- Bone marrow aspiration/biopsy for morphologic analysis as well as cytogenetics, chimerism studies, viral/bacterial cultures including 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 has less than 100 PMN at day +28 and most recent BM shows decreased marrow cellularity and paucity of donor cells (less than 20%) by chimerism analysis, this may be considered impending primary graft failure (different from actual graft failure as defined in section 4.2.1). In a case of impending or actual graft failure, the patient will be treated at the discretion of the treating physician.

Graft Rejection: Graft rejection will be defined by absence of evidence of donor hematopoiesis with evidence of host hematopoiesis on or before day 42.

In patients experiencing delayed or failed engraftment, serologic assessment of HHV6 and CMV will be performed.

7.7.4. Early Discontinuation of Follow-up

Reasons for withdrawal of the patient prior to Day 365 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.

Patients who do not receive a NiCord® infusion but are given a backup CBU are part of the intent to treat analysis and should be followed for ANC engraftment, secondary graft failure, survival, and relapse.

For early termination patients that withdraw/are withdrawn from the study post transplant, any assessments due at the time of withdrawal (according to Table 9) are requested.

Patients who experience graft failure or relapse 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 relapse.

7.7.5. 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 365 days 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

7.8. Data Reporting

7.8.1. Criteria for Forms Submission

Criteria for timeliness of submission for all study forms are detailed in the Data Management Handbook and User's Guide. [redacted]

[redacted]

Adverse Events will be reported as outlined in Section 9 of this protocol.

8.1. Description

8.1.1. NiCord®

[redacted]

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.

NiCord® CF and NF manufacturing will be performed by the Sponsor's central production site in Israel.

Myeloablative, GvHD prophylaxis, immunotherapy support and other supportive care, as detailed in Section 6, will be supplied by the study site.

8.3. Manufacturing

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

Quality control (QC) tests are performed throughout the course of the manufacturing and on the final product and their results are documented. The testing includes in-process quality controls (IPQC) and final process quality controls (FPQC) performed according to [redacted]. 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 and include both Bioassays and Safety tests as detailed in the table below.

Table 9:

[redacted]

Table 10: [redacted]

[redacted]

Table 11:

[redacted]

All the safety and some of the IPQC and FPQC bioassays 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]

8.3.1. Safety OOS Results

In the event that a safety test result failed to meet its specification, an immediate investigation is initiated. The resulting report will be attached to the deviation report and filed in the Batch Record.

[redacted]

[redacted]

In the case of European clinical site, the product is shipped with a QP "release for shipment" certificate and the different CoAs are faxed/emailed to the clinical sites with the QP "release for infusion" certificate.

8.4. Handling of NiCord®

[redacted]

Shipment

NiCord® [redacted] will be shipped under quarantine status with all available CBU segments to the clinical site in a cryoshipper equipped with a calibrated data logger prior to transplantation with all necessary documentations.

[redacted]

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 [redacted]
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. Treatment-emergent AEs are any AEs that occur or worsen (i.e. increase in grade) during or after the infusion of the study product.

9.1.2. Infusion Reaction

Any adverse event that occurs or worsens (i.e. increases in grade) between the start of the cord blood infusion and 24 hours after the end of the cord blood 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 study product 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 will use the following question when assessing causality of an adverse event to study product: Is there a reasonable possibility that the study product caused the event? An affirmative answer designates the event as a suspected adverse reaction.

9.1.6. 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 adverse events or suspected adverse reactions that are mentioned in the investigator's brochure but are not specifically mentioned as occurring with the particular study product under investigation.

9.1.7. Toxicity Grading

GvHD symptoms will be graded according to the Consensus Conference on Acute GvHD grading[52] for acute GvHD and National Institute of Health consensus grading criteria[51] for chronic GvHD.

Infections will be graded according to the infection grading scale provided in the Data Management Handbook.

