A Prospective and Retrospective Data Collection Study to Evaluate Outcomes in males <= 17 years of age undergoing Allogeneic Hematopoietic Stem Cell Transplantation for the Treatment of Cerebral Adrenoleukodystrophy.

Published: 19-03-2015
Last updated: 21-04-2024

-Evaluate the safety and efficacy of allogeneic hematopoietic stem cell transplantation (allo-HSCT) in male subjects

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Neurological disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON47132

Source
ToetsingOnline

Brief title
ALD-103

Condition

- Neurological disorders congenital

Synonym
Adrenoleukodystrophy, bronze Schilder disease

Research involving
Human

Sponsors and support

Primary sponsor: bluebird bio
Source(s) of monetary or material Support: bluebird bio

Intervention

Keyword: adrenoleukodystrophy, cerebral, males <= 17 years of age, transplantation

Outcome measures

Primary outcome

Safety Endpoints

Assessed for all allo-HSC infusions (i.e. including successful and failed

all-HSCTs)

• Incidence of transplant-related mortality (TRM) as defined as death due to

any trans-plantation-related cause other than disease relapse, through 100 and

365 days post-allo-HSC infusion

• Incidence and timing of neutrophil engraftment

• Incidence and timing of platelet engraftment

• Incidence of engraftment failure or allograft rejection

• Incidence of primary donor-derived chimerism of >=50% by 100 days

post-allo-HSC infusion

• Frequency and severity of National Cancer Institute (NCI) Common Terminology

Criteria for Adverse Events (CTCAE) >=Grade 3 AEs, CTCAE >=Grade 3 infections,

and all SAEs (Note: non-clinically significant laboratory AEs [i.e. do not

require additional medical intervention] and hematological toxicities related

to conditioning medication for first 30 days after any allo-HSC infusion will

NOT be collected)

• Proportion of subjects who experience either >=Grade II acute GVHD or chronic GVHD (Note: acute GVHD graded on the Acute GVHD Grading Scale (I-IV); chronic GVHD as assessed by the Investigator)

• incidence of >=Grade 2 acute GVHD

• incidence of chronic GVHD

Efficacy Endpoints:

Assessed from baseline up to and including the M24 and M48 Visits following the most recent allo-HSC infusion (i.e. from successful allo-HSCT)

• Incidence of Major Functional Disabilities (MFDs); (defined as any of the following: loss of communication, cortical blindness, tube feeding, total incontinence, wheelchair dependence, or complete loss of voluntary movement)

• Change from Baseline in Loes score

• Change from Baseline in NFS

• Frequency and timing of resolution of gadolinium enhancement on MRI, if applicable

• MFD-free survival

• Overall survival

Secondary outcome

Exploratory Endpoints:

Assessed from Baseline up to and including the M24 and the M48 Visits of the most recent allo-HSC infusion, and up to day of engraftment failure or allograft rejection for subjects with failed allo-HSCT:

• IQ using the age-appropriate Wechsler test

• VLCFA levels in fasting serum

• Matrix metalloproteinases in cerebrospinal fluid,

• chitotriosidase in plasma and cerebrospinal fluid,

• overall QL score (PedsQL and UMN QL), including 30, 60 and 100 days post-allo-HSC infusion, and at the M6, M12, M24, M36 and M48 Visits

Study description

Background summary

X-Linked adrenoleukodystrophy (ALD) is a rare genetic disease caused by a defect in the breakdown of very long chain fatty acids (VLCFAs) in the peroxisome, and their resulting accumulation is associated with a cerebral inflammatory response that can lead to widespread demyelination. The incidence of ALD is approximately 1:20,000 males; cerebral ALD (CALD) develops in boys typically between 3 to 15 years of age, and represents approximately 30% to 35% of patients with ALD.
Transplantation of allogeneic hematopoietic stem cells (allo-HSCT) is the only effective therapy to date, and is capable of arresting disease progression in a substantial proportion of patients if performed at an early stage of brain demyelination. Although allo-HSCT can improve outcomes, it is associated with significant morbidity and mortality, particularly for patients who undergo unrelated or human leukocyte antigen (HLA)-mismatched allo-HSCT; a matched sibling donor is available for <= 30% of patients.
From 2009 through 2012, there were 20 to 24 allo-HSCTs performed on patients with CALD per year reported in the US, and the percentage of transplanted patients who had unrelated allo-HSCT donors consistently increased from 75% to 92% from 2008 to 2012.

