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

Published: 14-12-2016
Last updated: 17-01-2025

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

Ethical review	Approved WMO
Status	Completed
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON49347

Source
ToetsingOnline

Brief title
GC P#05.01.020

Condition

- Leukaemias

Synonym
cancer in white blood cells, leukemia

Research involving
Human

Sponsors and support

Primary sponsor: Gamida Cell ltd.
Source(s) of monetary or material Support: industry - Gamida Cell Ltd.

Intervention

Keyword: hem. malignancies, Stem/Progenitor Cells transplant, umbilical cord blood derived

Outcome measures

Primary outcome

To assess the time to neutrophil engraftment following transplantation.

Neutrophil engraftment is defined as achieving an absolute neutrophil count

(ANC) >= 0.5 x 109/L on 3 consecutive measurements on different days with

subsequent donor chimerism (<=10% host cells by peripheral blood chimerism or

bone marrow chimerism if peripheral blood chimerism is not available). The day

of neutrophil engraftment is designated as the first of the 3 consecutive

measurements and must occur on or before 42 days post transplant (and also

prior to infusion of any additional stem cell product)

Secondary outcome

To Assess the following endpoints.

Secondary Endpoints:

* Incidence of grade 2/3 bacterial or invasive fungal infections by 100 days

following transplantation

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

* Platelet engraftment by 42 days following transplantation

*

Tertiary Endpoints:

* Non-relapse mortality by 210 days following randomization

Exploratory Endpoints:

Neutrophil engraftment by 16 days following transplantation

* Time from transplantation to platelet engraftment

* Duration of primary hospitalization

Non-relapse mortality by 130 days and 15 months following randomization

* Overall survival at 210 days and 15 months following randomization

* Disease-free survival at 15 months following randomization

* Neutrophil engraftment by 42 days following transplantation

* Acute GvHD grade II-IV and III-IV by 100 days following transplantation

* Chronic GvHD (mild/moderate/severe) by 180 days and 1 year following transplantation

* Secondary graft failure by 1 year following transplantation

* Grade 3 viral infections by 180 days and 1 year following transplantation

* Safety and tolerability of NiCord® transplantation

* Relapse by 15 months following randomization

* Relapse mortality by 15 months following randomization

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

Supplemental immune reconstitution assessments at a central laboratory (optional)

Health-related quality of life

Long-term clinical outcomes up to 5 years following transplantation

(optional)

Study description

Background summary

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.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. 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. However, a major drawback of UCB is the low stem cell dose available for transplantation, compared to mobilized peripheral blood (PB) or bone marrow. This low stem cell dose can compromise the chances of engraftment and contributes to delayed kinetics of neutrophil and platelet recovery. The delay in graft function may negatively impact transplant outcome 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. Ex vivo expansion is still an experimental approach.

Study objective

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

Study design

Open-label, controlled, multicenter, Phase III, randomized study of transplantation of NiCord® versus unmanipulated cord blood in patients with hematological malignancies.
Patients who enroll in the optional long-term follow up sub-study will be followed for up to 5 years post-transplantation.

Intervention

NiCord® is a cryopreserved stem/progenitor cell-based product comprised of:
1) Ex vivo expanded, umbilical cord blood-derived hematopoietic CD34+ progenitor cells (NiCord® cultured fraction (CF))
2) The non-cultured cell fraction of the same CBU (NiCord® Non-cultured Fraction (NF)) consisting of mature myeloid and lymphoid cells.

Patients will be randomized to a transplantation with either NiCord or unmanipulated umbilical cord blood.

Study burden and risks

1. slow recovery of blood counts
2. Graft failure
3. GVHD
4. complications of umbilical cord blood infusion (chest tightness, hig/low BP and abnormal labtests may occur, less commonly, allergic reaction to the cord blood may occur. This can be treated with medications. Rarely, small clots in the cord blood can be transferred, resulting in shortness of breath that may require oxygen for a few hours.).
see ICF for more details
5. other: complications from central venous catheter insertion, Damage to the vital organs, Veno-occlusive disease, Serious infections, Relapse or progression of disease, sterility and future childbearing potential, Drug

interactions,
6.Transfusions might be required
7. Blood Drawing: pain, bleeding, burning, dizziness, fainting, or a bruise or an infection at the site where the needle was inserted to take the blood.
total amount of blood taken: 450 to 630ml. (standard care)

Several options exist for a stem cell donor for transplantation, but because each option has limitations, these patients still have an unmet medical need.

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

For ethical reasons, the study will only enroll patients who do not have an adequate suitably matched and readily available stem cell donor.

Contacts

Public
Gamida Cell ltd.

Nahum Hafzadi, Beit Ofer 5
Jerusalem 9548401
IL
Scientific
Gamida Cell ltd.