All other AEs will be graded using NCI's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

An AE that is assessed as CTCAE 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

The following events meet the criteria for expedited reporting and require submission of an Adverse Event Form [redacted] within 24 hours of knowledge of the event (note that all SAEs require reporting within 24 hours of knowledge of the event, although not all SAEs will require expedited reporting to regulatory authorities).

- Grade 3-5 infusion reactions
- Non-engraftment at 42 days post NiCord® infusion
- All serious, unexpected, suspected adverse reactions as defined in 21 CFR312.32 and Directive 2001/20/EC

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

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

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

9.2. Observation, Detection and Recording of AEs and SAEs

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

[redacted]

- Serious Adverse Events post transplant will be reported on SAE summary forms

[redacted]

Serious Adverse Events

At all times after the start of conditioning, SAEs, grade 3-5 infusion reactions and non-engraftment at day 42 post transplant will be reported on SAE summary forms. These events may require reporting on other forms as well (e.g. Death form when applicable), however they should not be reported on the Adverse Event Log form. SAEs should be reported within 24hrs of the sites' knowledge of the event.

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

For every SAE that occurs between the time of patient consent and the participant's final study visit, the Investigator is responsible for reviewing all documentation (e.g., hospital progress notes, laboratory test results, and diagnostic reports) relating to the event. For events that occur after the start of conditioning, the Investigator or designee will then record all relevant information about an SAE onto the appropriate page of the CRF. The Investigator must review, sign, and date an SAE summary report form to confirm the accuracy of the recorded information. The signed report will be maintained in the site's study files. It is not acceptable for the Investigator to send photocopies of the subject's medical records in lieu of completion of the appropriate CRF pages. Unless otherwise requested, transfer of subjects' medical records with the CRF should be restricted to hospital admission and progress notes, laboratory and radiology reports, discharge

summaries and autopsy reports, if available. When sending medical records, all subject identifiers (i.e., name, medical record number) must be obliterated prior to faxing the documents to the designated project contact.

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 the original source document and maintained in the site's study files.

9.4. Medical Monitor Review

Both the [redacted] Medical Monitor (MM) and the sponsor will be alerted [redacted]

- Grade 3-5 infusion reactions
- Non-engraftment at 42 days post NiCord® infusion
- All serious adverse events

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

9.5. Clinical Laboratory Evaluations

All laboratory measurements will be evaluated for abnormalities. An abnormal laboratory value should be primarily interpreted in the context of the disease or the condition leading to it. The latter (instead of the laboratory abnormality itself) should be reported as adverse event and graded, whenever possible. A laboratory adverse event i.e., a laboratory abnormality not associated with any particular clinical findings (e.g., symptoms, signs), will be reported when judged clinically significant by the investigator.

An abnormal laboratory finding is not by itself considered to be an AE or SAE unless the investigator considers the abnormal finding to be of clinical significance. The abnormal laboratory finding does not have to be associated with the use of NiCord® to be considered clinically significant. If a laboratory adverse event is reported, it will be graded using the CTCAE toxicity grading scale version 4.03. A laboratory adverse event with a value falling within the specified CTCAE grade 4 boundaries will only be considered life-threatening from a regulatory perspective if it results in an actual life-threatening consequence i.e., its occurrence places the subject at immediate risk of death. Grade 4 laboratory adverse events that are not life-threatening should not be reported as serious adverse events unless they meet other seriousness regulatory criteria.

9.6. Pregnancy

Pregnancy will not be considered 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.

9.7. Patient Withdrawal from Study Procedures due to Adverse Events

Any patient can 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.

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 or modification of the study.

9.9. Regulatory Authorities and IRB/ECs

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

The Sponsor is responsible for reporting all unexpected fatal or life-threatening suspected adverse reactions to regulatory authorities, as per the concerned authorities' requirements no later than seven calendar days after knowledge of the event. All grade 3-5 infusion reactions, non-engraftment at 42 days post NiCord® infusion, and all other serious, unexpected, suspected adverse reactions are reported to the regulatory authorities by the Sponsor within 15 calendar days of receipt of the information.

