A phase I/II, open-label, uncontrolled, single-dose, dose-ascending, multi-centre trial investigating an adeno-associated viral vector containing a codon-optimized human factor IX gene (AAV5-hFIX) administered to adult patients with severe or moderately severe haemophilia B

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

Summary

ID

NL-OMON46967

Source
ToetsingOnline

Brief title
Phase I/II trial of AAV5-hFIX in severe or 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: uniQure biopharma B.V.
Source(s) of monetary or material Support: uniQure biopharma B.V.

Intervention

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

Outcome measures

Primary outcome

The primary objective will be assessed based on adverse events.

Secondary outcome

Efficacy Objectives

- To investigate the effect of AAV5-hFIX on FIX activity level

- To investigate the effect of AAV5-hFIX on the use of FIX replacement therapy

- To investigate the effect of AAV5-hFIX on bleeding episodes

- To investigate the effect of AAV5-hFIX on quality of life parameters

Safety Objectives

- To monitor shedding of the vector in various body matrices (i.e.

fluids/excretions)

- To monitor the immune responses against AAV5 capsid proteins in response to

AAV5-hFIX

- To monitor for immune responses against FIX protein after administration of

AAV5-hFIX

- To investigate the effect of AAV5-hFIX on inflammatory markers

Study description

Background summary

Current treatment for haemophilia B in the western world involves intravenous infusions of recombinant FIX concentrates at the time of a bleed (*on demand* therapy). This is highly effective at arresting haemorrhages, but cannot prevent spontaneous bleeds or any chronic damage that ensues after a bleed. In patients with severe haemophilia B, spontaneous bleeding episodes can be dramatically reduced when plasma FIX levels are maintained continuously at, or are above 1% of normal (0.01 IU/mL) by prophylactic administration of FIX protein. However, the relatively short half-life of hFIX necessitates frequent intravenous administration of concentrates (2-3 times a week) at 40 U/kg or even higher to maintain minimum trough levels of * 1%. Frequent intravenous injections are invasive, inconvenient and highly problematic for children. Since prophylaxis can reduce the risk of spontaneous bleeds and help reduce or prevent joint damage, it is becoming the standard of care in countries with access to adequate quantities of clotting factor concentrates. For Western countries, standard of care is to start prophylaxis at 1 year of age, or after first joint bleed.

The treatment by prophylactic regular intravenous injections is not curative and is very demanding. To make regular injections easier a port-a-cath, or implantable venous access device, can be implanted under the skin, usually in the upper chest. Use of port-a cath has made prophylactic treatment easier as they provide venous access, however these devices are also associated with a risk of bacterial infections.

Approximately 3-5% of patients with severe haemophilia B develop alloantibody inhibitors that can neutralize both recombinant and plasma-derived administered FIX. Inhibitor development is considered the most severe problem in haemophilia care today as it affects the efficacy of patient treatment, increases the risk of developing joint disease, increases the cost of haemophilia care, and leads to increased morbidity.

Therapy adherence drops sharply when patients reach the teenage. As many as 41% of patients report that they do not always follow their prescribed regimen. This is of serious concern considering that as few as one to two bleeds can trigger progressive, irreversible joint disease.

The burden of the disease is high, both for the individual patient and their families and for society. Patients may not be able to participate in certain activities (e.g. contact sports), and they encounter long-term impairments in mobility and functional status leading to absence from school or work. Issues may surface with social participation and peer integration, particularly when children are growing up. Haemophilia patients are less likely to proceed into full-time employment and occupational disability is more frequent.
Living with haemophilia can have a substantial effect on mental wellbeing, particularly among young people and signs of major depressive disorder are not uncommon. The economic burden for the society is significant. Haemophilia patients are accredited with requiring 2-3 times the health care resources per inhabitant in developed countries. The described use of FIX replacement therapy varies considerably across national economies, even among the wealthiest of countries. Trends suggest that the reported FIX usage increases with increasing economic capacity and has been increasing over time. Trends also suggest that consumption of FIX has been increasing at a greater rate in high income countries. However, approximately 70*80% of the world*s haemophilia B population, primarily in the developing world, receives inadequate or no treatment because of
unavailable and/or unaffordable factor concentrates.

