A Phase 1/2, Open-Label Safety and Dose-Finding Study of Adeno-Associated Virus (AAV) Serotype 8 (AAV8)-Mediated Gene Transfer of Glucose-6-Phosphatase (G6Pase) in Adults with Glycogen Storage Disease Type Ia (GSDIa)

Published: 13-07-2018
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Primary Objective: To determine the safety of single intravenous (IV) doses of DTX401 in adultswith GSDIa, including the incidence of dose-limiting toxicities (DLTs).Secondary Objective:To establish a dose of DTX401 that achieves symptom-free...

Ethical review	Approved WMO
Status	Completed
Health condition type	Congenital and hereditary disorders NEC
Study type	Interventional

Summary

ID

NL-OMON48684

Source
ToetsingOnline

Brief title
401GSDIA01

Condition

- Congenital and hereditary disorders NEC

Synonym
GSDI, Von Gierke disease

Research involving
Human

Sponsors and support

Primary sponsor: Ultragenyx Pharmaceutical, Inc.
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Adeno-Associated Virus serotype 8 (AAV8), Glucose-6-Phosphatase (G6Pase), Glycogen Storage Disease Type Ia (GSDIa)

Outcome measures

Primary outcome

Primary Endpoints:

The incidence of adverse events (AEs), including the incidence of DLTs at

each dose level, treatment-emergent adverse events (TEAEs), and serious

adverse events (SAEs) for each dosing cohort, assessed by severity and

relationship to study product.

Secondary outcome

Secondary Endpoints:

The change from baseline in time (in minutes) to first hypoglycemic event

(defined as glucose <60 mg/dL [<3.33 mmol/L]) during a controlled fasting

challenge at 6, 12, 24, and 52 weeks after IV administration of DTX401.

Study description

Background summary

Previous animal studies demonstrated long-term correction of the disease sequelae, including correction of fasting hypoglycemia; reduction of uric acid, triglycerides, and cholesterol; improved growth; reduction in hepatomegaly and nephromegaly; and a reduction in lactic acidosis (canine model). Histologically, there was also a reduction in glycogen deposition in the liver, and recent data demonstrated prevention of both HCAs and HCCs.
Glucose-6-phosphatase gene transfer is expected to be effective for the treatment of GSDIa because the disease is caused by mutations within a single gene. Currently, no gene transfer product has been approved for the treatment of GSDIa. Based on previous clinical experience with AAV8, DTX401 is expected to result in sustained (at least 3 years following vector infusion) expression of G6PC. Therefore, unlike current treatment options (ie, dietary supplementation), G6PC gene transfer offers the potential to correct the underlying deficiency for a prolonged period of time with a single IV infusion. Furthermore, increasing G6Pase activity should allow patients with GSDIa to avoid hypoglycemic episodes and long-term complications associated with GSDIa, which should greatly improve their quality of life (QoL).

Study objective

Primary Objective:
To determine the safety of single intravenous (IV) doses of DTX401 in adults with GSDIa, including the incidence of dose-limiting toxicities (DLTs).

Secondary Objective:
To establish a dose of DTX401 that achieves symptom-free euglycemia (glucose >=60 mg/dL [>=3.33 mmol/L]) in a setting of a controlled fasting challenge to allow further clinical development.

Study design

This is a Phase 1/2, open-label, single-arm, multicenter, safety and dose-finding study of DTX401 in adults with GSDIa. The primary objective of the study is to determine the safety of single IV doses of DTX401, including the incidence of DLTs. The secondary objective of the study is to identify the optimal biological dose (OBD) of DTX401 by assessing the time (in minutes) to first

hypoglycemic
event (defined as glucose <60 mg/dL [<3.33 mmol/L]) during a controlled fasting challenge, which will end when either hypoglycemia occurs or 15 hours is reached.
Eligible subjects will receive a single IV infusion of DTX401. Three subjects will
be enrolled in Cohort 1 and in each subsequent cohort. After the third patient in a
cohort reaches the 12-week time point, the continual reassessment method (CRM) will propose a dose for the next cohort using the collected data from the previous
cohort. The decision to proceed will be made after the data monitoring committee (DMC) has evaluated at least 12 weeks of safety data for all subjects in a dosing
cohort.
Subjects enrolled in Study 401GSDIA01 will be monitored for 52 weeks. During the informed consent process for this study, subjects will be informed of the long-term 4-year follow-up study in order to maximize subject retention into this
extension study.

