A Phase 3 Study of Lenti-D Drug Product After Myeloablative Conditioning Using Busulfan and Fludarabine in Subjects <=17 Years of Age With Cerebral Adrenoleukodystrophy (CALD)

Published: 31-01-2019
Last updated: 14-12-2024

To evaluate the efficacy and safety of Lenti-D Drug Product (also known as elivaldogene autotemcel or Skysona, hereafter referred to as eli-cel) after myeloablative conditioning with busulfan and fludarabine in subjects with CALD

Ethical review	Approved WMO
Status	Completed
Health condition type	Neurological disorders congenital
Study type	Interventional

Summary

ID

NL-OMON54719

Source
ToetsingOnline

Brief title
ALD-104

Condition

- Neurological disorders congenital

Synonym
CALD, cerebral adrenoleukodystrophy

Research involving
Human

Sponsors and support

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

Intervention

Keyword: children, Gene therapy, Hematopoietic stem cell transplantation, X-linked adrenoleukodystrophy

Outcome measures

Primary outcome

The primary endpoint is the proportion of patients who are alive and have none

of the 6 major functional disabilities at Month 24 (as per protocol).

Secondary outcome

The secondary endpoints include the proportion of patients without gadolinium

enhancement at Month 24, value and change in neurological function, MFD-free

survival over time, overall survival and Detectable vector copy number in

peripheral blood cells by Month 6 (as per protocol).

Study description

Background summary

Lenti-D Drug Product has been investigated in a Phase 2/3 open-label, single-arm study to assess efficacy and safety of Lenti-D Drug Product after myeloablative conditioning with busulfan and cyclophosphamide (Study ALD-102; EudraCT number: 2011-001953-10). As of January 2023, 51 subjects have been treated with Lenti-D Drug Product in Study ALD-102 and ALD-104. Study ALD-104 is conducted to enable access to Lenti-D Drug Product upon completion of ALD-102 enrolment and advance understanding of the suitability of alternative conditioning regimens with Lenti-D Drug Product treatment

Study objective

To evaluate the efficacy and safety of Lenti-D Drug Product (also known as

elivaldogene autotemcel or Skysona, hereafter referred to as eli-cel) after myeloablative conditioning with busulfan and fludarabine in subjects with CALD

Study design

This will be an international, non-randomized, open-label, multi-site study in malesubjects with CALD (<=17 years of age at enrollment). Approximately 35 subjects will be infused with Lenti-D Drug Product after myeloablative conditioning with busulfan and fludarabine.
The study has 4 distinct phases after informed consent/assent:
• Screening
• CD34+ Cell Collection, Transduction, Disposition of Lenti-D Drug Product, and Re-confirmation of Eligibility
• Conditioning and Washout, followed by Lenti-D Drug Product Infusion on Day 1
• Maintenance (Follow-up) (Day 2 through 24 ± 1 months [Month 24])

Intervention

Lenti-D drug product infusion.

Study burden and risks

The majority of the burden and risks are those associated to the procedures that participants will undertake.
Risks associated to the investigational procedures are the following: pain and discomfort associated to blood sample and to potential bone marrow biopsies.
Risks associated to MRI are the following: adverse effects associated to the contrast agents (gadolinium) and adverse effects to sedation or potential general anaesthesia.
Additionally, there are specific potential risks associated with the gene therapy, including the risk of cancer (e.g. myelodysplastic syndrome). Those risks will be closely monitored during this study
This study is conducted in order to monitor the disease status of participants and look for any side effects. It is possible that if any side effects do occur, the monitoring patients receive while on this study will ensure they receive proper treatment earlier than they might have otherwise.
This study may help researchers understand more fully whether gene transfer to treat CALD is safe and effective.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Informed consent is obtained from a competent custodial parent or guardian with legal capacity to execute a local Institutional Review Board (IRB/)/ Independent Ethics Committee (IEC) approved consent. Informed assent will be sought from capable subjects, in accordance with the directive of the IRB/IEC and with local requirements.,
2. Males aged 17 years and younger, at the time of parental/guardian consent and, where appropriate, subject assent., 3. Active cerebral ALD as defined by:,
a. Elevated very long chain fatty acids (VLCFA) values, and
b. Active central nervous system (CNS) disease established by central radiographic review of brain magnetic resonance imaging (MRI) demonstrating
i. Loes score between 0.5 and 9 (inclusive) on the 34-point scale, and
ii. Gadolinium enhancement (GdE) on MRI of demyelinating lesions.,
4. Neurologic Function Score (NFS) <=1.

