NCT02730299

STATISTICAL ANALYSIS PLAN

For

Study Title: A Multicenter, Randomized, Phase III Registration Trial of Transplantation of NiCord®, Ex Vivo Expanded, Umbilical Cord Blood-derived, Stem and Progenitor Cells, versus Unmanipulated Umbilical Cord Blood for Patients with Hematological Malignancies

Version 5.0

March 8, 2020

Study Chairs

[redacted]

Distributed by:

[redacted]

This communication is privileged and confidential.

STUDY TITLE: A Multicenter, Randomized, Phase III Registration Trial of Transplantation of NiCord®, Ex Vivo Expanded, Umbilical Cord Blood-derived, Stem and Progenitor Cells, versus Unmanipulated Umbilical Cord Blood for Patients with Hematological Malignancies

Short Title:	Transplantation of NiCord® vs Unmanipulated Umbilical Cord Blood Cells for Patients with Hematological Malignancies
Development Phase:	Phase III, Registration
Products:	NiCord®
IND Number:	14459
EudraCT Number:	2016-000704-28
Form/Route:	Single ex-vivo expanded cord blood unit transplantation
Indication Studied:	Hematological malignancies
Sponsor:	Gamida Cell Ltd Jerusalem, Israel
Protocol Chairs:	[redacted]
DCC Medical Monitor:	[redacted]
Clinical Trial Initiation Date:	December 20, 2016
Clinical Trial Completion Date:	TBD
Date of the Analysis Plan:	March 8, 2020
SAP Version Number:	5.0

This study will be performed in compliance with Good Clinical Practice.

SIGNATURE PAGE

SPONSOR: Gamida Cell Ltd

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Principal Study Statistician:

Signed: _____ Date: _____

[redacted]

Signed: _____ Date: _____

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List of Abbreviations

AE	Adverse Event
AEP	ANC-Engrafted Population
aGvHD	Acute Graft-versus-host Disease
ALL	Acute Lymphoblastic Leukemia
ALT	Alanine Transaminase
AML	Acute Myelogenous Leukemia
ANC	Absolute Neutrophil Count
APL	Acute Promyelocytic Leukemia
AST	Aspartate Transaminase
BM	Bone Marrow
BMT	Bone Marrow Transplant
BMTS	Bone Marrow Transplantation Subscale
CB	Cord Blood
CBB	Cord Blood Bank
CBU	Cord Blood Unit
cDLCO	Corrected Diffusing Capacity of the Lungs for Carbon Monoxide
CF	Cultured Fraction
cGvHD	Chronic Graft-versus-host Disease
CI	Confidence Interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CML	Chronic myeloid leukemia
CMMoL	Chronic myelomonocytic leukemia
CNS	Central Nervous System
DCC	Data Coordinating Center
DLCO	Diffusing Capacity of the Lungs for Carbon Monoxide
DMC	Data Monitoring Committee
DRI	Disease Risk Index
EBV	Epstein-Barr Virus
FACT-BMT	Functional Assessment of Cancer Therapy – Bone Marrow Transplant Module
FACT-G	Functional Assessment of Cancer Therapy - General
FEV1	Forced Expiratory Volume in One Second
FISH	Fluorescent In Situ Hybridization
FVC	Forced Vital Capacity
FWE	Family-wise Error Rate
GvHD	Graft-versus-host Disease
HCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen

HQL	Health-related Quality of Life
IPSS	International Prognostic Scoring System
ITT	Intent to Treat
IUD	Intrauterine contraceptive Device
KM	Kaplan-Meier
LCL	Lower Confidence Limit
LVEF	Left Ventricular Ejection Fraction
MDS	Myelodysplastic Syndrome
MFI	Mean Fluorescence Intensity
MLL	Myeloid/Lymphoid Leukemia
MMF	Mycophenolate Mofetil
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
NF	Non-cultured Fraction
NIH	National Institutes of Health
PA	Physician Assistant
PCR	Polymerase Chain Reaction
PEP	Platelet-Engrafted Population
PT	Preferred Term
QOL	Quality Of Life
ROC	Receiver Operating Characteristic
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCID	Severe Combined Immunodeficiency
SCT	Stem Cell Transplant
SOC	System Organ Class
SP	Safety Population
TBI	Total Body Irradiation
TKI	Tyrosine Kinase Inhibitor
TNC	Total Nucleated Cell
TP	Transplanted Population
UCB	Umbilical Cord Blood
UCL	Upper Confidence Limit
WBC	White Blood Cell

1. PREFACE

The Statistical Analysis Plan (SAP) for Transplantation of NiCord® vs Unmanipulated Umbilical Cord Blood Cells for Patients with Hematological Malignancies provides additional detail for the statistical information described in the protocol. This trial is sponsored by Gamida Cell, Ltd., and is implemented at multinational sites. [redacted] serves as the Data Coordinating Center (DCC) for this trial.

The protocol itself provides details on conduct of the study and the operational aspects of clinical assessments. This document provides a review of the study design, statements of general statistical considerations, detailed and comprehensive sections regarding the statistical analysis methods for efficacy and safety outcomes, and a list of proposed tables and figures. Any deviation from this SAP will be described and justified in subsequent SAP amendments and/or in the Complete Study Report (CSR), as appropriate.

2. INTRODUCTION

The overall study objective is to compare the safety and efficacy of conditioning therapy followed by either NiCord® single *ex vivo* expanded cord blood unit (CBU) transplantation or unmanipulated cord blood unit CBU transplantation in patients with hematological malignancies for whom allogenic SCT is currently a recommended and potentially lifesaving treatment. Patients will be randomized to NiCord® or unmanipulated CBU transplantation. Sites may choose to use one of the protocol-specified conditioning regimens for all patients, or according to primary diagnosis/age group. Patients will undergo the conditioning regimen, and then have the assigned transplant. Patients are evaluated at post transplant study Days 1-7, 14, 21, 28, 35, 42, 56, 70, 100, 180, 270, and 365 for safety and efficacy endpoints. Patients are also evaluated at 15 months post randomization for survival and relapse status. The primary endpoint is based on time to neutrophil engraftment with chimerism, where ANC engraftment must first be documented by Day 42. Secondary endpoints include incidence of grade 2/3 bacterial or fungal infections by 100 days post transplant, days alive and out of hospital in the first 100 days post transplant, and platelet engraftment by Day 42 post transplant. Non-relapse mortality by Day 210 post randomization will be a tertiary endpoint. Exploratory endpoints are described in Section 8.5.4.