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

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

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

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

10. STATISTICAL METHODOLOGY

Patients & Analysis Cohorts

10.4. Statistical Analysis

Primary Objectives

- Assess the cumulative incidence of patients with NiCord®-derived neutrophil engraftment at 42 days following transplantation.
- Assess the incidence of secondary graft failure at 180 days following transplantation of NiCord®

Secondary Objectives

- Time from infusion to neutrophil engraftment
- Time from infusion to platelet engraftment
- Incidence of platelet engraftment at 100 days
- Proportion of non-relapse mortality at 100 days
- Incidence of acute GvHD grade II-IV and III-IV at 100 days
- Incidence of chronic GvHD (limited or extensive) at 180 days and 1 year
- Incidence of secondary graft failure at 1 year following transplantation of NiCord®
- Overall survival at 180 days and 1 year

Exploratory Objectives

- Immune reconstitution at 70, 100, 180, and 365 days

10.4.1. Primary Endpoints

10.4.1.1. 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 prior to engraftment will be considered as a competing risk.

10.4.1.2. Incidence of Secondary Graft Failure

The cumulative incidence of secondary graft failure out of those who had initial engraftment will be described using the cumulative incidence estimator, treating death and disease relapse/progression prior to secondary graft failure as a competing event.

10.4.2. Secondary Endpoints

10.4.2.1. Time from Infusion to Neutrophil Engraftment

The incidence of initial neutrophil engraftment will be estimated with a cumulative incidence curve with death as a competing risk. Median time to neutrophil ($>0.5x10^9$/L) engraftment will be estimated among those in whom engraftment is achieved.

10.4.2.2. Time from Infusion to Platelet Engraftment

The incidence of platelet engraftment (>20x10^9/L and >50 x10^9/L) will be estimated with a cumulative incidence curve with death as a competing risk. Median time to platelet (>20x10^9/L and >50 x10^9/L) engraftment will be estimated among those in whom engraftment is achieved.

10.4.2.3Incidence of Platelet Engraftment at 100 days

The incidence of platelet engraftment (>20x10^9/L and >50 x10^9/L) will be estimated with a cumulative incidence curve with death as a competing risk.

10.4.2.4. Non-Relapse Mortality

To assess the incidence of non-relapse mortality, a cumulative incidence curve of death occurring in a subject not preceded by relapse will be computed along with a 95% confidence interval at 100 days post-transplant. Relapse and progressive disease will be considered as a competing risk.

10.4.2.5. 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 and second transplant will be considered as a competing risk in the estimation.

10.4.2.6. Chronic GvHD

The cumulative incidence of patients who experience chronic GvHD will be computed along with a 95% confidence interval at 180 days and 365 days post transplant. Death and second transplant will be considered as a competing risk in the estimation.

10.4.2.7. Overall survival

The proportion of patients alive at 180 days and 365 days post transplant will be estimated using the Kaplan-Meier method.

10.4.2.8. Safety and Tolerability of NiCord® Transplantation

The safety and tolerability of NiCord® transplantation will be evaluated by the nature, incidence and frequency of adverse experiences and an estimation of the relationship to NiCord®, as well as infections and laboratory data follow-up, with special emphasis on safety of cell therapy, including the detection of infusion reactions, transmission of infections, new malignancies and autoimmune diseases.

10.4.3. Exploratory Endpoints

10.4.3.1. Immune Reconstitution

The distributions of total immunoglobulin levels at days 70, 100, 180, and 365 (mean, standard deviation, median, quartiles) will be estimated. The distributions of the numbers

and proportions of different lymphocyte subpopulations at days 70, 100, 180, and 365 (mean, standard deviation, median, quartiles) will also be estimated. The distributions of T-cell excision circles at days 100, 180, and 365 (mean, standard deviation, median, quartiles) will also be estimated. Patients who have graft failure, who relapse, or who die before target day (70, 100, 180, or 365 respectively) will be excluded from this analysis.

