A Phase I/IIb extension study assessing the long-term safety and efficacy of an adeno-associated viral vector containing a codon-optimized human factor IX gene (AAV5-hFIX) previously administered to adult patients with severe or moderately severe haemophilia B during the CT-AMT-060-01 Phase I/II study.

Published: 27-08-2020
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This study has been transitioned to CTIS with ID 2024-512603-39-00 check the CTIS register for the current data. Primary: To assess the long-term safety (6-10 years after dosing) of a systemic administration of AAV5-hFIX, an AAV vector containing a...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coagulopathies and bleeding diatheses (excl thrombocytopenic)
Study type	Observational invasive

Summary

ID

NL-OMON54158

Source
ToetsingOnline

Brief title
Extension study of AAV5-hFIX in severe/moderately severe haemophilia B

Condition

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

Synonym
Christmas disease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Extension, Factor IX, Genetic Vectors, Hemophilia B

Outcome measures

Primary outcome

The primary endpoint is to demonstrate the long-term safety (6-10 years) after

dosing of AAV5-hFIX.

Primary safety endpoints include the following:

- AEs possibly or probably related to previous AAV5-hFIX administration

- ALT/aspartate aminotransferase (AST) levels

- Liver pathology (assessed by ultrasound)

- Alpha-fetoprotein (AFP)

Secondary outcome

The secondary endpoints will focus on the long-term efficacy (6-10 years) after

dosing of AAV5-hFIX on FIX activity, overall FIX utilization, bleeding events,

any procedures and Quality of Life.

Secondary efficacy endpoints include the following:

- Endogenous FIX activity

- Utilization of FIX-replacement therapy

- Annualized bleeding rate; including the following:

o All bleeds (treated and untreated)

o Spontaneous bleeds

o Traumatic bleeds

o Joint bleeds

- Procedures (including major and minor surgeries)

- Short form (SF-36) and EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) QoL scores

- Hemophilia Joint Health Score (HJHS)

Study description

Background summary

Congenital haemophilia B is characterized by an increased bleeding tendency due to either a partial or complete deficiency of the essential blood coagulation Factor IX (FIX). Haemophilia B is an X-linked, recessive condition. Approximately 1 in 25,000 live male newborns have haemophilia B. The number of diagnosed haemophilia B patients globally is about 25,000. Individuals with severe haemophilia B are usually diagnosed during the first year of life. The severity of symptoms can vary, and the severe forms become apparent early in life. Bleeding is the main symptom of the disease and usually increases when the infant becomes mobile. Internal bleeding may occur anywhere and bleeding into joints is common.
Haemophilia B is caused by a variety of genetic anomalies distributed throughout the gene on the long arm of the X chromosome, with the most common being single base-pair changes that result in missense, frame shift, or nonsense mutations. With a deficiency or absence of FIX, activation of coagulation factor X becomes severely impaired leading to delayed and insufficient thrombin burst for normal haemostasis. The haemostatic plug formed in these patients is fragile and easily dissolved by normal fibrinolytic activity with impaired haemostasis, prolonged bleeding episodes and re-bleeding as the consequences.
About 1/3 of individuals with haemophilia B have a severe disorder characterized by functional FIX levels that are less than 1% of normal. Mild and moderate haemophilia B are each observed in about 1/3 of patients.
Factor IX is synthesized as a single polypeptide chain that undergoes extensive post-translational modifications. The liver is the primary site of FIX

synthesis and haepatocytes directly secrete FIX into the plasma.
Somatic gene therapy for haemophilia B offers the potential benefit for a shift of the disease severity from severe to a moderate or mild haemophilia phenotype through continuous endogenous production of FIX after a single administration of vector. The identified risks are considered low and manageable and not affecting the risk/benefit balance in an unfavorable way. CSL Behring*s optimized AAV5 approach has the potential to further limit the risks currently associated with AAV gene therapy approaches.
Interim results from the parent Phase I/II study (Study CT-AMT-060-01) demonstrated that a single intravenous infusion of AMT-060, in patients with moderately-severe to severe haemophilia B, was safe and well tolerated. Patients demonstrated a modest increase in FIX activity, which was robust and sustainable, resulting in a reduction/elimination in the use of FIX replacement therapy and lowering the risk of spontaneous bleeding events over 4 years after infusion. In addition, the level of FIX protein expression could be achieved without inducing unacceptable alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevations.
The purpose of this Phase I/IIb extension study is to assess the long-term safety and efficacy of AMT-060 (6-10 years from the time of initial dosing), and to further describe its safety profile and endogenous FIX activity.

Study objective

This study has been transitioned to CTIS with ID 2024-512603-39-00 check the CTIS register for the current data.

Primary: To assess the long-term safety (6-10 years after dosing) of a systemic administration of AAV5-hFIX, an AAV vector containing a codon-optimized human coagulation hFIX gene, to adult subjects with severe or moderately severe haemophilia B.
Secondary: To assess the long-term efficacy of a systemic administration of AAV5-hFIX, an adeno-associated viral (AAV) vector containing a codon-optimized human coagulation Factor IX (hFIX) gene, to adult subjects with severe or moderately severe haemophilia B.

Study design

This is an open-label, extension study enrolling patients who have successfully completed all assessments in Study CT-AMT-060-01 (Years 1-5). Patients will be asked, during the final scheduled visit of the CT-AMT-060-01 study, to participate in this study and give informed consent (within ± 2 weeks). There will be no screening or baseline period. Patients will return to the same study site every 6 months for safety and efficacy assessments. Patient-reported outcome (PRO) assessments will be collected yearly at the study visit. Assessment phase will begin at Visit 36 (the first clinical visit in this extension study, approximately 5.5 years after the initial dosing visit Study

CT-AMT-060-01) and go to Visit 45 (10-years post-dosing in Study CT-AMT-060-01). After giving consent, patients will enter the 5-year extension phase to determine safety and efficacy of AMT-060. During this study, patients will visit the same study site as in Study CT-AMT-060-01 every half year (6 months) for evaluation of safety and efficacy parameters. Patients reported outcomes will be completed yearly. Occurrence of adverse events (AEs) related to previous AAV5-hFIX administration will be continuously monitored.

Study burden and risks

There will be a total of 10 scheduled study site visits. If the investigator deems it necessary, there may be additional unscheduled visits. Procedures and tests performed at the different visits include: Informed consent Procedure. Review of concomitant treatment and adverse events. Physical examination. Blood samples for variety of measurements. Abdominal ultrasound. Qol questionnaire completion.

If this study shows positive results it could be the first step towards making this product available to all patients with haemophilia B.However, there is no guarantee that the subject will gain any benefit from this study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Subjects with congenital hemophilia B who completed Study CT-AMT-060-01

2. Able to provide informed consent following receipt of verbal and written information about the trial.

Exclusion criteria

Enrolled subjects will have already been assessed based on the exclusion criteria for Study CT-AMT-060-01.

Study design

Design

Study phase:	2
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-03-2021
Enrollment:	6
Type:	Actual

Ethics review

Approved WMO Date:	27-08-2020
Application type:	First submission
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:	13-11-2020
Application type:	First submission
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:	12-04-2022
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:	11-01-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-03-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-04-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-06-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-07-2023
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
EU-CTR	CTIS2024-512603-39-00
EudraCT	EUCTR2020-000739-28-NL
CCMO	NL74194.000.20