Patients may enroll in an optional long-term follow up substudy in which they will be followed for up to 5 years post-transplantation. The analyses for the substudy are provided in the protocol's Appendix J.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

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

Primary Objective: Assess the time to neutrophil engraftment following transplantation.

Secondary Objectives: Assess the secondary, tertiary and exploratory study endpoints.

3.2 Study Endpoints

Secondary Endpoints:

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

Tertiary Endpoint:

- Non-relapse mortality by 210 days following randomization

Exploratory Endpoints:

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

3.3 Study Definitions and Derived Variables

3.3.1 Date of randomization

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

3.3.2 Date of transplant

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

3.3.3 Neutrophil engraftment

Neutrophil engraftment is defined as achieving an absolute neutrophil count (ANC) ≥ 0.5 x 10^9/L on 3 consecutive measurements on different days with subsequent donor chimerism (≤ 10% host cells by peripheral blood chimerism or bone marrow chimerism if peripheral blood chimerism is not available) any time on or after the day of engraftment up to the earlier of day 100 post-transplant, date of relapse, date of secondary graft failure, or date of death. The first day of the three *ANC* measurements will be designated the day of neutrophil engraftment and must occur on or before 42 days post transplant and also prior to any competing risks. Chimerism from whole blood assessments on peripheral blood or bone marrow may be used, and myeloid (CD15 or CD33 lineage) may also be used to determine if the patient had <=10% host cells.

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 also be considered primary graft failure, with the following exception:

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

The date of primary graft failure will be designated as Day 43 post transplant.

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

3.3.4 Platelet engraftment

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

3.3.5 Grade 2/3 Bacterial Infections and Grade 3 Viral infections

The infection grading criteria are provided in protocol Appendix G.

3.3.6 Invasive Fungal Infection

Invasive fungal infection is defined as any grade 3 fungal infection. The infection grading criteria are provided in the protocol Appendix G.

3.3.7 Duration of Primary Hospitalization

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

3.3.8 Days Alive and out of Hospital

A day alive and out of hospital is defined as a full day (calendar day) in which the patient was alive and not hospitalized. Partial days alive and out of hospital, such as the day of admission, day of discharge and day of death, do not count as a day alive and out of hospital. The day of transplant will not count as a day alive and out of hospital [redacted]

3.3.9 Overall Survival

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

3.3.10 Disease Relapse

Relapse of malignancy

Testing for recurrent malignancy in the blood, marrow or other sites will be used to assess relapse after transplantation. For the purpose of this study, relapse is defined by either morphological or cytogenetic evidence of AML, ALL, CML, MDS, or Lymphoma consistent with pre-transplant features. For the purposes of the analyses, the date entered in the Disease Progression/Relapse (DPR) form as the progression/relapse date will be the relapse date.

Minimal residual disease (MRD)

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

Acute Leukemia

Relapse can be defined as any of the following.

[redacted]

[redacted]

Chronic Myelogenous Leukemia (CML)

Hematological relapse can be diagnosed when:

[redacted]

Cytogenetic relapse can be diagnosed when:

[redacted]

MDS

Relapse can be defined as any of the following.

[redacted]

Lymphoma

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

[redacted]

3.3.11 Disease-free Survival

Disease-free survival is defined as the survival without disease relapse or death from any cause, whichever comes first.

3.3.12 Non-relapse Mortality

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

3.3.13 Relapse Mortality

Relapse mortality is defined as any death preceded by relapse.

3.3.14 Acute GvHD

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

3.3.15 Chronic GvHD

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

3.3.16 Immune Reconstitution

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

3.3.17 Health-Related Quality of Life (HQL)

Patient-reported health-related quality of life (HQL) outcomes will be assessed during the trial using two standardized measures including the Functional Assessment of Cancer Therapy –Bone Marrow Transplant Module (FACT BMT) and the EuroQol EQ-5D.

3.3.17.1 FACT-BMT

[redacted]

3.3.17.2 EQ-5D

[redacted]

3.3.18 Safety and Tolerability of NiCord® Transplantation

The safety and tolerability of NiCord® transplantation will be evaluated based on infusion reactions, common events post-transplant, uncommon events post-transplant, infections, and hospitalizations.

An infusion reaction is any adverse event that initiates or worsens (i.e., increases in grade above grade 1) between the start of the graft infusion and 24 hours after the end of the graft infusion.

Common events post-transplant are summarized in Appendix D of the protocol and reported [redacted]. Some additional events reported [redacted] may be classified as common events based on a supplemental list provided prior to database closure (e.g., infections, relapse, febrile neutropenia, events related to GvHD). Uncommon events are any adverse events that are not summarized in Appendix D and not on the supplemental list. Non-serious uncommon events are reported on [redacted] and serious uncommon adverse events are reported on [redacted].

4. INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

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

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

Eligible patients will be randomized to receive either NiCord® or unmanipulated cord blood transplantation. Randomization will be performed using a minimization algorithm.

For patients randomized to the NiCord® transplantation arm, the CBU chosen for production (Treatment CBU #1) will be shipped from the Cord Blood Bank (CBB) to the manufacturing site. Upon release, NiCord® CF + NF will be shipped to the clinical site before transplantation. NiCord® CF will be thawed and infused first, followed by the NiCord® NF. If NiCord® fails to meet its required release specifications,

the backup CBU(s), or a different backup source of stem cells will be transplanted as detailed in section 8.3 of the protocol.