10.5. Missing Data

Unless otherwise specified, patients with missing data will be excluded from the analysis in which their data is missing. For descriptive analyses of multiple timepoints, patients with data missing at some timepoints but not others will be censored from the analysis of those timepoints in which their data is missing. For survival and incidence curves patients with missing data will be included and censored at the time of missing data, unless otherwise specified as a competing risk.

10.6. Analysis Plan Deviations

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

10.7. 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.

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[52]:

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

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

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

Clinical Manifestations and Staging of Acute Graft-versus-Host Disease		
Organ	Clinical Manifestations	Staging
Skin	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	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	Upper: nausea, vomiting, anorexia. Lower: diarrhea, abdominal cramps, distention, ileus, bleeding.	Stage 1: diarrhea >500 ml/day or persistent nausea Stage 2: diarrhea >1000 ml/day Stage 3: diarrhea >1500 ml/day Stage 4: large volume diarrhea and severe abdominal pain +/- ileus

Chronic GvHD Definition

Chronic GvHD will be assessed from day 100 until day 365 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

<table>
<tr><th>During Conditioning up to Start of NiCord Infusion</th><th>During NiCord Infusion through 24 hours Post NiCord Infusion</th><th>> 24 hours Post NiCord Infusion through Day 42</th><th>Day 43 through Day 365</th></tr>
<tr><td rowspan="3">Complete a Toxicity form with the highest grade of all common* adverse events</td><td>Complete a Toxicity form with the highest grade of all common* adverse events

Grade 3-5 events also require completion of SAE summary forms (AD1-AD5)

All grade 1-2 uncommon non-serious adverse events must be listed individually on the Adverse Event Log form.#</td><td>Complete a weekly Toxicity form with the highest grade of all common* adverse events during that week.

Non-engraftment at day 42 requires completion of SAE summary forms (AD1-AD5)

All other uncommon non-serious adverse events must be listed individually on the Adverse Event Log form.#</td><td>All grade 3-4 non-serious adverse events must be listed individually on the Adverse Event Log form. #</td></tr>
<tr><td colspan="3">Infection form is required when applicable</td></tr>
<tr><td colspan="3">Scheduled GvHD data collection at every visit on either the GVH or the CGV form.</td></tr>
<tr><td colspan="4">Any event that also meets the definition of an SAE, requires submission of SAE summary forms (AD1-AD5). If the SAE is unexpected and associated with NiCord®, then an expedited report must be submitted.</td></tr>
<tr><td colspan="4">A Hospitalization form (ADM) and/or Death form (DTH) required if applicable</td></tr>
</table>

* See appendix C for a list of common adverse events

With the exception of infections and GvHD symptoms which are reported on the Infection form and GvHD forms respectively.

APPENDIX C. COMMON ADVERSE EVENTS

Cardiac
Cardiac Arrhythmias

Gastrointestinal
Abdominal distension
Nausea
Vomiting
Constipation
Dyspepsia
Dysphagia
Mucositis

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

Injury/Poisoning/Procedural Complications
Bruising
Hemorrhage
Vascular access complications

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

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

Musculoskeletal
Generalized muscle weakness

Neurologic
Dizziness
Dysgeusia
Somnolence
Syncope
Tremors

Psychiatric
Anxiety
Depression
Insomnia

Renal
Non-infectious cystitis

Respiratory
Cough
Dyspnea
Epistaxis
Hypoxia

Skin
Alopecia
Dry skin
Pruritis
Skin hyperpigmentation

Vascular
Hypertension
Hypotension

APPENDIX D. COMMON TERMINOLOGY CRITERA FOR ADVERSE EVENTS V4.03 (CTCAE)[53]

APPENDIX E: DRUG LABELS

See attached documents.

