A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study of Adeno-Associated Virus Serotype 8-Mediated Gene Transfer of Glucose-6-Phosphatase in Patients with Glycogen Storage Disease Type Ia

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This study has been transitioned to CTIS with ID 2023-508750-25-00 check the CTIS register for the current data. Primary: To evaluate the efficacy of DTX401 to reduce or eliminate dependence on exogenous glucose replacement therapy needed to...

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

Summary

ID

NL-OMON56166

Source
ToetsingOnline

Brief title
DTX401-CL301 (GlucoGene)

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

Percent change from Baseline to Week 48 in daily cornstarch intake for the

DTX401 Group compared with the Placebo Group

Secondary outcome

(subject to multiplicity)

• Change from Baseline to Week 48 in number of total daily doses of cornstarch.

• Change from Baseline to Week 48 in percentage of glucose values in

hypoglycemic range (<70 mg/dL [3.9 mmol/L]), assessed for noninferiority; if

non-inferiority is established, the endpoint will be tested for superiority

• PGIC assessment score at Week 48.

(not subject to multiplicity)

• Change from Baseline to Week 48 in time to hypoglycemia (<54 mg/dL [3.0

mmol/L]) during the CFC

• Change from Baseline to Week 48 in percentage of glucose values in the range

of 70-120 mg/dL (3.9-6.7 mmol/L), assessed for noninferiority; if

non-inferiority is established, the endpoint will be tested for superiority

• Incidence, severity, and relationship to investigational product of TEAEs,

TEAEs of special interest, serious TEAEs, related TEAEs, discontinuations from

study or investigational product due to AEs, and fatal AEs.

Study description

Background summary

DTX401 is a gene therapy that is being developed for the treatment of glycogen storage disease type Ia (GSDIa). Patients with GSDIa have a deficiency in the glucose-6-phosphatase protein (G6Pase) enzyme and therefore cannot release glucose from glycogen storage in the liver during times of fasting (ie, during the period between meals) and are at risk for severe fasting hypoglycemia. DTX401 therapy is expected to provide G6Pase activity resulting in efficient release of glucose from glycogen stores in the liver, thereby reducing the risk of hypoglycemia during periods of fasting and the long-term complications associated with GSDIa.

The purpose of this study is to investigate the efficacy and safety of DTX401 in pediatric (8 to <*18 years) and adult (>= 18 years) subjects with GSDIa.

Study objective

This study has been transitioned to CTIS with ID 2023-508750-25-00 check the CTIS register for the current data.

Primary:
To evaluate the efficacy of DTX401 to reduce or eliminate dependence on exogenous glucose replacement therapy needed to maintain glucose control

Secondary:

subject to multiplicity:
•To evaluate the effect of DTX401 on reducing the frequency of exogenous glucose replacement therapy
•To evaluate the effect of DTX401 on glucose control
•To evaluate the effect of DTX401 on subject experience of disease

not subject to multiplicity:
•To evaluate the effect of DTX401 on glucose control

•To evaluate the safety of DTX401

Study design

Study DTX401-CL301 is a Phase 3, randomized, double-blind, placebo-controlled study to determine the efficacy and confirm the safety of DTX401 in patients 8 years and older with GSDIa.

This study includes the following sequential stages:

Screening (Day -122 to Day -10): The site must obtain written informed consent for participation in the study before performing any study-specific screening tests or evaluations. (For pediatric subjects, a legal guardian must provide written informed consent, and the subject must provide age-appropriate assent to participate.)

During the Screening Period, the subject will be given a continuous glucose monitoring (CGM) system, a meter for capillary glucose measurements (self-monitored blood glucose [SMBG]), and the electronic diary (eDiary) to start collecting baseline data.

Randomization (Day -10 to Day 0): Screening ends when the subject is randomized. Using the interactive response technology (IRT) system, the site will randomly assign the subject to DTX401 or placebo treatment and schedule the investigational product (IP; ie, DTX401 or placebo) infusion at least 10 business days before the IP infusion to allow time for IP and the prophylactic oral prednisolone/placebo kit to be delivered to the site.

Baseline (Day 0): The day before IP administration (ie, Day 0), the subject will be admitted to the hospital or research facility for Baseline assessments.

Day 1 IP Administration: On Day 1, subjects randomly assigned to DTX401 will receive a single, blinded, peripheral intravenous (IV) infusion of DTX401 at 1.0×10^{13} genome copies (GC)/kg. Subjects randomly assigned to placebo will receive a single, blinded, peripheral IV infusion of normal saline.