For patients randomized to the unmanipulated cord blood transplantation arm, either one CBU (Treatment CBU #1) or two CBUs (Treatment CBU #1 and #2) chosen for transplantation will be shipped from the CBB to the clinical site and transplanted.

Prior to the start of conditioning, the investigator must confirm patient suitability for transplant according to standard site practice. The conditioning regimen will consist of one of three options. In general, each transplant center should commit to use the same conditioning regimen for all patients transplanted at their center, or according to primary diagnosis/age group [redacted]. In any case, the determination of the choice of conditioning regimen must be made prior to randomization.

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

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

Patients will have post-transplant study visits on Days 1-7, 14, 21, 28, 35, 42, 56, 70, 100, 180, 270, and 365. The patient survival and relapse status should be assessed at 15 months or later post-randomization.

4.2 Discussion of Study Design, Including Choice of Control Groups

The study design was guided by the following considerations:

Choice of control group

The patients on the trial have hematological malignancies for which allogeneic SCT is currently a recommended and potentially lifesaving treatment. For ethical reasons, the study will only enroll patients who do not have an adequate suitably matched and readily available stem cell donor. [redacted]. This treatment has been selected as the control treatment for this trial.

Blinding and randomization prior to preparation of CBU

Treatment assignment is not blinded in this protocol because there is a delay between randomization and transplant due to different processing times required by the two treatments. Randomization is completed prior to preparation of the NiCord® product or CBU(s) so that the randomization represents the clinical decision to initiate treatment with either standard of care or NiCord®.

Randomization method

Patients will be randomized to treatment by NiCord® or by unmanipulated cord blood (single or double unit). The method of minimization will be used so as to provide balanced treatment assignment across selected factors of prognostic importance including: treatment center, age group, disease risk group, and intent to perform double or single CBU transplant.

Conditioning Regimens

Over the years, a number of different conditioning regimens have been established as standard of care for unrelated CB transplantation in adults, generally divided into TBI – based versus non-TBI. In this study, the choice of conditioning regimen and GvHD prophylaxis agents is kept limited, in order to confirm the use of optimal patient care and to allow for clear interpretation of study results, while still providing the flexibility to choose between TBI-based and non-TBI regimens, and to allow for individual country and site accepted practices and experience.

4.3 Selection of Study Population

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

4.4 Inclusion Criteria

Patients must meet all the following criteria to be eligible for study enrollment:

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

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

- Chronic myelogenous leukemia (CML) at one of the following phases:
- [redacted]
- Myelodysplastic Syndrome (MDS) with history of one or more of the following:
- [redacted]
- Biphenotypic/undifferentiated/Prolymphocytic/Dendritic Cell Leukemias and Natural Killer Cell Malignancies [redacted], adult T-cell leukemia/lymphoma [redacted]
- Lymphoma, meeting one or more of the following criteria:
    - Burkitt's lymphoma [redacted]

      OR
    - High risk lymphomas [redacted]

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

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

3. CBU criteria as described per protocol
4. Patients who will be starting conditioning prior to NiCord release for infusion (i.e., NiCord arrival on site in adequate condition) must have an additional partially HLA-matched CBU reserved as a backup to the NiCord arm (in case of production failure).
   [redacted]
5. [redacted]
6. Patient's Performance score ≥70% by Karnofsky or Lansky

7. Patient has sufficient physiologic reserves including:
    - Cardiac [redacted].
    - Pulmonary function tests [redacted].
    - Renal [redacted]
    - Hepatic [redacted]
8. Females of childbearing potential, defined [redacted].
9. Patient (or legal guardian) signs the written informed consent after being aware of the nature of the patient's disease and willingly consents to the treatment program after being informed of alternative treatments, potential risks, benefits, and discomforts.

4.5 Exclusion Criteria

1. MDS or CML with "marked" or "3+" fibrosis
2. CLL
3. Fewer than 21 days have elapsed since initiation of the patient's last chemotherapy cycle and the initiation of the stem cell transplant preparative regimen [redacted]
4. Persistent clinically significant toxicities [redacted]
5. Evidence of donor specific anti-HLA antibodies to the selected treatment CBU #1 (MFI>3000 to HLA A, B, C, or DRB1)
6. Evidence of HIV infection or HIV positive serology

7. Evidence of active Hepatitis B, or Hepatitis C as determined by serology or PCR
8. Pregnancy, as indicated by a positive serum or urine human chorionic gonadotrophin (HCG) test, or lactation
9. Active malignancy other than that for which the UCB transplant is being performed within 12 months of enrollment. Fully resected cutaneous squamous cell or basal cell carcinoma or cervical carcinoma in situ within 12 months of enrollment will be permitted.
10. Evidence of uncontrolled bacterial, fungal or viral infections or severe concomitant diseases, [redacted]
11. Patients with presence of leukemic blasts in the central nervous system (CNS)
12. Patients with an 8/8 allele level HLA-matched and readily available related or unrelated donor (whose stem cells can be collected in a timely manner without jeopardizing recipient outcome). Patients who have haploidentical related donors or syngeneic donors will not be excluded
13. Prior allogeneic hematopoietic stem cell transplant
14. Allergy to bovine products, gentamicin, or to any other product that may interfere with the treatment
15. Psychologically incapable [redacted]
16. Enrolled in another interventional clinical trial or received an investigational treatment within 30 days prior to the anticipated date of randomization, [redacted]

4.6 Treatments

4.6.1 Treatments Administered

NiCord® is a cryopreserved cell-based product of allogeneic, ex vivo expanded, umbilical cord blood-derived, hematopoietic $CD34^+$ progenitor cells (NiCord® CF) and the non-expanded cell fraction of the same cord blood unit (NiCord® NF) consisting of mature myeloid and lymphoid cells.

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

Prior to transplant, all patients will be treated with a conditioning regimen that is selected by the site from the protocol's three options, and patients will be administered GHVD prophylaxis medications pre- and post-transplant.