APPENDIX F: PROTOCOL AMENDMENT SUMMARY

Protocol Version	Approved Sites	Main Reason(s) for Amendment
Original	• Duke University Medical Center	N/A
Amendment I	• Duke University Medical Center	Expand patient population and clarify eligibility criteria
Amendment II	▪ Cedars Sinai Medical Center ▪ Cleveland Clinic ▪ Steven and Alexandra Cohen Children's Medical Center of New York ▪ Duke University Medical Center ▪ Vanderbilt University Medical Center	Change in manufacturing procedure to cryopreserved product. Modify eligibility criteria. Additional option for conditioning regimen
Amendment II.1	▪ Hospital Universitario y Politécnico La Fe Hospital Universitari Vall d´Hebrón ▪ Istituto Giannina Gaslini of Genoa ▪ AOU San Luigi Gonzaga of Turin	Add safety objective. Define childbearing potential and appropriate contraception.
Amendment II.2	• University Medical Center Utrecht	Additional option for conditioning regimen.
Amendment III	▪ Cedars Sinai Medical Center ▪ Cleveland Clinic ▪ Steven and Alexandra Cohen Children's Medical Center of New York ▪ Duke University Medical Center ▪ Vanderbilt University Medical Center ▪ Hospital Universitario y Politécnico La Fe ▪ Hospital Universitari Vall d´Hebrón	Modify eligibility criteria. Additional regimen specific stopping guidelines. Additional supportive and viral monitoring care guidelines. Update AE reporting guidelines.
Amendment IV	▪ Cedars Sinai Medical Center ▪ Cleveland Clinic ▪ Steven and Alexandra Cohen Children's Medical Center of New York	Increase number of patients for study enrollment, modify eligibility criteria, COA release criteria, GvHD prophylaxis medication

	▪ Duke University Medical Center ▪ Vanderbilt University Medical Center ▪ Hospital Universitario y Politécnico La Fe ▪ Hospital Universitari Vall d´Hebrón	administration and assessment grading criteria,

REFERENCES

1. 1 Cottler-Fox, M. H., T. Lapidot, et al. (2003). "Stem cell mobilization." Hematology Am Soc Hematol Educ Program: 419-437.

2. 2 Wagner, J. E. (2009). "Should double cord blood transplants be the preferred choice when a sibling donor is unavailable?" Best Pract Res Clin Haematol 22(4): 551-555.

3. 3 Aljitawi, O. S. (2012). "Ex vivo expansion of umbilical cord blood: where are we?" Int J Hematol 95(4): 371-379.

4. 4 Yamazaki, R., M. Kuwana, et al. (2006). "Prolonged thrombocytopenia after allogeneic hematopoietic stem cell transplantation: associations with impaired platelet production and increased platelet turnover." Bone Marrow Transplant 38(5): 377-384.

5. 5 Brunstein, C. G., J. A. Gutman, et al. (2010). "Allogeneic hematopoietic cell transplantation for hematological malignancy: relative risks and benefits of double umbilical cord blood." Blood.

6. 6 Ramirez, P., C. G. Brunstein, et al. (2010). "Delayed platelet recovery after allogeneic transplantation: a predictor of increased treatment-related mortality and poorer survival." Bone Marrow Transplant.

7. 7 MacMillan, M. L., D. J. Weisdorf, et al. (2009). "Acute graft-versus-host disease after unrelated donor umbilical cord blood transplantation: analysis of risk factors." Blood 113(11): 2410-2415.

8. 8 Stanevsky, A., A. Shimoni, et al. (2010). "Double umbilical cord blood transplant: more than a cell dose?" Leuk Lymphoma.

9. [9] Verneris, M. R., C. G. Brunstein, et al. (2009). "Relapse risk after umbilical cord blood transplantation: enhanced graft-versus-leukemia effect in recipients of 2 units." Blood 114(19): 4293-4299.

[10] Sideri, A., N. Neokleous, et al. (2011). "An overview of the progress on double umbilical cord blood transplantation." Haematologica 96(8): 1213-1220.

10. 11 Scaradavou, A., K. M. Smith, et al. (2009). "Cord Blood Units with Low CD34+ Cell Viability Have a Low Probability of Engraftment After Double Unit Transplantation." Biol Blood Marrow Transplant.