Exclusion criteria

1. Prior receipt of an allogeneic transplant or gene therapy.,
2. Use of statins, Lorenzo's Oil, or dietary regimens used to lower VLCFA levels.,
3. Receipt of an investigational study drug or procedure within 3 months before Screening that might confound study outcomes. Use of investigational study drugs is prohibited throughout the course of the study.,
4. Any conditions that make it impossible to perform MRI studies (including allergies to anesthetics or contrast agents).,
5. Hematological compromise as evidenced by:,
a. Peripheral blood absolute neutrophil count (ANC) count <1500 cells/mm3, and either
b. Platelet count <100,000 cells/mm3, or
c. Hemoglobin <10 g/dL.
6. Hepatic compromise as evidenced by:,
a. Aspartate transaminase (AST) value >2.5 × upper limit of normal (ULN),
b. Alanine transaminase (ALT) value >2.5 × ULN,
c. Total bilirubin value >3.0 mg/dL, except if there is a diagnosis of Gilbert's Syndrome and the subject is otherwise stable.,
7. Baseline estimated glomerular filtration rate <70 mL/min/1.73 m2.,
8. Cardiac compromise as evidenced by left ventricular ejection fraction <40%.,
9. Immediate family member with a known or suspected Familial Cancer Syndrome.,
10. Clinically significant uncontrolled, active bacterial, viral, fungal, parasitic, or prion associated infection.,
11. Positive for human immunodeficiency virus type 1 or 2 (HIV-1, HIV-2); hepatitis B virus (HBV); hepatitis C virus (HCV); human T lymphotrophic virus 1 (HTLV-1). (Note that subjects who have been vaccinated against HBV [positive for HBV surface antibodies] who are negative for other markers of prior HBV infection [e.g., negative for HBVhepatitis B core antibody {HBVc Ab]}] are eligible. Subjects with past exposure to HBV [HBcAb [HBc antibodies {Ab} positive and/or hepatitis B e-antigen antibody {HBeAb}-positive] are also eligible for the study provided they have a negative test for HBV deoxyribonucleic acid [DNA.]. Also note that subjects who are positive for anti-hepatitis C Ab are eligible as long as they have a negative hepatitis C viral load).
12. Any clinically significant cardiovascular, haematological or pulmonary disease, or
other disease or condition that would be contraindicated for any of the other study procedures.
13. Absence of adequate contraception for fertile subjects. Male subjects and their female partners are required to use two different effective methods of contraception from Screening through at least 6 months after eli-cel infusion. If subjects are truly sexually abstinent (where true sexual abstinence is defined as being in line with the preferred and usual lifestyle of the subject), no second method is required.

14. Any contraindications to the use of G-CSF or plerixafor during the mobilization of hematopoietic stem cells (HSCs), and any contraindications to the use of busulfan or fludarabine, including known hypersensitivity to the active substances or to any of the excipients in their formulations.
15. known hypersensitivity to protamine sulphate

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	24-01-2019
Enrollment:	6
Type:	Actual

Ethics review

Approved WMO Date:	31-01-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	24-06-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	29-07-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-08-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-09-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-12-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-03-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-03-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-04-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-05-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	24-06-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-10-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-01-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-06-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-07-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-09-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-11-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-12-2021

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-12-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-08-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-08-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-02-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-02-2023
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	EUCTR2018-001145-14-NL
ClinicalTrials.gov	NCT03852498
CCMO	NL68243.000.18