4.7 Method of Assigning Patients to Treatment Groups

Enrolled patients will be assigned to the NiCord® or unmanipulated UCB arm based on minimization. This method will be used because of the limited number of patients, the potentially large number of participating centers, and the existence of several known important factors. Minimization controls the balance of prognostic factors across the treatment groups more tightly than does stratified block randomization. A version of minimization will be used that includes assignment to the "optimal" group with a probability of 0.9, where "optimal" refers to the assignment that best balances the treatment groups with respect to the minimization factors.

The minimization algorithm will be based on four factors:

1. Treatment center
   - [redacted]
2. Disease risk group
   - [redacted]
3. Age group
   - [redacted]
4. Intent to perform single or double cord blood transplant
   - [redacted]

Although age, disease/stage, and intent to perform single or double cord blood transplant may not strongly influence the primary endpoint (time to neutrophil engraftment), there is an advantage in keeping them well balanced across the treatment groups for the purposes of comparing other important endpoints, including overall mortality and non-relapse mortality.

To implement the minimization randomization, a measure of treatment group imbalance will be calculated for each new patient. For a given patient, the algorithm will compare the numbers of patients previously assigned to NiCord® at the same levels of the four factors as the current patient to the numbers of patients on unmanipulated UCB at the same levels of the four factors as the current patient.

That is,

- If nNicord< nUCB then assign to NiCord® with 90% probability.
- If nNicord= nUCB then assign to NiCord® with 50% probability.
- If nNicord> nUCB then assign to NiCord® with 10% probability.

where

- nNicord= count of those assigned to NiCord® in this patient's disease risk group
  + count of those assigned to NiCord® in this patient's age group
  + count of those assigned to NiCord® in this patient's Center

+ count of those assigned to NiCord® where the intent was to perform a transplant of the same type (single/double) as this patient's

- nUCB= count of those assigned to unmanipulated UCB in this patient's disease risk group

  + count of those assigned to unmanipulated UCB in this patient's age group

  + count of those assigned to unmanipulated UCB in this patient's Center

  + count of those assigned to unmanipulated UCB where the site intended to perform a transplant of the same type (single/double) as this patient's

After the site completes the enrollment screening form in [redacted] and the patient meets all of the inclusion criteria and none of the exclusion criteria, and the site enters information regarding the patient's disease risk group, age, and whether single or double cord blood transplant would be done, then the nNicord and nUCB scores are calculated by within the [redacted] system. Depending on which score is lower, the system will choose from the appropriate list of treatment assignments that are based on random uniform numbers. Three lists will be used, so that one list will have NiCord® treatment assignments if the random number is less than or equal to 0.9, one will have unmanipulated UCB treatment if the random number is greater than 0.5, and one will have NiCord® treatment if the random number is less than or equal to 0.1.

If a site incorrectly enters data for one or more of the minimization factors, and if it has been verified that change needs to be made to a minimization factor, a manual data change will be implemented. The change in the factor will be incorporated into the analyses as described in section 8.5.1.1.2.

5. SAMPLE SIZE CONSIDERATIONS

The primary endpoint is time from transplant to neutrophil engraftment and the analysis will be based on the Mann Whitney test statistic if there are no losses to follow-up before Day 42.

[redacted]

[redacted]

The primary hypothesis is:

H_0: there no difference in time to neutrophil engraftment by treatment group
H_A: there is a difference in time to neutrophil engraftment by treatment group

[redacted]

The protocol targets an [redacted] sample size of 120 patients for the following reasons:

a) to provide an extensive safety database for NiCord®

b) to determine whether a difference exists between the two groups for the primary endpoint and ensure that the statistical significance [redacted]

c) [redacted]

With the addition of a 12-17y age group in December 2017, the statistical power was recalculated, [redacted] **A cap on the number of 12-17y olds to be entered into the trial will be set at 30.**

6. GENERAL STATISTICAL CONSIDERATIONS

6.1 General Principles

Unless otherwise specified, all continuous variables will be summarized using the following statistics: n, mean, standard deviation (and/or median and quartiles or interquartile range (IQR), as appropriate), maximum, minimum. All categorical variables will be summarized using the frequency and percentages of observed levels. Statistics will be based on non-missing sample sizes unless methods for analyzing the missing data have been pre-specified. Summary tables will be structured with a column or row for NiCord® and for Control (unmanipulated UCB) patients.

If a patient is lost to follow up, the day of loss to follow up is defined as the day after the date of last study contact.

6.2 Timing of Analyses

The primary analysis and related neutrophil engraftment analyses will be conducted after all patients entered have completed follow-up necessary to evaluate the primary endpoint.

[redacted].

6.3 Analysis Populations

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

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

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

As treated (AT) population includes all patients randomized who received a cord blood transplant on or before 90 days post randomization, grouped by treatment actually performed. Patients who received a cord blood transplant that was out of specifications are not included in the AT population. Analysis of the AT population is for supportive purposes.

ANC engrafted population (AEP) includes all patients who received a cord blood transplant on or before 90 days post randomization and achieved neutrophil engraftment by Day 42 with subsequent chimerism; analysis is focused on the treatment actually performed. Analysis of the AEP is for supportive purposes.

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

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

A cord blood transplant includes a NiCord® transplant or a transplant from any cord blood unit, including unit(s) that differed from the unit(s) intended for transplant at the time of randomization. All analysis

populations will include the patients as defined, even if the patients are later determined to have not met the eligibility criteria.

6.4 Covariates and Subgroups

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

1. Disease risk group as defined in section 4.7 (low, moderate and high/very high risk).
2. Age group [redacted].
3. Intention to perform single versus double CB transplant
4. Disease (ALL, AML, CML, MDS, Lymphoma, and other)
5. HCT-specific co-morbidity index (0, 1-2, 3+)
6. Gender (male, female)
7. Race/Ethnicity (e.g., White/Hispanic or Latino, White/Not Hispanic or Latino, Black/Hispanic or Latino, Black/Not Hispanic or Latino, Asian/Hispanic or Latino, Asian/Not Hispanic or Latino, etc.)
8. Geographical region

The subgroup categories for race/ethnicity and geographical region will be added after 70% of the patients have been enrolled in the study.