12 Ramirez, P., J. E. Wagner, et al. (2012). "Factors predicting single-unit predominance after double umbilical cord blood transplantation." Bone Marrow Transplant 47(6): 799-803.

11. 13 Majhail, N. S., C. G. Brunstein, et al. (2006). "Double umbilical cord blood transplantation." Curr Opin Immunol 18(5): 571-575.

14 Newell, L. F., F. Milano, et al. (2012). "Early CD3 Peripheral Blood Chimerism Predicts the Long-Term Engrafting Unit Following Myeloablative Double-Cord Blood Transplantation." Biol Blood Marrow Transplant.

12. 15 Eldjerou, L. K., S. Chaudhury, et al. (2010). "An in vivo model of double-unit cord blood transplantation that correlates with clinical engraftment." Blood 116(19): 3999-4006.

13. 16 Moretta, A., G. Andriolo, et al. (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.

17 Kelly, S. S., S. Parmar, et al. (2010). "Overcoming the barriers to umbilical cord blood transplantation." Cytotherapy 12(2): 121-130.

14. 18 Dahlberg, A., C. Delaney, et al. (2011). "Ex vivo expansion of human hematopoietic stem and progenitor cells." Blood 117(23): 6083-6090.

15. 19 Delaney, C., M. Z. Ratajczak, et al. (2010). "Strategies to enhance umbilical cord blood stem cell engraftment in adult patients." Expert Rev Hematol 3(3): 273-283.

16. 20 De Lima, M., S. Robinson, et al. (2010). "Mesenchymal Stem Cell (MSC) Based Cord Blood (CB) Expansion (Exp) Leads to Rapid Engraftment of Platelets and Neutrophils." ASH Annual Meeting Abstracts 116(21): 362-.

21 De Lima M, McNiece I, et al. Cord-blood engraftment with ex vivo mesenchymal-cell coculture. N Engl J Med. 2012 Dec 13;367(24):2305-15.

17. 22 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.

18. 23 Ando, K., T. Yahata, et al. (2006). "Direct evidence for ex vivo expansion of human hematopoietic stem cells." Blood 107(8): 3371-3377.

19. 24 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.

20. 25 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.

26 Szilvassy SJ, Bass MJ, Van Zant G, Grimes B. Organ-selective homing defines engraftment kinetics of murine hematopoietic stem cells and is compromised by Ex vivo expansion. Blood. Mar 1 1999;93(5):1557-1566.

27 Ahmed F, Ings SJ, Pizzey AR, Blundell MP, Thrasher AJ, et al. (2004) Impaired bone marrow homing of cytokine-activated CD34+ cells in the NOD/SCID model. Blood 103: 2079–2087

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

29 Von Drygalski A, Alespeiti G, Ren L, Adamson JW. Murine bone marrow cells cultured ex vivo in the presence of multiple cytokine combinations lose radioprotective and long-term engraftment potential. Stem cells and development. Feb 2004;13(1):101-111.

30 Xu R, Reems JA. Umbilical cord blood progeny cells that retain a CD34+ phenotype after ex vivo expansion have less engraftment potential than unexpanded CD34+ cells. Transfusion. Feb 2001;41(2):213-218.

31 Szilvassy SJ, Meyerrose TE, Grimes B. Effects of cell cycle activation on the short-term engraftment properties of ex vivo expanded murine hematopoietic cells. Blood. May 1 2000;95(9):2829-2837.

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

[33] Hofmeister CC, Zhang J, Knight KL, Le P, Stiff PJ. Ex vivo expansion of umbilical cord blood stem cells for transplantation: growing knowledge from the hematopoietic niche. Bone Marrow Transplant. Jan 2007;39(1):11-23.

[34] Peled T, Shoham H, Aschengrau D, et al. Nicotinamide, a SIRT1 inhibitor, inhibits differentiation and facilitates expansion of hematopoietic progenitor cells with enhanced bone marrow homing and engraftment. Experimental Hematology. Apr 2012;40(4):342-355 e341.

