A PHASE III TRIAL OF ALD-101 ADUVANT THERAPY of UNRELATED UMBILICAL CORD BLOOD TRANSPLANTATION (UCBT) IN PATIENTS WITH INBORN ERRORS OF METABOLISM

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Primary objective of this study is: To assess the efficacy of adjuvant therapy of ALD-101 in accelerating platelet engraftment in patients also receiving a standard unrelated UCBT for treatment of inborn errors of metabolismThe secondary objective...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metabolic and nutritional disorders congenital
Study type	Interventional

Summary

ID

NL-OMON32439

Source
ToetsingOnline

Brief title
UCBT-002

Condition

- Metabolic and nutritional disorders congenital

Synonym
genetic metabolic diseases, inborn errors of metabolism

Research involving
Human

Sponsors and support

Primary sponsor: Aldagen, Inc.
Source(s) of monetary or material Support: Aldagen;Inc (bedrijf)

Intervention

Keyword: Inborn errors of metabolism, Umbilical cord blood transplantation, Unrelated donor

Outcome measures

Primary outcome

Platelet Engraftment (50k): Platelet engraftment will be defined as the first

day that the patients has achieved a platelet count > 50,000/mm3 and is

platelet transfusion independent for a minimum of seven days and will be

required to have >90% donor chimerism.

Neutrophil Engraftment: Neutrophil engraftment is defined as achieving ANC >

500/mm3 for three consecutive measurements over three or more days by Day 42

and will be required to have >90% donor chimerism.

Secondary outcome

Infusional toxicity

Adverse events

Primary graft failure

Overall survival

Incidence of infection

Immune reconstitution

Acute graft-versus-host disease

Study description

Background summary

Umbilical cord blood is a good source of haematopoietic stem cells for patients who need a haematopoietic stem cell transplant but who are without a matched sibling or unrelated bone marrow donor. However, significant disadvantages of CBT compared to bone marrow transplantation are the relative delays in post-transplant platelet and neutrophil recovery. The delay in platelet engraftment is particularly pronounced and is managed by support with platelet transfusions, restriction of physical activities, and local measures to control bleeding when possible. Patients typically are neutropenic for a period of 3 to 4 weeks and are susceptible to potentially life-threatening bacterial and fungal infections during that period. These neutropenia-associated infections represent the major cause of death following cord blood transplant.

The hypothesis underlying this trial is that infusion of ALD-101 cells manufactured from umbilical cord blood administered 4-8 hours after a conventional UCBT will facilitate rapid, sustained hematopoietic engraftment in patients undergoing UCBT. This will result in accelerated restoration of normal levels of circulating platelets and neutrophils in patients receiving ALD-101 after a conventional UCB graft.

The current trial which started in the US is being expanded to Europe. Goal is to demonstrate efficacy and safety of ALD-101 in patients with inborn errors of metabolism who will undergo a umbilical cord blood transplant.

Study objective

Primary objective of this study is: To assess the efficacy of adjuvant therapy of ALD-101 in accelerating platelet engraftment in patients also receiving a standard unrelated UCBT for treatment of inborn errors of metabolism
The secondary objective of this study is: To assess the safety of adjuvant therapy of ALD-101 in infusional toxicity, adverse events, and primary graft failure. To assess the efficacy of ALD-101 in accelerating neutrophil engraftment
The exploratory objectives of this study are: To assess the improvement of 180-day survival To describe the clinical outcomes in these patients in terms of incidence of infection, incidence of acute GvHD, and restoration of immune function

Study design

Open label study

Intervention

An adjuvant infusion of ALD-101 4 to 8 hours following a standard cord blood transplant

Study burden and risks

The burden to the patient resulting from participation in this study is limited to one additional infusion of umbilical blood via a venous catheter the patient already as a result of the standard procedure.

No infusional toxicity or unexpected adverse reactions were noted in patients receiving ALDHbr cells in UCBT-001. It may however always happen dat unexpected, not previously reported adverse event occur. To date no serious, ALD-101 related adverse events have been reported but only adverse events related to the standard procedure.