[redacted]

6.5 Missing Data

If data for transplant or the primary or secondary endpoints are missing, the primary analyses of these endpoints will be adjusted for the missing data.

[redacted]

[redacted]

[redacted]

6.6 Interim Analyses and Data Monitoring

In addition, periodic data review will be conducted by the Data Monitoring Committee (DMC). Policies and composition of the DMC are described in the DMC Charter. Baseline characteristics, engraftment, infection, hospitalization, survival, relapse, GvHD, graft failure, toxicity, adverse events, and immune reconstitution will be summarized and reported to the DMC at each interim data review. *Additional outcomes or data may be provided to the DMC at their request.*

[redacted]. No formal hypothesis testing of endpoints will be performed unless specifically requested by a majority of the DMC.

[redacted] The procedures for monitoring these data will be specified in the protocol or DMC charter.

6.7 Multicenter Studies

It is anticipated that up to [redacted] sites will participate in this study, and site is one of the factors for minimization randomization. Site will not be included as an adjustment factor in the analyses but patient disposition, accrual, demographics, and baseline characteristics will be reported combined and separately by site to assess unanticipated site differences.

6.8 Multiple Comparisons/Multiplicity

All statistical tests will be conducted against a two-sided alternative hypothesis, employing a significance level of 0.05. For the secondary endpoints, p-values will be adjusted for multiple testing using Hommel's method that controls the family-wise error (FWE) rate. [1]

[redacted]

7. Study Patients

7.1 Patient Disposition

Patient disposition will be described in tables by site and randomized treatment group. A CONSORT diagram will describe the patient disposition and loss to follow-up through the course of the study.

7.2 Protocol Deviations

Patient-specific and site-specific protocol deviations will be described. Listings will include a description of the deviation and any action taken as a result.

8. Efficacy evaluation

8.1 Demographic and other baseline characteristics

Demographics and relevant baseline information (e.g., medical history, HCT-specific co-morbidity index, center, disease, disease risk group, intended treatment (single or double), weight) will be presented and summarized with appropriate descriptive statistics by site and overall. The comparability of the baseline factors between the treatment groups will be assessed. These summaries will be based on the ITT population.

Descriptive statistics will be provided for cell doses, based on the ITT and AT population.

8.2 Concurrent illnesses and medical conditions

Hospitalizations and infections will be analyzed as secondary endpoints.

8.3 Prior and concurrent medications

No formal analyses or summaries of prior and concurrent medications will be completed by transplant group.

8.4 Measurements of treatment compliance

Deviations from the conditioning regimen, infusion support, supportive cytokine therapy, transplant, and GvHD prophylaxis will be described based on the ITT population.

[redacted]

8.5 Efficacy Analyses

The endpoints for efficacy include the primary efficacy endpoint, secondary endpoints, tertiary, and exploratory endpoints.

General note on statistical testing and on confidence intervals for estimated parameters
Because minimization is used for the treatment allocation method, we will employ re-randomization tests throughout (described below), for any intent-to-treat analysis to test for differences between the NiCord® and Control (unmanipulated UCB) groups.

[redacted]

[redacted]

Re-randomization confidence interval

(i) Introduction:

[redacted]

(ii) General method:

[redacted]

(iii) Application to the primary endpoint:

[redacted]

(iv) Application to the secondary endpoint, probability of grade 2-3 bacterial/fungal infection by 100 days post-transplant:

[redacted]

(v) Application to the other secondary endpoints:

[redacted]

(vi) Validation of the proposed method:

[redacted]

8.5.1 Primary Efficacy Analysis

8.5.1.1 Time to neutrophil engraftment

Tables will be included to provide descriptive statistics for time to transplant from randomization, and to provide reasons for not receiving a transplant by day 90 (if applicable).

For the primary analysis of the primary endpoint of time from transplant to neutrophil engraftment (ANC engraftment with chimerism), the following data will be used for time to neutrophil engraftment:

Primary Endpoint Outcome	Assigned analysis day
Met definition for neutrophil engraftment[1] on or before Day 42	First day of 3 different days of consecutive measurements of ANC≥0.5

Primary Endpoint Outcome	Assigned analysis day
	x 10^9/L with donor chimerism $\leq$ 10% of host cells documented as defined
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[1] ANC recovery must occur on or before 42 days post transplant and donor chimerism must occur any time on or after the day of engraftment up to the earlier of day 100 post-transplant, date of relapse, date of secondary graft failure, or date of death.

[2] [redacted]

[3] [redacted]

8.5.1.1.1 Test Statistic

We will use the Mann-Whitney statistic, calculated on the engraftment times as defined in the table in Section 8.5.1.1. That table was formed by defining as competing risks the following events: (i) failure to receive a transplant within 90 days following randomization (counted as a competing risk event at day 0), (ii) relapse, (iii) death, and (iv) second transplant.

[redacted]

8.5.1.1.2 Re-randomization Distribution

[redacted]

8.5.1.1.3 Confidence Intervals for P* and for the difference in median times to engraftment

[redacted]

[redacted]

8.5.1.1.4 Missing Data for the Primary Endpoint

No Loss to Follow-up Prior to Day 42

[redacted]

Sensitivity Analysis If No Loss to Follow-up Prior to Day 42

[redacted]

Loss to Follow-up Prior to Day 42

[redacted]

[redacted]

Sensitivity analysis for loss to follow-up

[redacted]

8.5.1.1.5 Cumulative Incidence

[redacted]

8.5.1.2 Secondary analyses of time to neutrophil engraftment

[redacted]

[redacted]

8.5.1.3 Clarification with regard to relapse before transplant

[redacted]

[redacted]

8.5.2 Secondary Efficacy Analyses

8.5.2.1 Incidence of grade 2/3 bacterial or invasive fungal infections by 100 days following transplantation

[redacted]

8.5.2.1.1 Missing Data

[redacted]

[redacted]

Sensitivity analysis

[redacted]

8.5.2.1.2 Secondary analyses

[redacted]

[redacted]

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

[redacted]

8.5.2.2.1 Missing Data

[redacted]

[redacted]

Sensitivity Analysis

[redacted]

8.5.2.2.2 Secondary Analyses

[redacted]

8.5.2.3 Platelet engraftment by 42 days following transplantation

[redacted]

[redacted]

8.5.2.3.1 Missing Data

[redacted]

Sensitivity Analysis

[redacted]

8.5.2.3.2 Secondary Analyses

[redacted]

8.5.3 Tertiary Endpoint

8.5.3.1 Non-relapse mortality by Day 210 post randomization

The primary analysis will be performed on the ITT population.