Day 15: Subjects randomly assigned to DTX401 will start an oral prophylactic prednisolone regimen to minimize or prevent potential vector-induced hepatic effects (eg, transaminase elevations). Subjects randomly assigned to placebo IP infusion will receive a matching oral placebo regimen to maintain the study blind.

The Primary Efficacy Analysis Period (PEAP; Day 1 to Week 48): The PEAP is the time from Day 1 postdose through the completion of the Week 48 controlled fasting challenge. The primary endpoint and secondary efficacy endpoints will be analyzed after the last enrolled subject completes the Week 48 assessments.

Week 48 IP Administration: At Week 48, after all Week 48 assessments are completed, subjects will receive a second blinded infusion of IP: subjects randomly assigned to DTX401 at baseline will receive placebo at Week 48, while eligible subjects randomly assigned to placebo at baseline will receive a single, blinded, peripheral IV infusion of DTX401 at 1.0 × 10^13 GC/kg at Week 48 (if still eligible for IP infusion).

Subjects will begin an oral prophylactic prednisolone regimen or matching oral placebo regimen 14 days after the Week 48 IP administration.

Follow-up Period (Week 48 through Week 144): Study assessments during the Follow-up Period will further characterize the efficacy and safety of DTX401 administration to inform the overall risk-benefit profile.

Upon completion of this study (Week 144 or Early Withdrawal), all subjects who receive DTX401 will be asked to enroll in a long-term follow-up study (GSDIa disease monitoring program [DMP]) to evaluate the long-term safety and effectiveness of DTX401 via the disease DMP for at least 10 years (total duration from first infusion) after DTX401 administration.

Intervention

Subjects will receive a single IV infusion of DTX401 and placebo (cross-over).

Study burden and risks

Taking part in the study can have these cons:

You may experience the side effects or adverse effects of AAV8 gene therapy vector, as described in Section 6.

There may be some discomfort from the measurements during the study. For example: taking a blood sample can be a little painful. Or you could get a bruise as a result.

Taking part in the study will cost you extra time, for example to complete the electronic diary.

You will need to wear a CGM monitoring device for a prolonged period of time

During the controlled fasting challenge, you may experience symptoms of hypoglycemia (dizziness, shakiness, sweating, hunger, inability to concentrate, confusion, and irritability or moodiness). You will need to inform your study doctor right away if this happens.

You need to be hospitalised.

You have to comply with the study agreements.

What are the possible discomforts you may experience with checks or measurements during the study?

There may be discomforts associated with the study procedures, such as irritation from the sticky pads used during the ECG, or distress due to the closed space you are in during the MRI. You can read more about the discomforts and risks associated with the study procedures in Appendix E.

It is possible that an accidental discovery is made during an MRI scan or during a genetic examination that is not directly related to the research but does concern your health or that of your family members. If this happens, your own doctor or specialist will discuss with you what needs to happen next. The cost of this will fall under your own insurance policy.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

1. Males and females >=*8 years of age at time of informed consent or assent.

2. Subject has a diagnosis of GSDIa confirmed by deficient enzymatic activity (on liver biopsy), or by molecular testing of G6PC gene revealing 2 pathogenic mutations; in case of a single pathogenic mutation, clinical diagnosis is compatible with GSDIa and absence of characteristic features of GSDIb (ie, chronic neutropenia, inflammatory bowel disease).

3. Subject is currently receiving a therapeutic regimen of cornstarch (or equivalent) following international guidance/recommendations (Appendix 1) with stable nutrition, glycemic, and clinical status as evidenced by:
a. no more than a 10% variation in weekly average daily cornstarch (or equivalent) intake over the last 4 weeks.
b. no more than a 25% variation in weekly average daily non-cornstarch carbohydrate over the last 4 weeks.
c. No more than 15% variation in weekly percentage of values in the target blood glucose range (60-120 mg/dL) over the last 4 weeks as measured by CGM and corroborated by SMBG. If adequate corroboration is not observed, this assessment should be made by SMBG.
d. No hospitalization for hypoglycemia and no severe hypoglycemic event (SHE) during the 4-week period preceding randomization and dosing (see Section 10.4.2 for more detail on SHE), notwithstanding events of hypoglycemia due to unavoidable and unforeseeable events (eg, infection, trauma) that transiently prevent the subject from tolerating enteral intake or acutely change the subject's metabolic demands, provided that the subject quickly returns to their prior physiologic state.