First, ALD-101 adjuvant therapy potentially could delay engraftment because patients do not receive the full UCB unit. Rather, they receive the unmanipulated 80% fraction and then only the ALDHbr cell population derived from the 20% fraction as an adjuvant. The ALDHbr population is a small percentage of the 20% fraction. However, the 80% fraction alone must meet criteria for standard of care for minimally acceptable total cell dose of 2.5 X 10*7 cells. The efficacy data from the UCBT-001 trial suggests that this is not a significant risk. Patients receiving ALD-101 engrafted neutrophils and platelets at an accelerated rate compared to the COBLT historical control cohort. Indeed, this is the basis for the proposed UCBT-002 trial. Consequently, we assess this outcome to be a low risk to patients.

Second, infusing patients with ALD-101 raises the risk of infection from potential contamination during cell sorting or from impurities introduced during manufacturing. No increase in infection in the frequency of infection or other toxicological event was observed in the treated patients during the UCBT-001 trial. All cell products prepared during that trial passed release criteria that included sterility tests. The manufacturing process for ALD-101 has been simplified, and fewer in-process reagents and processing steps are involved. Existing manufacturing and quality control procedures have been effective in managing this risk to date.

Third, manufacturing reagents used to identify ALDHbr cells potentially could be transferred with the cells into patients and cause pathologic reactions. However, the sorting process involves efflux of all detectable reagents and reaction products as described below. Exposure to these reagents is the only difference between the cells in ALD-101 and the other cells in cryopreserved cord blood that are administered to patients at doses that are average 10,000 fold higher than the ALD-101 in this protocol. Preclinical studies explored the

effects of very high doses of the reagents used to detect ALDH in tissue culture and in animals in standard preclinical toxicology assays. In addition, high doses of the ALDH substrate were directly injected into dog hearts, and the animals were subsequently assayed by histological and electrophysiological methods for acute and chronic pathological effects. No adverse effects of the reagents were detected. It was demonstrated that ALDHbr cells manufactured from UCB rapidly efflux all BAA, the ALDH reaction product, detectable by cytofluorimetry within minutes of being incubated at room temperature. Because of this, the amount of reagent transferred to patients is very low. Calculations show that the maximum possible estimated dose of reagents administered to patients with cells in ALD-101 is 104 to 109 times lower than the doses used in the preclinical toxicology tests that showed no toxic effects of the reagents. Thus, the risk to patients from administered reagents is acceptably low.

Contacts

Public
Aldagen, Inc.

2810 Meridian Parkway, Suite 148
Durham, NC27713
Verenigde Staten
Scientific
Aldagen, Inc.

2810 Meridian Parkway, Suite 148
Durham, NC27713
Verenigde Staten

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)

Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Patients must have a confirmed diagnosis of inborn error of metabolism. Diagnosis to be confirmed by two appropriate tests (enzyme or mutation analysis) before study entry.
Patients must be < 16 years of age at the time of study enrollment.
Patients must be >= 5 kg in weight.
Patients must have a good performance status (Lansky >= 80%).
Patients must have adequate function of other organ systems.
Patients must have a minimum life expectancy of at least 6 months.
Patient must be determined to be a good candidate for a standard UCBT according to the investigator and standard eligibility work-up at the site.

Exclusion criteria

Patients that are HIV, Hepatitis B and/or Hepatitis C positive.
Patients that are concurrently involved in any other clinical study that affects engraftment or immune reconstitution (e.g., other hematopoietic growth factors).
Patients with uncontrolled infections.
Patients with prior allogeneic stem cell transplant with cytoreduction preparative therapy within 12 months of enrollment.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-06-2010

Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cels allogenic

Ethics review

Approved WMO Date:	10-11-2009
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-12-2009
Application type:	First submission
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	EUCTR2009-017026-39-NL
ClinicalTrials.gov	NCT00654433

Register	ID
CCMO	NL30416.000.09