[redacted]

8.5.3.1.1 Missing Data

[redacted]

Sensitivity Analysis

[redacted]

8.5.3.1.2 Secondary Analyses – Non-relapse mortality by Day 180 Post-Transplant

[redacted]

8.5.4 Exploratory Efficacy Analyses

8.5.4.1 Neutrophil engraftment by 16 days following transplantation

This analysis will be conducted on the ITT population.

[redacted]

8.5.4.2 Time from transplantation to platelet engraftment

[redacted]

8.5.4.3 Duration of primary hospitalization

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

[redacted]

[redacted]

8.5.4.4 Non-relapse mortality by 130 days following randomization

The primary analysis will be performed on the ITT population.

[redacted]

8.5.4.5 Non-relapse mortality by 15 months following randomization

[redacted]

[redacted]

8.5.4.6 Overall survival by 210 days following randomization

The primary analysis will be performed on the ITT population.

[redacted]

8.5.4.7 Overall survival by 15 months following randomization

[redacted]

8.5.4.8 Disease-free survival by 15 months following randomization

This analysis will be performed on the ITT population.

[redacted]

[redacted]

8.5.4.9 Neutrophil engraftment by 42 days following transplantation

The primary analysis will be conducted on the ITT population.

[redacted]

[redacted]

8.5.4.10 Acute GvHD grade II-IV by 100 days following transplantation

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

[redacted]

8.5.4.11 Acute GvHD grade III-IV by 100 days following transplantation

[redacted]

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

[redacted]

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

[redacted]

8.5.4.14 Secondary graft failure by 1 year following transplantation

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

[redacted]

[redacted]

8.5.4.15 Grade 3 viral infections by 180 days following transplantation

[redacted]

8.5.4.16 Grade 3 viral infections by one year following transplantation

[redacted]

8.5.4.17 Relapse by 15 months following randomization

This analysis will be conducted on the ITT population.

[redacted]

8.5.4.18 Relapse mortality by 15 months following randomization

This analysis will be conducted on the ITT population.

[redacted]

8.5.4.19 Immune reconstitution at 28, 70, 100, 180, and 365 days following transplantation

[redacted]

8.5.4.20 Health-related quality of life

Patient-reported health-related quality of life outcomes will be assessed on the ITT population using two standardized measures including the FACT BMT and the EuroQol EQ-5D.

[redacted]

[redacted]

8.5.5 Sub group analyses

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

1. Disease risk group (low, moderate and high/very high risk).
2. Age group [redacted].
3. Intention to perform single vs. double CB transplant
4. Disease (ALL, AML, CML, MDS, Lymphoma, and other)
5. HCT-specific co-morbidity index (0, 1-2, 3+)
6. Gender (male, female)
7. Race/ethnicity (e.g., White/Hispanic or Latino, White/Not Hispanic or Latino, Black/Hispanic or Latino, Black/Not Hispanic or Latino, Asian/Hispanic or Latino, Asian/Not Hispanic or Latino, etc.)
8. Geographical region

[redacted]

9. Safety Monitoring

The DMC will be provided monthly data [redacted]

10. Safety Evaluation

The safety evaluations will be conducted on the safety population (SP).

The analysis of adverse events, serious adverse events, and toxicities will be primarily descriptive. [redacted].

10.1 Solicited Adverse Events and Symptoms

10.1.1 Infusion Reactions

Infusion reactions will be described by nature and severity. The proportion of patients experiencing any infusion reaction and severe (Grade 3-5) infusion reactions at any time from start of infusion to 24 hours post infusion [redacted]

A table will be provided to summarize the maximum severity of infusion reaction reported per patient. The table will show maximum severity levels and the number of patients and the percentage of patients in that treatment group with that maximum severity level.

10.1.2 Infections

All grade 2 or 3 infections post randomization will be reported on an infection form. Grade 2-3 bacterial infections or invasive fungal infections will be analyzed as a secondary endpoint. Grade 3 viral infections will be analyzed as an exploratory endpoint.

10.1.3 Graft versus Host Disease

All AEs associated with GvHD will be reported on GvHD forms and used to calculate GvHD grade. GvHD will be analyzed as an exploratory endpoint. Some of the GvHD AEs may also be reported on the Serious Adverse Event form; these will be included in the safety evaluation analyses.

10.1.4 Common Events Post Transplant

Common events post transplant will be reported on the Adverse Event Form, Non Serious Adverse Event Log, and a Transplant Toxicity Summary form. Common events will include those listed in protocol Appendix D, plus additional events in a supplemental list. The summary of common events post transplant will not include symptoms from the GvHD forms unless they are also reported on the Adverse Event Forms, Adverse Event Logs, or Toxicity forms.

[redacted]

10.2 Other Adverse Events

- Non-serious uncommon events post transplant will be reported on an Adverse Event Log.
- Serious Adverse Events post signing of consent will be reported on SAE forms set until at least 30 days post transplant and then up until the earlier of end of patient's final study visit, date of post-transplant relapse, or date of graft failure. Following date of post-transplant relapse or graft failure only SAEs resulting in death or with suspected causal relationship to the infused product will be reported. However, SAEs must be reported on SAE summary forms set for at least 30 days post transplant even if post-transplant relapse or graft failure occur prior to that time point.
- For patients who do not undergo transplant within 90 days following randomization and are enrolled in the post-randomization follow-up, only SAEs resulting in death will be reported after Day 90. Hospital admission reporting is due from time of the start of the conditioning regimen until end of study; this is reported on the Hospital Admission Summary form.