Nahum Hafzadi, Beit Ofer 5
Jerusalem 9548401
IL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. 12-65 years of age;2. Patients with one of the following hematological malignancies:
- Acute lymphoblastic leukemia (ALL) at one of the following stages:
a. High risk first complete morphologic remission (CR1),
b. Second or subsequent remission
- Acute myelogenous leukemia (AML) at one of the following stages:
a. First complete morphologic remission (CR1) that is NOT considered as favorable-risk.
b. Patients in CR1 with one or more of the favourable risk criteria but with additional high risk features may be considered eligible upon consultation with the study chairs.
c. Second or subsequent remission
- Chronic myelogenous leukemia (CML) at one of the following phases:
a. Chronic phase
b. Accelerated phase
c. Prior blast crisis (myeloid or lymphoid) currently in chronic phase or in complete morphologic or molecular remission
-CMMol or MDS/CMMol overlap with spleen size <13cm
-Myelodysplastic Syndrome (MDS) with history of one or more of the following:
International Prognostic Scoring System (IPSS) risk category of INT-1 or greater. MDS patients categorized as INT-1 on primary presentation must have life threatening neutropenia or thrombocytopenia.
Revised International Prognostic Scoring System (IPPS-R) risk category of intermediate or greater
- Biphenotypic/undifferentiated/Prolymphocytic/DC Leukemias and NK Cell Malignancies in first or subsequent CR, adult T-cell leukemia/lymphoma in first or subsequent CR
- Lymphoma, meeting one or more of the following criteria:
Burkitt's lymphoma in second or subsequent CR
Or High risk lymphomas in first CR, including enteropathy-associated T cell lymphoma and hepatosplenic gammadeltaT cell lymphoma
Or Chemotherapy-sensitive (at least stable disease) lymphomas that have failed at least 1 prior regimen of multi-agent chemotherapy and are not candidates for an autologous transplant. (Patients with CLL are not eligible regardless of disease status);3. CBU criteria as described above.;4. Patients who will be starting conditioning prior to NiCord release for infusion (i.e. NiCord arrival on site in adequate condition) must have an additional partially HLA-matched CBU reserved as a backup to the NiCord arm in case of production failure. The backup CBU must be HLA-matched at 4-6/6 HLA class I (HLA-A & HLA-B, low resolution) and II (HLA-DRB1, high resolution) loci with the patient.
A second backup CBU is recommended to be added in the below cases:
- if the backup CBU is HLA-matched at 5-or 6/6, and contains a pre-cryopreserved (post processing) total nucleated cell dose of <2.5x107 TNC/kg, OR a pre-cryopreserved (post

processing) CD34+ cell dose of <1.2 x105 CD34+ cells/kg.
- if the backup CBU is HLA-matched at 4/6, and contains a pre-cryopreserved (post processing) total nucleated cell dose of <3.5x107 TNC/kg, OR a pre-cryopreserved (post processing) CD34+ cell dose of <1.7 x105 CD34+ cells/kg.
In case of two backup CBUs, the second backup CBUs must also be HLA-matched at 4-6/6 HLA class I (HLA-A&HLA-B, low resolution) and II (HLA-DRB1, high resolution) loci with the patient. The backup CBUs are recommended to have a combined pre-cryopreserved (post processing) total nucleated cell dose of at least 3x107 TNC/kg.;5. Patient*s Performance score >=70% by Karnofsky or Lansky;6. Patient has sufficient physiologic reserves including:
a. Cardiac: Left ventricular ejection fraction (LVEF) of >=40% by echocardiogram, radionuclide scan or cardiac MRI, or Left ventricular shortening fraction >= 29%
b. Pulmonary function tests (prior to treatment with bronchodilators) demonstrating FVC and FEV1 of >50% of predicted for age and cDLCO > 50% of predicted for patients in whom pulmonary function testing can be performed (If PFT testing included the use of bronchodilators, then the baseline results during testing prior to the administration of any medications should be used when determining eligibility)
c. Renal: Creatinine clearance test (by Cockcroft-Gault equation) >=60 mL/min
d. Hepatic: Serum Bilirubin < 2.0 mg/dl; Hepatic transaminases (ALT and AST) < 3 x upper limit of normal range;7. Females of childbearing potential, defined as any female who has experienced menarche and is not postmenopausal (defined as not having a menstrual period for at least 24 months) or permanently sterilized (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy), agree to use an appropriate method of contraception from at least 7 days prior to conditioning regimen therapy until completion of follow-up procedures. An appropriate method of contraception is defined as one that results in a low failure rate (i.e., less than 1 percent per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine contraceptive devices (IUDs), true sexual abstinence (when this is in line with the preferred and usual lifestyle of the patient), or a vasectomized partner.;8. Patient (or legal guardian) signs the written informed consent.

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 (radiotherapy, intrathecal agents, hydroxyurea, tyrosine kinase inhibitors, hypomethylating agents, rituximab, , blinatumomab and lenalidomide are not considered chemotherapy);4. Persistent clinically significant toxicities that, in the investigator*s opinion, make the patient unsuitable for transplant;5. Evidence of donor specific anti-HLA antibodies to the selected treatment CBU #1 (MFI>3000 to HLA A, B, C, or DRB1);6. Evidence of HIV infection or HIV positive serology;7. Evidence of active Hepatitis B or Hepatitis C as determined by serology or PCR;8. Pregnancy, 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, which in the judgment of the Principal investigator indicate that the patient could not tolerate transplantation;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 of undergoing bone marrow transplant (BMT) with associated strict isolation or documented history of medical non-compliance and/or psychiatric illness and/or social situations that would limit compliance with study requirements;16. Enrolled in another interventional clinical trial or received an investigational treatment within 30 days prior to the anticipated date of randomization, unless documented approval obtained from Sponsor prior to randomization

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	28-11-2017
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cels allogenic

Ethics review

Approved WMO Date:	14-12-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-07-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-12-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-02-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-05-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-07-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-07-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	01-11-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-01-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-02-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-03-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-04-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-01-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-01-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-01-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	27-01-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-02-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-01-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-01-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-000704-28-NL

Register	ID
ClinicalTrials.gov	NCT02730299
CCMO	NL59195.000.16