A phase 1/2 open-label safety and dose-finding study of BAY 2599023 (DTX201), an adeno-associated virus (AAV) hu37-mediated gene transfer of B-domain deleted human factor VIII, in adults with severe hemophilia A

Published: 07-08-2018
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This study has been transitioned to CTIS with ID 2023-505827-29-00 check the CTIS register for the current data. The purpose of this first in human study is to determine if the gene transfer study product, BAY 2599023 (DTX201), is safe and has...

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

Summary

ID

NL-OMON55861

Source
ToetsingOnline

Brief title
FVIII gentherapie-onderzoek Get8

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)

Synonym
bleeding disease, Hemophilia A

Research involving

Human

Sponsors and support

Primary sponsor: Bayer
Source(s) of monetary or material Support: Bayer A.G.

Intervention

Keyword: adeno-associated virus, Gene therapy, Hemophilia A

Outcome measures

Primary outcome

Investigate the safety and tolerability of single ascending intravenous (IV)

doses of BAY 2599023 (DTX201) in adult patients with severe hemophilia A, who

have been previously treated with FVIII products.

Secondary outcome

Identify a dose of BAY 2599023 (DTX201) that will achieve sustained expression

of vector-derived B-domain deleted (BDD) human factor VIII (hFVIII) above 5% at

6 months & 12 months following an IV administration.

Study description

Background summary

Hemophilia A is a blood clotting deficiency due to low level of factor VIII protein caused by a gene defect. Gene transfer may offer a way to make factor VIII protein in the blood to stop or lower the risk of bleedings.

Study objective

This study has been transitioned to CTIS with ID 2023-505827-29-00 check the CTIS register for the current data.

The purpose of this first in human study is to determine if the gene transfer study product, BAY 2599023 (DTX201), is safe and has beneficial effects for

treating hemophilia A.

Study design

This is a Phase 1/2, first in man, open label single escalating dose study with 4 dose steps and safety follow up period up to 52 weeks (Part A) and a safety follow up extension for additional 4 years (Part B), for a total of 5 years.

Intervention

The test drug will be administered in a single IV administration in multiple doses.

Study burden and risks

Treatment with BAY 2599023 (DTX201) may have therapeutic or curative benefit but this cannot be guaranteed. This study will be the first administration of the study product to humans. For this reason, unforeseen side effects may occur. The main possible risks associated with gene transfer of FVIII include: mild liver inflammation, antibody development to factor VIII protein (inhibitors), antibody development to the study product, cancer, the transfer of vector to sperm cells.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

• Males >= 18 years of age, • Subjects with severe hemophilia A (baseline FVIII activity FVIII:C <1%), • Previously treated with FVIII concentrate(s) (plasma derived or recombinant) or cryoprecipates for a minimum of 150 exposure days (ED), • Are on one of the following therapies: Prophylaxis, and is able and willing to stop prophylactic treatment at specified time points throughout the study or On-demand: have had > 4 bleeding events in the last 52 weeks, • Subjects must agree to use double barrier and effective contraception methods. Vasectomized subjects must agree to use condoms. This is applicable from the time of the study drug administration until notified by the investigator. Time until discontinuation of contraception will be at a minimum of 6 months, and will progressively increase with increasing dose. Recommendation to investigators is to continue the contraception until three consecutive blood and semen samples BLOD of shed virus have been obtained. Acceptable methods of contraception include, but are not limited to, (i) condoms with a spermicidal agent (ii) diaphragm or cervical cap with spermicide; if an intra-uterine device or hormone-based contraception is used by the patient*s partner, an additional barrier method must be used., • Male subjects must agree not to donate cells, semen, blood, tissue or organs from the time of study drug administration.

Exclusion criteria

• Current evidence of inhibitor to FVIII with a titer >= 0.6 BU/mL • History of inhibitor to FVIII with a titer >= 0.6 BU, or clinical history suggestive of inhibitor requiring modification of treatment . Family history of inhibitors will not exclude the subject• Have significant underlying liver disease as evidenced by any of the following: portal hypertension, splenomegaly, ascites, esophageal varices, hepatic encephalopathy, reduction below normal limits of serum albumin or a liver biopsy with evidence of stage 3 fibrosis, • Any of the following: Hemoglobin <11 g/dL; Platelets <100,000 cells/µL; Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >1.5 × ULN; Alkaline phosphatase (AP) >2.5 × ULN; Total bilirubin

>1.5 × ULN; Prothrombin time (PT) or international normalized ratio (INR) >1.0 × ULN; Serum creatinine >1.5 mg/dL • Have active hepatitis B or C infection, as reflected by HBsAg or HCV-RNA viral load positivity, • Currently on antiviral therapy for hepatitis B or C., • Serological evidence of active HIV-1 or HIV-2 as measured by CD4+ cell count <200 cells/mm3 and a viral load >50 gc/mL • Anti-AAVhu37 neutralizing antibody titer >=1:5, • Any major and/or orthopedic surgery within screening period prior to trial product administration, and at least 6 months thereafter, • History of a malignancy for which the subject has received treatment in the past 2 years except for prostate cancer being monitored without medical intervention, or surgically removed non-melanoma skin cancer, • Known or suspected autoimmune diseases, • Known prior history of hypersensitivity or anaphylaxis associated with any FVIII or immunoglobulin administration., • Known or suspected hypersensitivity or allergic reaction to trial product(s) or related FVIII products or any component of BAY 2599023 (DTX201), or a contraindication to prednisolone (as of amendment 6) • Live vaccines and COVID-19 vaccines within the last 30 days prior to the study drug administration; live vaccines may be re-introduced after viral shedding has been cleared , • Subjects on treatment with immunomodulatory agents within the last 3 months prior to study entry or during the study, • Any individual who requires any pre-medication to tolerate FVIII treatment (e.g., antihistamines), • Prior use of emicizumab within 3 months before dosing, • Clinically relevant findings in the physical examination considered critical by the treating physician, including obesity with BMI > 35 kg/m2. •

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	26-03-2019
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO Date:	07-08-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-12-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-05-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-07-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-01-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-03-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-07-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	27-08-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-11-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-12-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-01-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-02-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-04-2021
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:	26-07-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	17-08-2021
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
EU-CTR	CTIS2023-505827-29-00
EudraCT	EUCTR2017-000806-39-NL
ClinicalTrials.gov	NCT03588299
CCMO	NL66590.000.18