Uncommon adverse events will be described by time period (Day 0-42, Day 42-365), MedDRA System Organ Class (SOC), Preferred Term (PT), severity, seriousness, and relationship to study product.

[redacted]

10.3 Grade 3-5 and/or Serious Adverse Events during or post transplant

Both common and uncommon severe grade 3-5 and/or serious adverse events will be described overall and pre-Day 42 and post-Day 42.

[redacted]

A separate table will be provided to summarize the number of patients within each treatment group reporting serious adverse events by SOC/PT combination for events reported Day 0-42 and post Day 42.

10.4 Treatment Emergent Adverse Events

For this study, a treatment emergent adverse event is defined as an event that emerges during or after infusion having been absent pre-infusion, or worsens relative to the pre-infusion event. For events reported on the toxicity form, any event marked not clinically significant is considered as a grade 0 event for the purpose of the treatment emergent analyses. All grade 1/2 events in categories in which the clinically significance question is present are analyzed as not clinically significant. When the severity of an event on the toxicity form is missing or indicated as not evaluated at a visit, it is ignored when considering whether an event has worsened.

An overview table of treatment emergent adverse events will be shown. Additionally, tables by treatment group will summarize the number and percent of patients with treatment emergent events. In these tables, the number of people reporting an event within each SOC/PT combination will be counted for:

- Grade 3-5 treatment emergent events in any SOC/PT combination that are related to study product
- Treatment emergent events in any SOC/PT combination that are related to study product and that are reported as related to study product in at least 3% of the safety population
- Grade 3-5 treatment emergent events in any SOC/PT combination that are reported in at least 3% of the safety population

10.5 Maximum Severity of Adverse Events

A table will be provided by treatment group that shows, on a patient level, the maximum severity of each SOC/PT combination reported for any adverse event or toxicity during the Day 0 – Day 42 and post Day 42 time periods. Similar tables restricted to serious adverse events will be provided.

10.6 Deaths

Primary cause of death will be summarized by treatment group.

[redacted]

10.7 Pregnancies

Pregnancies on study will be followed until outcome and described.

10.8 Clinical Laboratory Evaluations

Clinical laboratory evaluations will not be analyzed per se, however, clinically significant abnormal values will be reported as adverse events and analyzed as referenced above. A separate table summarizing the number of patients reporting laboratory adverse events by SOC and PT will be provided by treatment group. Descriptive statistics for serum chemistry values and hepatic enzymes will also be provided by treatment group. All post-randomization assessments will be used.

10.9 Vital Signs and Physical Evaluations

Vital sign and physical examination data including height and weight will not be analyzed for treatment group differences. A table summarizing the number of patients reporting vital sign adverse events by SOC and PT will be provided by treatment group. Descriptive statistics for vital signs will also be provided by treatment group. All post-randomization assessments will be used.

10.10 Concomitant Medications

No formal statistical tests will be conducted on concomitant medication use. A separate analysis will be conducted on resource utilization, including some concomitant medications. Details will be provided in a separate document.

Listings for conditioning medications, GvHD prophylaxis medications, GvHD treatment medications, infection treatment medications, and concomitant medications will be provided.

11. Pharmacokinetics

No pharmacokinetics analyses are planned in this study.

12. Other Analyses

The planned analyses are described above.

[redacted]

13. Technical Details

SAS® version 9.4 or higher software and R version 3.1 or higher will be used for statistical analysis and data reporting of the information collected in this study.

14. Summary of Changes in the Conduct of the Study or Planned Analyses

This section will be updated as necessary at the time of analysis or amendment to the SAP. Deviations from the final statistical analysis plan will be reported in the final study report.

Changes that do not affect the analyses or are not changes in the conduct of the study are not summarized.

Summary of SAP Changes in Conduct of Study or Planned Analyses
(Version 1.0 to Version 5.0)

Section Updated (Numbering based on latest SAP version)	**Summary of Update**
[redacted]	• [redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Section Updated (Numbering based on latest SAP version)	**Summary of Update**
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
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[redacted]	[redacted]

Section Updated (Numbering based on latest SAP version)	Summary of Update
[redacted]	[redacted]
[redacted]	[redacted]
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[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	• [redacted]
[redacted]	[redacted]

15. Listing of Tables, Figures, and Data Listings

The appendix contains potential table shells, figure outlines, and data listings. Titles and structures of the TFL are intended to be descriptive only and not restrict designation of the publication table titles and structures. Further alternate data presentations may be considered as requested by investigators or for publication. Additional data listings, including listings for any of the tables in the analysis, may also be provided. A listing for any table may also provide additional patient details (e.g., age, gender, diagnosis).

16. References

[1]Hommel G. A stagewise rejective multiple test procedure based on a modified Bonferroni test. Biometrika 1988; 75(2):383-386.

CHANGES RELATED TO COVID-19 PUBLIC HEALTH EMERGENCY

Version 1.0

31AUG2020

Executive Summary

- This addendum was incorporated to the SAP to document the assessment of the impact of the COVID-19 Public Health Emergency on the collection, analysis and interpretation of study GC P#05.01.020. The chapter was incorporated after the primary endpoint was analyzed and reported, and prior to analysis and review of any other study data, including the secondary and tertiary endpoints.
- The potential impact was assessed by collecting and documenting all relevant changes that occurred in patient treatment, surveillance, and care. These changes will be reported and summarized in the Clinical Study Report (CSR). A detailed survey was conducted with the study sites to assess specifically any practice changes that may have impacted patient follow up or care for all study patients under the period of COVID-19 effect.
- The interpretation of the information collected concludes that no specific change to the analysis of the study endpoints is currently warranted.

Data Collection and Monitoring During the COVID-19 Public Health Emergency

In response to the COVID-19 public health emergency occurring during the follow-up period of protocol GC P#05.01.020, several steps were undertaken to address any potential changes in data collection and monitoring that were required.