[35] Berger, F., Ramírez-Hernández, M. H. and Ziegler, M. (2004) The new life of a centenarian: signalling functions of NAD(P). Trends Biochem. Sci. 29, 111–118

[36] Banasik M, Komura H, Shimoyama M, and Ueda K (1992) Specific inhibitors of poly(ADP-ribose) synthetase and mono(ADP-ribosyl)transferase. J Biol Chem 267: 1569–1575.

[37]Corda D, Di Girolamo M. Functional aspects of protein mono-ADP-ribosylation. Embo J. May 1 2003;22(9):1953-1958.

[38] Krebs C, Adriouch S, Braasch F, et al. CD38 controls ADP-ribosyltransferase-2-catalyzed ADP-ribosylation of T cell surface proteins. J Immunol. Mar 15 2005;174(6):3298-3305.

[39] Glowacki G, Braren R, Firner K, et al. The family of toxin-related ecto-ADP-ribosyltransferases in humans and the mouse. Protein science : a publication of the Protein Society. Jul 2002;11(7):1657-1670.

[40] Papaccio G, Ammendola E, Pisanti FA. Nicotinamide decreases MHC class II but not MHC class I expression and increases intercellular adhesion molecule-1 structures in non-obese diabetic mouse pancreas. The Journal of endocrinology. Mar 1999;160(3):389-400.

[41] Sato F, Mitaka T, Mizuguchi T, Mochizuki Y, Hirata K. Effects of nicotinamide-related agents on the growth of primary rat hepatocytes and formation of small hepatocyte colonies. Liver. Dec 1999;19(6):481-488.

[42] Miura M, Kameda Y. Nicotinamide promotes long-term survival and extensive neurite outgrowth in ultimobranchial C cells cultured from chick embryos. The Journal of comparative neurology. Nov 21 2005;492(3):334-348.

[43] Munshi CB, Graeff R, Lee HC. Evidence for a causal role of CD38 expression in granulocytic differentiation of human HL-60 cells. J Biol Chem. Dec 20 2002;277(51):49453-49458.

[44]Iwata K, Ogata S, Okumura K, Taguchi H. Induction of differentiation in human promyelocytic leukemia HL-60 cell line by niacin-related compounds. Bioscience, biotechnology, and biochemistry. May 2003;67(5):1132-1135.

[45] Denu JM. The Sir 2 family of protein deacetylases. Current opinion in chemical biology. Oct 2005;9(5):431-440.

[46] Bitterman K.J., Anderson, R.M., Cohen, H.Y., Latorre-Esteves, M., and Sinclair, D.A. 2002. Inhibition of silencing and accelerated aging by nicotinamide, a putative negative regulator of yeast Sir2 and human SIRT1. J. Biol. Chem. 277: 45099–45107

[47] Vaca P, Berna G, Martin F, Soria B. Nicotinamide induces both proliferation and differentiation of embryonic stem cells into insulin-producing cells. Transplant Proc. Aug 2003;35(5):2021-2023.

[48] Blander G, Bhimavarapu A, Mammone T, Maes D, Elliston K, Reich C, Matsui MS, Guarente L, Loureiro JJ. J Invest Dermatol. 2009 Jan;129(1):41-9. Epub 2008 Jun 19.

[49] Kim MJ, Ahn K, Park SH, et al. SIRT1 regulates tyrosine hydroxylase expression and differentiation of neuroblastoma cells via FOXO3a. FEBS Lett. Apr 2 2009;583(7):1183-1188.

[50] Bartelink I, et al (2012). "Body Weight-Dependent Pharmacokinetics of Busulfan in Paediatric Haematopoietic Stem Cell Tranplantation Patients." Clin Pharmacokinet 51(5); 331-345.

[51] Filipovich A, Weisdorf D, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. Diagnosis and Staging Working Group Report Biology of Blood and Marrow Transplant. Dec 2005; 11(12): 945–956

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

[53] Cancer Therapy Evaluation, D., NCI, NIH, DHHS (2009). "Common Terminology Criteria for Adverse Events v4.0 (CTCAE).