4. Subject is willing and able to comply with study procedures, requirements, and study medication, including periodic inpatient hospitalization or admission in a research facility; CFC studies; frequent blood collection; wearing a CGM device for the duration of the study (and excluding the use of any non-study CGM or flash glucose device); performing capillary glucose measurements according to the protocol using a study approved glucometer (and excluding the use of any other glucometer); completing an eDiary to track daily cornstarch,

diet intake, and reasons for doing SMBG routinely throughout the study as required by the protocol; and completing patient-reported questionnaires. Subject must strictly comply with prednisolone/placebo prednisolone prescription including changes in prescription that may be implemented during the study by the Investigator, if needed. (See Section 9.2, Prednisolone Taper.) If < 18 years (or as required by region), has a parent or legal guardian willing and able to assist with study requirements.

5. From the period following informed consent through the duration of participation in the study, female subjects of childbearing potential and fertile male subjects must consent to use highly effective contraception as defined by the Food and Drug Administration (FDA) and Clinical Trial Facilitation Group Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials (Version 1.1 dated 21 Sep 2020). Female subjects must agree not to become pregnant and male subjects must agree not father a child or donate sperm for at least 48 weeks after the last dose of IP if they decide to withdraw early from the study.

6. Subject is willing and able to provide written informed consent after the study has been explained and before any study-related procedures are performed. If < 18 years (or as required by region), willing and able to provide written assent and have a parent or legal guardian willing and able to provide written informed consent after the study has been explained and before any study-related procedures are performed.

Exclusion criteria

Detectable pre-existing antibodies to the AAV8 capsid during Screening.

History of liver transplant, including hepatocyte cell therapy/transplant.

History of severe hepatic fibrosis or cirrhosis as evidenced by any of the following: portal hypertension, ascites, splenomegaly, esophageal varices, hepatic encephalopathy, or a liver biopsy with evidence of stage III fibrosis.

Presence of liver adenoma >*5*cm in size or presence of liver adenoma >*3*cm and <=*5*cm in size with a documented annual growth rate of >=*0.5*cm per year.

Significant hepatic injury or dysfunction as evidenced by imaging or any of the following laboratory abnormalities from 2 consecutive samples (collected at least 4 weeks apart). Liver function tests may be repeated during Screening at the Investigator's discretion; those with initially abnormal values may be retested and the subject will qualify for this criterion if the most recent results during Screening are within the allowed range:
- ALT or aspartate aminotransferase >*2.5*×*the ULN

- Total bilirubin >*ULN (unless the subject has Gilbert*s syndrome)
- Alkaline phosphatase >*ULN, with gamma-glutamyl transferase > ULN

Presence or history of hepatitis*B virus infection, hepatitis*C virus infection, or both.

Non-fasting triglycerides >=*1000*mg/dL. For the purposes of this study, non-fasting refers to the longest fasting period that each individual subject is able to tolerate. Depending on the meal and cornstarch schedule, the blood draw could occur in the morning before breakfast or before the first dose of cornstarch.

Human immunodeficiency virus infection AND any of the following: CD4+ cell count <*350*cells/mm3, change in antiretroviral therapy regimen within 6*months before baseline, or plasma viral load >*200*copies/mL on 2*separate occasions as measured by polymerase chain reaction.

Presence or history of any disease or condition that, in the Investigator*s opinion, would interfere with the subject*s safety or ability to participate in the study or would significantly affect interpretation of study results. This includes any intercurrent febrile or nonfebrile illness including common viral infections, epidemic influenza, and other viral illnesses, and coronavirus disease 2019 (COVID-19) until full clinical recovery.

Female subjects of childbearing potential who have a positive pregnancy test who are unwilling to use contraception, or are unwilling to have additional pregnancy tests during the study.

Pregnant, breastfeeding, or planning to become pregnant (self or partner) at any time during the study.

Presence or history of any hypersensitivity to the excipients of DTX401 or placebo or to prednisolone, or inability to swallow capsules that, in the judgment of the Investigator, places the subject at increased risk for adverse effects.

Current or previous participation in another gene transfer study.

Use of any IP or investigational medical device within 3*months preceding screening or planning to use at any time during the study.

History of illicit drug use within 60 days prior to Screening or positive results from a 9-panel urine drug screen prior to dosing and completed at 2 time points at least 4 weeks apart. Positive results that are due to a prescribed medication may be allowed if not impacting glycemic control and liver function and after agreement with the Sponsor. For the purposes of this protocol, the use of recreational cannabis products is not allowed, even if

legal in the region where the patient lives.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-05-2022
Enrollment:	6
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	14-10-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-03-2022
Application type:	First submission

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-04-2022
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:	13-05-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-06-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-07-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-07-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-08-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	15-12-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-02-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-03-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-05-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-06-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-08-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-09-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-12-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	09-01-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-01-2024
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	CTIS2023-508750-25-00
EudraCT	EUCTR2020-004184-12-NL
CCMO	NL77275.000.21