Somatic gene therapy for haemophilia B offers the potential 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, especially since a small rise in circulating FIX can substantially ameliorate the bleeding phenotype.

Non-clinical data suggest that intravenous administration of AAV5-hFIX is able to mediate sustained levels of FIX, and that such administration is not associated with any significant safety concerns.

Study objective

The primary objective of this study is to investigate the safety of systemic administration of AAV5-hFIX, an adeno-associated viral vector containing a codon-optimized hFIX gene, to adult patients with severe or moderately severe haemophilia B.

Secondary objectives will be addressing the efficacy and safety of systemic administration of AAV5-hFIX to adult patients with severe or moderately severe haemophilia B.

Study design

This trial has an open-label, uncontrolled, single-dose, dose-ascending design. The trial consists of two cohorts, each of 5-7 subjects.

Each subject will receive a single dose of IMP (AAV5-hFIX) and will thereafter be followed for five years with respect to safety and with respect to efficacy measured as levels of FIX, bleeding patterns and consumption of FIX replacement therapy.

Intervention

The Investigational Medicinal Product (IMP), AAV5-hFIX, will be administered once by means of intravenous infusion.

Subjects will be allocated to one of two cohorts with the following planned dose levels:
- Cohort 1 (5 subjects): AAV5-hFIX 5 × 10E12 gc/kg
- Cohort 2 (5-7 subjects): AAV5-hFIX 2 × 10E13 gc/kg

Study burden and risks

During the entire course of the study, there will be 35 scheduled regular study visits at the clinic. As deemed necessary by the study doctor, or the study subject, there may be additional visits. There will also be additional visits during the period of taprering of the prophilactic FIX replacement therapy, and after stopping the prophilactic FIX replacement therapy.
During every visit the study subject will see his physician/investigator, adverse events and concomitant medication will be recorded, there will be a physical examination, bloodpressure/puls/body temperature will be measured, blood samples will be taken, and there will be an interview regarding the data the subjects has entered into his electronic diary in between the visits.
During selected visits there will also be an assessment of the joint status, and the subject will be asked to complete a health related quality of life questionnaire.
In the first 12 weeks after infusion, the subject will visit the clinic twice weekly; one of those visits will only be a blood sampling appointment to monitor liver enzymes and FIX production (these visits are marked *b* in the clinical trial protocol and ICF document). With these visits included, there will be a total of 47 scheduled visits to the clinic per trial subjects during the entire course of the study.

There following possible risks/side effects can be experienced after administration of AAV5-hFIX:
* There may be a risk of AAV5-hFIX infusion-related side effects.
* Intravenous administration of AAV5-hFIX may lead to elevated values of liver enzymes.
* Following the intravenous infusion the AAV vector is distributed throughout the body, and thereby potentially entering other cells than the liver cells.
* There is a risk that the immune system has pre-existing antibodies against the AAV5 vector, which may neutralize the effect of the AAV5-hFIX. There also

is the risk that the body will develop antibodies against the AAV5 vector after the AAV5-hFIX infusion.
* Although this has not been observed in studies with similar products, there is a risk that the immune system will develop antibodies against the expressed factor IX (FIX) which may develop to neutralize the effect of the FIX.
* If the replacement therapy is stopped too soon after AAV5-hFIX dosing, there is a risk of bleedings.
* During the study visits, blood samples will be drawn. When blood samples are taken from a vein, there is a risk of bruising at the site, soreness and possible bleeding. Sometimes a person may become dizzy or faint for a short period of time. There is a low risk of infection.

The study doctor and the study team will regularly the subject during the course of this study and the subject will be closely monitored. However, there is no guarantee that the subject will gain any benefit from this study. If this study shows positive results it could be the first step towards making this product available to all patients with haemophilia B.