Protocol Conduct Memorandum

The trial sponsor distributed a memorandum on 24MAR2020 regarding “Protocol conduct during the COVID-19 pandemic” to all active sites. [redacted]

Reporting Requirements

The electronic case report forms (eCRFs) were modified to collect information about whether alternative methods were used, and to consistently track those assessments that were missed due to the COVID-19 pandemic. The Status Summary form was to be collected at all scheduled visits from Day 42 to Day 365 post transplant and at Month 15 post randomization for transplanted patients and at all scheduled visits from Day 90 to Month 15 post randomization for non-transplanted patients; participants who were not transplanted by Day 90 were provided with the applicable subset of the questions. Data were captured retrospectively beginning with forms version 11.01 (released on 20MAR2020) or higher and on all new Status Summary eCRFs entered after 20MAR2020. The questions include:

- Was the patient seen at the original transplant center for the [XX] study visit? (Yes/No)
  If the patient was physically seen in-person at the original transplant center, select "Yes."

- Was the site's ability to perform any of the patient's study visit assessments affected by the restrictions implemented on patient visit/site staff/resources due to the COVID-19 pandemic? (Yes/No)
- Were any required tests performed at a laboratory not listed on the FDA 1572 Form? (Yes/No)
    - [redacted]
- Was the patient assessed by non-study team physician (or physician extender)? (Yes/No)
    - Acute and/or chronic GvHD (Yes/No)
    - Physical examination (Yes/No)
- Were additional alternative methods (e.g. telemedicine) used to collect data at this study visit? (Yes/No)
    - If yes, specify the additional alternative methods of data collection.

In addition, the following question was added to all Hospital Admission Summary eCRFs entered after November 27, 2019:

- Was the patient's date of discharge delayed or accelerated due to the COVID-19 pandemic? If yes, provide an explanation.

The study report will include data listings of these responses, including a list of patient visits conducted with a remote assessment, listings of hospital durations, missing forms exceptions, and patient visits, and protocol deviations related to the COVID-19 public health emergency.

The sponsor reviewed and allowed the implementation of alternative methods for assessing patients if it was determined that the alternative methods did not materially change the protocol and allowed for continuing the study without impacting the integrity or quality of the data. The sponsor also allowed for the study data to be remotely monitored through form uploads to the electronic data collection system and through remote viewing of the electronic medical record when permitted by the clinical site and by the local regulations. Remote monitoring of the patients medical record was done through secure systems and in accordance with Good Clinical Practice (GCP), the Declaration of Helsinki, the provisions of the International Conference on Harmonization (ICH) Guidelines and all local applicable privacy laws and regulations.

Sites Survey

In addition to the data collected through the eCRF, the study monitors surveyed each site to assess changes in patient management, including hospitalization/discharge policies and supportive care, and

any changes to patient follow-up and the ability to detect outcome events. Sites were surveyed to determine whether site practice changes affected study outcomes. The survey questions were designed to capture any and all procedural changes related to the pandemic regardless of their direct relevance to the study endpoints. This was meant to ensure that potentially impactful changes would not be missed because of a misunderstanding by site staff on what might be considered relevant. These questions included:

[redacted]

Assessment of the Potential Impact of COVID-19 Public Health Emergency on Study Data

The follow-up time extends either 42 days or 100 days post-transplant for the evaluation of the secondary endpoints and extends 210 days post randomization (which corresponds to minimum of 180 days post transplant) for evaluation of the tertiary endpoint. Table 1 summarizes the number and percent of patients who remained under evaluation for the secondary or tertiary endpoints during the period when COVID-19 practices had taken effect. According to the site survey responses, COVID-19 related practice changes were implemented during March 2020 in most sites. Therefore, March 15, 2020 was selected as a pivot-point for follow-up conducted before or during COVID-19 practice changes.

Table 1. Number of Randomized Patients with Evaluation Period Completed before March 15, 2020

		Randomized to NiCord (N=62)		**Randomized to Unmanipulated UCB (N=63)**	
Endpoint	**Criteria Met before March 15, 2020**	**N**	**%**	**N**	**%**
First grade 2/3 bacterial or grade 3 fungal infection by Day 100 post-transplant					

		Randomized to NiCord (N=62)		Randomized to Unmanipulated UCB (N=63)	
Endpoint	**Criteria Met before March 15, 2020**	**N**	**%**	**N**	**%**
Number of days alive and out of hospital in the first 100 days post-transplant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platelet engraftment by Day 42 post-transplant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-relapse mortality by Day 210 post-randomization	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

As shown in Table 1, approximately [redacted] of the study patients had completed their evaluation period for the secondary endpoints. Thus, only a limited number of study patients were at risk for any potential impact of COVID-19 on the evaluation of the study secondary endpoints. In addition, these patients were similarly distributed between the two study arms.

[redacted] sites did not have any patients in follow-up during the COVID-19 public health emergency. [redacted] were sent the survey and [redacted] sites responded, representing [redacted] patients potentially affected by the COVID-19 public health emergency. Written responses were followed by a conversation to clarify the responses as needed. Site responses did not indicate any changes that would have impacted the endpoints of the study. Changes to standard practice included:

- addition of COVID-19 specific testing requirements and patient education
- use of telemedicine, home visits and local labs to limit potential exposure
- visitor limitations and masking requirements
- one site indicated some delays in getting lab results
- completion of Health Related Quality of Life Questionnaires at home

There was no indication of any changes in:

- the likelihood or length of hospitalization
- frequency of non-COVID infection surveillance
- threshold to initiate infection work up and testing for respiratory symptoms
- antimicrobial prophylaxis or treatment
- platelet transfusion policies
- frequency or timing of disease assessments
- frequency of lab testing

A detailed summary of the changes in practices will be provided in the CSR.

Based on the survey responses and the data in Table 1, the study sponsor and principal study statistician determined that the planned analyses for the study endpoints do not need to be changed from the pre-determined plan described in the study's statistical analysis plan (SAP).