bluebird bio is evaluating Lenti-D Drug Product to treat male subjects with CALD (<= 17 years of age at the time of parental/guardian consent and, where appropriate, subject assent) in Study ALD-102. Retrospective data collected on

both untreated and allo-HSCT-treated CALD subjects in Study ALD-101 informed the design of ALD-102 along with results from a clinical study using a similar lentiviral vector (Study TG04.06.01), and feedback from key opinion leaders and regulatory agencies. The clinical trial success criterion for Study ALD-102 is based on a comparison of its primary efficacy endpoint with data obtained on untreated subjects in Study ALD-101. Clinical data from allo-HSCT-treated subjects from Study ALD-101 will provide additional context, in particular for the evaluation of safety of Lenti-D Drug Product but also for efficacy as a supportive analysis.

Study ALD-103 was designed to collect data both prospectively (subjects who will undergo allo-HSCT during the study) and partially prospectively and retrospectively (subjects who have undergone allo-HSCT up to 24 months before study site activation) on all CALD patients eligible for allo-HSCT, using a study design consistent with that described in Study ALD-102 with respect to safety and efficacy assessments and their timing. It is anticipated that a subset of the ALD-103 subjects will have similar baseline characteristics as those treated in ALD-102.

Study objective

-Evaluate the safety and efficacy of allogeneic hematopoietic stem cell transplantation (allo-HSCT) in male subjects <= 17 years of age with cerebral adrenoleukodystrophy (CALD)

Study design

Study ALD-103 will be a multi-site, global pro-spective and partially retrospective study that is designed to evaluate outcomes of allo-HSCT in male subjects with CALD <= 17of age. Retro-spective subjects will be <= 17 years of age at the time of treatment, prospective subjects will be <= 17 years of age at the time of con-sent).

This is a prospective and retrospective study and does not involve the use of an investiga-tional drug or medicinal product, and allows the collection of a defined subset of the data from these procedures.

Suitability for allo-HSCT and the choice of the treatment protocol utilized for these subjects will be determined by the subjects* treating physicians as per their institutional poli-cies/protocols and other local treatment guidelines. Procedures to be performed will be those according to institutional protocols and the accepted management of CALD, including supportive care, choice of graft source, allo-HSCT protocol, prophylaxis and management of GVHD.

Subjects will be monitored from Screening before allo-HSC infusion, through their Month 48 Visit after allo-HSC infusion. Follow-up will include monitoring

of outcome measures at months 1, 2, 3, 6, 9, 12, 18, 24, 36 and 48 after allo-HSC infusion (prospective analysis).

In addition to the subjects in the prospective analysis, subjects who received an allo-HSCT on or after January 1, 2013 and died before study data collection retrospective), or subjects who will be available prospectively on-study for at least the Month 24 visit (24 ± 1 month after allo-HSC infusion) (partial prospective/retrospective) may also be en-rolled and followed for up through their Month 48 Visit after their most recent allo-HSC infusion.

In summary, subjects will be enrolled in the following three cohorts:
• allo-HSCT (prospective): subjects who will be consented before they received an allo-HSC infusion. They will be consented and enrolled on the study during the Screening Period.
• allo-HSCT (partial prospective/retrospective): subjects who will be consented after they received an allo-HSC infusion but before they reach 24 months post-infusion. Subjects in this cohort will prospectively participate in at least the Month 24 Visit in order to obtain on-study data for this and all visits after M24.
• allo-HSCT retrospective: subjects who received an allo-HSC infusion on or after January 1, 2013 and have died before study data collection.