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. Male
2. Age * 18 years
3. Patients with congenital haemophilia B classified as one of the following:
- Known severe FIX deficiency with plasma FIX activity level <1% and a severe bleeding phenotype defined by one of the following:
o Currently on prophylactic FIX replacement therapy for a history of bleeding
o Currently on on-demand FIX replacement therapy with a current or past history of frequent bleeding defined as four or more bleeding episodes in the last 12 months or chronic haemophilic arthropathy (pain, joint destruction, and loss of range of motion) in one or more joints
- Known moderately severe FIX deficiency with plasma FIX activity level between * 1% and * 2% and a severe bleeding phenotype defined by one of the following:
o Currently on prophylactic FIX replacement therapy for a history of bleeding
o Currently on on-demand FIX replacement therapy with a current or past history of frequent bleeding defined as four or more bleeding episodes in the last 12 months or chronic haemophilic arthropathy (pain, joint destruction, and loss of range of motion) in one or more joints
4. More than 150 previous exposure days of treatment with FIX protein.
5. Acceptance to use a condom during sexual intercourse in the first three months after IMP administration or until AAV5 has been cleared from semen after a period of 75 days following IMP administration, as evidenced by the central laboratory from negative analysis results for at least 3 consecutively collected semen samples (this criterion is applicable also for subjects who are surgically sterilized)
6. Following receipt of verbal and written information about the trial, the subject has provided signed informed consent before any trial related activity is carried out.

Exclusion criteria

1. History of positive FIX inhibitor test
2. Positive FIX inhibitors test at Screening (measured by the local laboratory)
3. Neutralizing antibodies against AAV5 at Screening (measured by the central laboratory)
4. Screening laboratory values (measured by the central laboratory):
a. ALT > 2 times upper normal limit
b. AST > 2 times upper normal limit
c. total bilirubin > 2 times upper normal limit
d. ALP > 2 times upper normal limit

e. creatinine > 1.5 times upper normal limit
5. Positive HIV serological test at Screening, not controlled with anti-viral therapy as shown by CD4+ counts * 200 per µL or by a viral load of >200 copies per mL (measured by the central laboratory)
6. Active infection with Hepatitis B or C virus as reflected by Hepatitis B Surface Antigen (HBsAg), Hepatitis B extracellular Antigen (HBeAg), Hepatitis B Virus DeoxyriboNucleic Acid (HBV DNA) or Hepatitis C Virus RiboNucleic Acid (HCV RNA) positivity, respectively, at Screening (measured by the central laboratory).
7. History of Hepatitis B or C exposure, currently controlled by antiviral therapy
8. Any coagulation disorder other than haemophilia B
9. Thrombocytopenia, defined as a platelet count below 50 × 109 / L, at Screening (measured by the central laboratory)
10. Body mass index < 16 or * 35 kg/m2
11. Planned surgery for the initial 6 months after IMP administration in this trial
12. Previous arterial or venous thrombotic event (e.g. acute myocardial infarction, cerebrovascular disease and venous thrombosis)
13. Active severe infection or any other significant concurrent, uncontrolled medical condition including, but not limited to, renal, hepatic, haematological, 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
14. Known significant medical condition including disseminated intravascular coagulation, fibrinolysis and liver fibrosis which, in the opinion of the investigator, may confound, contraindicate or limit the interpretation of either safety or efficacy data
15. Known history of an allergic reaction or anaphylaxis to FIX products
16. Known uncontrolled allergic conditions or allergy/hypersensitivity to any component of the IMP excipients
17. Previous gene therapy treatment
18. Receipt of an experimental agent within 60 days prior to Visit 1
19. Current participation or anticipated participation within one year after IMP administration in this trial in any other interventional clinical trial involving drugs or devices.
20. Clinical signs and/or symptoms of an active viral infection with a helper virus

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-08-2015
Enrollment:	8
Type:	Actual

Ethics review

Approved WMO Date:	20-08-2014
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-06-2015
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-07-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-07-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-08-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-08-2015

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-11-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-12-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-12-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-01-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-01-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-02-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-08-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	08-10-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-12-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-12-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-05-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-06-2021
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	EUCTR2013-005579-42-NL
ClinicalTrials.gov	NCT02396342
CCMO	NL50200.000.14

Study results

Results posted: 28-03-2022

First publication
06-01-2022