Phase III, open-label, single-dose, multi-center multinational trial investigating a serotype 5 adeno-associated viral vector containing the Padua variant of a codon-optimized human factor IX gene (AAV5-hFIXco-Padua, AMT-061) administered to adult subjects with severe or moderately severe hemophilia B

Published: 06-07-2018
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This study has been transitioned to CTIS with ID 2024-510738-42-00 check the CTIS register for the current data. The primary aim of the trial is to demonstrate the non-inferiority of CSL222 (formerly AMT-061) (2 × 1013 gc/kg) during the 52 weeks...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Coagulopathies and bleeding diatheses (excl thrombocytopenic)
Study type	Interventional

Summary

ID

NL-OMON52495

Source
ToetsingOnline

Brief title
AMT6102 HOPE-B

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)
- Blood and lymphatic system disorders congenital

Synonym
Bleeder's disease, Christmas disease

Research involving
Human

Sponsors and support

Primary sponsor: CSL Behring LCC
Source(s) of monetary or material Support: CSL Behring LLC

Intervention

Keyword: Blood Coagulation, Factor IX Gene, Hemophilia B, Viral Vector

Outcome measures

Primary outcome

Primary efficacy endpoints

- ABR comparison between CSL222 (formerly AMT-061) and prophylaxis for non-inferiority between the lead-in phase and the 52 weeks following stable factor IX expression (months 6-18 post treatment)

Secondary outcome

Secondary efficacy endpoints

- Endogenous factor IX activity at 6 months after CSL222 dosing

- Endogenous factor IX activity at 12 months after CSL222 dosing

- Endogenous factor IX activity at 18 months after CSL222 dosing

- Annualized consumption of factor IX replacement therapy during the 52 weeks following stable factor IX expression (months 6-18 post-treatment), excluding factor IX replacement for invasive procedures, compared to the lead-in phase

- Annualized infusion rate of factor IX replacement therapy during the 52 weeks following stable factor IX expression (months 6-18 post-treatment), excluding

factor IX replacement for invasive procedures, compared to the lead-in phase

- Proportion of subjects remaining free of previous continuous routine prophylaxis during the 52 weeks following stable factor IX expression (months 6-18 post-treatment)

- Comparison of the percentage of subjects with trough factor IX activity <12% of normal between the lead in phase and after treatment with CSL222 over the 52 weeks following stable factor IX expression (months 6-18 post-treatment)

- ABR comparison between CSL222 and prophylaxis for superiority between the lead-in phase and the 52 weeks following stable factor IX expression (months 6-18 post-treatment)

- Rate of spontaneous bleeding events during the 52 weeks following stable factor IX expression (months 6-18 post-treatment) compared to the lead in phase

- Rate of joint bleeding events during the 52 weeks following stable factor IX expression (months 6-18 post treatment) compared to the lead-in phase

- Estimated ABR - during the 52 weeks following stable factor IX expression (months 6-18 post-treatment) - as a function of pre-IMP anti-AAV5 antibody titers using the luciferase based NAB assay (as a *correlation* analysis)

- Correlation of factor IX activity levels during the 52 weeks following stable factor IX expression (months 6-18 post-treatment) with pre-IMP anti-AAV5 antibody titers using the luciferase based NAB assay

- Occurrence of (and resolution of) new target joints during the 52 weeks following stable factor IX expression (months 6-18 post-treatment) and resolution of pre-existing target joints following CSL222 dosing

- Proportion of subjects with zero bleeds during the 52 weeks following stable

factor IX expression (months 6-18 post-treatment)

- PRO questionnaire scores from the international Physical Activity Questionnaire (iPAQ; total physical activity score) during the 12 months following CSL222 dosing compared with the lead-in phase

- PRO questionnaire scores from the EuroQol-5 dimensions-5 levels (EQ 5D 5L) visual analogue scale (VAS) score during the 12 months following CSL222 dosing compared with the lead-in phase

Secondary safety endpoints

- Adverse events (AE's)

- Changes in abdominal ultrasound

- Anti-AAV5 antibodies (total [IgM and IgG], neutralizing antibodies (NAB's))

- AAV5 capsid-specific T cells

- Anti-FIX antibodies

- FIX inhibitors and recovery

- Hematology and serum chemistry parameters

- ALT/AST levels, and corticosteroid use for ALT/AST increases

- Vector DNA in blood and semen

- Inflammatory markers: IL-1β, IL-2, IL-6, IFNγ, MCP-1

- Alpha-fetoprotein (AFP)

Study description

Background summary

Congenital hemophilia B is an inherited bleeding disorder characterized by an increased bleeding tendency due to a partial or complete deficiency of the essential blood coagulation Factor IX (FIX).

Approximately 1 in 20,000-50,000 live male newborns have hemophilia B. The number of diagnosed hemophilia B patients globally is about 30,000.
Bleeding is the main symptom of the disease. Mild cases may go unnoticed until later in life, when they occur because of surgery or trauma. In severe or moderate hemophilia internal bleeding may occur anywhere, but bleeding into joints is most common. Severe recurrent bleedings may result in chronic pain, disability and reduced quality of life (QoL).

There is no cure for hemophilia B. The primary goals of hemophilia B therapy are the prevention of bleeding episodes, treatment of bleeding episodes and provision of acceptable hemostasis during surgery and emergencies. Currently, these goals are met for hemophilia B subjects by intravenous (IV) injections.
The recent approvals of extended half-life FIX products allow for reduced frequency of factor administration (once every 7 to 14 days) and maintaining a higher FIX trough level.