Study burden and risks

This research collects a sub-set of the data generated under institutional standard of care protocols for patients with CALD undergoing treatment with allogenic-HSCT. The following study burdens and risks or not part of the standard of care:
- Completion of two surveys by the parents/legal guardian about the quality of life of their child pre-transplantation and at month 1, 3, 6, 12 and 24 post-transplantation.
- Blood samples collection for VLFCAs measurement
- Blood samples collection for biomarker analyses
- Optional blood sample collection
- Neuropsychological assessment at month 12, 36, 48
- MRI at month 12
- Collection of health economic data

MRI
MRI is a painless procedure that requires that the patient lies quietly on a padded table that gently glides him into the magnetic field. While the scanner is performing the scan, the patient will hear some humming and thumping sounds. These are normal and should not worry the patient. A contrast agent called gadolinium will be injected into the patient*s vein in order to give a clearer image of the area being examined. Anytime an injection is given, there is the potential for bruising or swelling at the injection site. Occasionally, minor allergic reactions occur in the form of itching, sneezing, hives, swelling of

the eyes, wheezing or nausea. These symptoms may require treatment with medication. Rarely, a more serious reaction will occur.
If the patient cannot lie still, he will likely need sedation or general anesthesia so that the investigator can perform the MRI.

Sedation
Conscious sedation is a term used when medication is given that causes the patient to relax and not feel pain but the patient is aware of what is going on around him. Conscious sedation is generally well tolerated; however, if too much of the medicine is given, problems with the patient*s breathing may occur. A doctor or nurse will be watching the patient during the entire procedure.

General Anesthesia
General anesthesia will be given if the patient cannot lie still for the brain MRI. The common risks from general anesthesia are nausea and vomiting when waking up, a sore throat or croaky voice caused by introduction of a tube in the trachea or throat to maintain respiration.
Rare events can include tooth damage, painful redness of the vein in which the products were injected, dullness or paralysis of an arm or a leg due to the prolonged position on the operating table, temporary memory difficulties or impaired concentration.

Intravenous Line Placement / Blood Collection
There may be pain, swelling, or bruising around the vein where IV line will be inserted or blood is collected. The patient may feel dizzy or may faint. The patient may get an infection at the place on his body where IV line will be inserted or his blood is collected.
The blood samples that are collected as part of the study will be collected at the same time as the blood collected for the standard of care assessments, so that blood only has to be collected once.

Quality of life questionnaires
The parents/legal guardian will be asked to complete two different Quality of Life questionnaires about their child during the study. Some of the questions asked may make them feel uncomfortable or embarrassed.

The research will lead to a better understanding of the outcomes of standard procedures related to allogenic-HSCT for CALD.

Contacts

Public
bluebird bio

Second Street 150
Cambridge MA 02141
US
Scientific
bluebird bio

Second Street 150
Cambridge MA 02141
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Subjects must:
1. Provide informed consent from a competent custodial parents or guardian with legal capacity to execute a local Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved consent. In addition, informed assent will be sought from capable subjects, in accordance with the directive of the IRB/IEC and with local requirements.
2. Be male and <=17 years of age at the time of treatment, for retrospective and partial prospective/retrospective subjects, or at time of parental/guardian consent and, where appropriate, subject assent.
3. Have a confirmed diagnosis of CALD as defined by abnormal VLCFA profile and cerebral lesion on brain MRI.
4. Depending on the cohort, the subject must:
- Be scheduled for allo-HSCT evaluation/procedure at a study site (prospective cohort only)
- Received an allo-HSC infusion and to be consented in time to complete the Month 24 Visit on study (partial prospective/retrospective cohort only) or
- Have received their most recent allo-HSC infusion on or after January 1, 2013 (retrospective cohort only).

Exclusion criteria

Subjects are excluded if they meet any of the following criteria.
1. Previous treatment with a gene therapy product.
2. Receipt of an experimental transplant procedure.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-04-2015
Enrollment:	6
Type:	Actual

Ethics review

Approved WMO Date:	19-03-2015
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	22-06-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	06-03-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-09-2018
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
CCMO	NL51193.000.14

Study results

Results posted: 15-06-2021

First publication
15-07-2020