Intervention

Subjects will receive a single IV infusion of DTX401.

Study burden and risks

This study is the first time that DTX401 will be given to humans. All of the side effects and discomforts associated with DTX401 that may occur in humans are not yet known. It is possible that you may experience inflammation of the liver if your immune system reacts to the AAV vector. Side effects associated with oral steroid use may include (but are not limited to) agitation, headache, increased blood sugar, irritability, and weight gain. In people with GSDIa, there may also be an increased risk of elevated blood levels of lactate and triglycerides that may lead to stomach pain (pancreatitis) and/or vomiting. There are also Potential Risks Associated with Study Procedures.

For this research it is necessary that patients will visit the site 8 times. Patients will be hospitalized for 5 times for 24 hours at the site (fasting challenge, max 15 hours). Besides 3 site visits will take place.
In a period of 12 weeks a (home) visit will take place every 4 or 5 days (18 visits in total). There are less alternatives for the patients available.

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. Willing and able to provide written informed consent.
2. Males and females >= 18 years of age.
3. Documented GSDIa with confirmation by molecular testing.
4. Documented history of >= 1 hypoglycemic event with glucose <60 mg/dL (<3.33 mmol/L).
5. Subject*s GSDIa disease is stable as evidenced by no hospitalization for severe hypoglycemia during the 4-week period preceding the screening visit.
6. Hematology and coagulation panel results are within the normal range or, if outside the normal range, are deemed not clinically significant in the opinion of the investigator.
7. No known allergic reaction to any component of DTX401.
8. Willing and able to comply with study procedures and requirements,

including periodic inpatient hospitalization, frequent blood collections, and 24-hour urine collection.
9. Males and females of childbearing potential must be willing to use effective contraception at the time of administration of DTX401 and for 52 weeks following administration of DTX401 to prevent the potential transmission of the AAV vector (Section 9.2.1).

Exclusion criteria

1. Screening or Baseline (Day 0) glucose level <60 mg/dL (<3.33 mmol/L); subjects may be rescreened after glucose is controlled and stable, at the discretion of the investigator.
2. Liver transplant, including hepatocyte cell therapy/transplant.
3. Presence of liver adenoma >5 cm in size.
4. Presence of liver adenoma >3 cm and >5 cm in size that has a documented annual growth rate of >= 0.5 cm per year.
5. Significant hepatic inflammation or cirrhosis as evidenced by imaging or any of the following laboratory abnormalities: alanine aminotransferase (ALT) or aspartate aminotransferase > the upper limit of normal (ULN), total bilirubin >1.5 × ULN, or alkaline phosphatase >2.5 × ULN. Liver function tests may be repeated during the screening period at the investigator*s discretion.
6. Serum creatinine >2.0 mg/dL.
7. Triglycerides >=1000 mg/dL at the time of the screening visit.
8. Presence of active, or history of treatment for, hepatitis B virus or hepatitis C
virus infection.
9. History of human immunodeficiency virus infection AND any of the following: CD4+ cell count <350 cells/mm3, change in antiretroviral therapy regimen within 6 months prior to Day 0, or viral load >200 copies/mL, on 2 separate occasions, as measured by polymerase chain reaction.
10. History of a malignancy for which the subject has received treatment in the past 2 years except for prostate cancer treated with watchful waiting or surgically removed nonmelanoma skin cancer.
11. Active infection (viral or bacterial).
12. Anti-AAV8 neutralizing antibody titer >=1:5.
13. Participation (current or previous) in another gene transfer study.
14. Participation in another investigational product study within 3 months of Screening.
15. Has a positive serum pregnancy test at Screening (females of childbearing potential only), a positive urine pregnancy test at Baseline (Day 0; females of childbearing potential only), or is nursing.
16. Has any other significant medical condition that the investigator feels would
be a risk to the subject or would impede the study.

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	17-10-2019
Enrollment:	1
Type:	Actual

Ethics review

Approved WMO Date:	13-07-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-12-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-03-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-03-2019

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-05-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-05-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-10-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-11-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-01-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-01-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-06-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	17-06-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-04-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-04-2021
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	EUCTR2016-003023-30-NL
ClinicalTrials.gov	NCT03517085
CCMO	NL65556.000.18

Study results

Date completed:	02-11-2021

Results posted: 09-01-2023

First publication
04-01-2023