Study objective

This study has been transitioned to CTIS with ID 2024-510738-42-00 check the CTIS register for the current data.

The primary aim of the trial is to demonstrate the non-inferiority of CSL222 (formerly AMT-061) (2 × 1013 gc/kg) during the 52 weeks following establishment of stable factor IX expression (months 6 to 18) post-treatment (CSL222 (formerly AMT-061)) follow-up compared to standard of care continuous routine factor IX prophylaxis during the lead-in phase, as measured by the annualized bleeding rate (ABR).

Secondary: To demonstrate additional efficacy and safety aspects of systemic administration of CSL222 (formerly AMT-061).

Study design

This is an open-label, single-dose, multi-center, multinational trial, with a screening period, a lead-in phase, a treatment + post-treatment follow-up phase, and a long-term follow-up phase.

Intervention

Subjects will receive a single infusion of CSL222 (formerly AMT-061). CSL222

(formerly AMT-061) will be administered at a dose of 2 x 10^13 gc/kg as a one-time infusion in a peripheral vein, subjects will be monitored for tolerance to the Investigational Medicinal Product and detection of immediate Adverse Events for three hours after dosing.

Study burden and risks

Risks: possible side effects of the research medication and research procedures
Burden: blood samples, completion of questionnaires

Contacts

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Scientific
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Male
2. Age >=18 years
3. Subjects with congenital hemophilia B with known severe or moderately severe FIX deficiency (<=2% of normal circulating FIX) for which the subject is on continuous routine Factor IX prophylaxis*
4. >150 previous exposure days of treatment with FIX protein
5. Have been on stable prophylaxis for at least 2 months prior to screening
6. Have demonstrated capability to independently, accurately and in a timely manner complete the diary during the lead-in phase as judged by the investigator
7. Acceptance to use a condom during sexual intercourse in the period from IMP administration until AAV5 has been cleared from semen, as evidenced by the central laboratory from negative analysis results for at least three consecutively collected semen samples (this criterion is applicable also for subjects who are surgically sterilized)
8. Able to provide informed consent following receipt of verbal and written information about the trial,

*Continuous routine prophylaxis is defined as the intent of treating with an a priori defined frequency of infusions (e.g., twice weekly, once every two weeks, etc.) as documented in the medical records

Exclusion criteria

1. History of FIX inhibitors
2. Positive FIX inhibitor test at screening and Visit L-Final (based on local laboratory results)
3. Screening and Visit L-Final laboratory values (based on central laboratory results):
a. ALT >2 times ULN
b. Aspartate aminotransferase (AST) >2 times ULN
c. Total bilirubin >2 times ULN (except if this is caused by Gilbert disease)
d. Alkaline phosphatase (ALP) >2 times ULN
e. Creatinine >2 times ULN limit
4. Positive human immunodeficiency virus (HIV) serological test at screening and Visit L-Final, not controlled with anti-viral therapy as shown by CD4+ counts <= 200/µL (based on central laboratory results)
5. 5. Hepatitis B or C infection with the following criteria present at screening:
i. Currently receiving antiviral therapy for this/these infection(s)
and/or
ii. Positive for any of the following (based on central laboratory results):
• Hepatitis B surface antigen (HBsAg), except if in the opinion of the investigator this is due to a previous Hepatitis B vaccination rather than active Hepatitis B infection
• Hepatitis B virus deoxyribonucleic acid (HBV DNA)

• Hepatitis C virus ribonucleic acid (HCV RNA)
6. Known coagulation disorder other than hemophilia B
7. Thrombocytopenia, defined as a platelet count below 50 × 109/L, at screening and Visit L-Final (based on central laboratory results)
8. Known severe infection or any other significant concurrent, uncontrolled medical condition including, but not limited to, renal, hepatic, cardiovascular, hematological, gastrointestinal, endocrine, pulmonary, neurological, cerebral or psychiatric disease, alcoholism, drug dependency or any other psychological disorder evaluated by the investigator to interfere with adherence to the protocol procedures or with the degree of tolerance to the IMP
9. Known significant medical condition that may significantly impact the intended transduction of the vector and/or expression and activity of the protein, including but not limited to:
• Disseminated intravascular coagulation
• Accelerated fibrinolysis
• Advanced liver fibrosis (suggestive of or equal to METAVIR Stage 3 disease; a FibroScan* score of >=9 kPa is considered equivalent)
10. Known history of an allergic reaction or anaphylaxis to factor IX products
11. Known history of allergy to corticosteroids
12. Known uncontrolled allergic conditions or allergy/hypersensitivity to any component of the IMP excipients
13. Known medical condition that would require chronic administration of steroids
14. Previous gene therapy treatment
15. Receipt of an experimental agent within 60 days prior to screening
16. Current participation or anticipated participation within one year after IMP administration in this trial in any other interventional clinical trial involving drugs or devices.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-02-2019
Enrollment:	15
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	etranacogene dezaparvovec
Generic name:	AAV5-hFIXco-Padua

Ethics review

Approved WMO Date:	06-07-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-10-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-11-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-01-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	13-02-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-03-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-05-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-07-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-07-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-11-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-11-2019
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:	29-01-2020
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:	23-04-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-05-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-06-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-12-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-02-2022
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:	08-04-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-08-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-11-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-01-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-10-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-03-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-05-2024
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
EU-CTR	CTIS2024-510738-42-00
EudraCT	EUCTR2017-004305-40-NL
ClinicalTrials.gov	NCT03569891
CCMO	NL65714.000.18