A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study of Adeno-Associated Virus Serotype 8 (AAV8)-Mediated Gene Transfer of Human Ornithine Transcarbamylase (OTC) in Patients with Late-Onset OTC Deficiency

Published: 28-12-2021
Last updated: 10-01-2025

This study has been transitioned to CTIS with ID 2024-514337-38-00 check the CTIS register for the current data. PrimaryTo evaluate the efficacy of DTX301 on the improvement of OTC function by maintaining safe plasma ammonia levelsSecondaryTo...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Endocrine disorders congenital
Study type	Interventional

Summary

ID

NL-OMON54260

Source
ToetsingOnline

Brief title
DTX301-CL301

Condition

- Endocrine disorders congenital

Synonym
Late-onset Ornithine transcarbamylase (OTC) deficiency

Research involving
Human

Sponsors and support

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

Intervention

Keyword: AAV8, Late-Onset OTC Deficiency, Ornithine Transcarbamylase

Outcome measures

Primary outcome

• Plasma ammonia as measured by 24-hour ammonia (AUC0 24) at Week 64 for all patients as assessed by the geometric mean ratio (Modified Intention-to-Treat [mITT], DTX301 vs Placebo, test for noninferiority)

• Percentage of patients at Week 64 who have achieved complete response (mITT, DTX301 vs Placebo, test for superiority)a

Secondary outcome

• Percentage of patients at Week 64 who have achieved complete response, response, or no response (mITT, DTX301 vs Placebo, test for superiority)a

• PGIC-Overall Change score (DTX301 vs Placebo) at Week 64

• Rate of HACs from baseline to Week 64 compared to the 15-month pre-enrollment period (DTX301 vs Placebo)

• Change in plasma ammonia (AUC0 24) after 64 weeks of DTX301 exposure (comparison between those who had a reduction of baseline disease management vs

not)

• Change in plasma ammonia (AUC0-24) from baseline to Week 64 for all patients

(DTX301 vs Placebo)

• Incidence of TEAEs, TESAEs, treatment-related TEAEs, treatment-related

TESAEs, and AESIs

• Clinically significant changes in laboratory values, physical examination

results, and vital sign measurements

• Development of anti-OTC antibodies

Study description

Background summary

OTC deficiency is caused by a change in the OTC gene. A gene contains the instructions of making proteins in your body, much like a cookbook recipe. When the OTC gene is changed, your body can no longer break down ammonia. The high levels of ammonia are toxic for your body.

DTX301 is an experimental gene transfer product. This means that DTX301 aims to deliver working copies of the OTC gene. The cells in your liver will now receive the correct instructions and should be able to break down ammonia.

To get the OTC gene to your liver, a transporter or *vector* is used. You can think of this vector as a car and the gene as a passenger in the car. The vector is made from a virus called adeno-associated virus serotype 8 (AAV8). The AAV8 vector used in DTX301 has been changed in the laboratory so it should not cause any infection or disease. Before receiving DTX301, your blood will be checked for the presence of pre-existing antibodies to AAV8. Antibodies are produced in response to infections or other foreign materials in your body. They are part of your body's natural defense against illness. This is done with a blood test called AAV8 DetectCDx, that is being developed for use with DTX301.

Study objective

This study has been transitioned to CTIS with ID 2024-514337-38-00 check the CTIS register for the current data.

Primary
To evaluate the efficacy of DTX301 on the improvement of OTC function by maintaining safe plasma ammonia levels
Secondary
To evaluate the efficacy of DTX301 in 3 response categories
To evaluate the effect of DTX301 on OTC deficiency patient health outcomes
To evaluate the effect of DTX301 on occurrence of HACs
To evaluate the effect of DTX301 on plasma ammonia over time
To evaluate the safety of DTX301
To characterize the immune response to OTC protein (anti-OTC antibodies)
Tertiary
To evaluate the effect of DTX301 on executive and verbal function (Cogstate Cognitive Assessment)
To evaluate the effect of DTX301 on ureagenesis
To evaluate the effect of DTX301 on total body nitrogen (serum ammonia plus glutamine)
To evaluate the effect of DTX301 on citrulline
To evaluate the effect of DTX301 on patient health outcomes and disease care burden

Study design

Study Design:
This study includes the following sequential stages (see Figure 1):
• Screening (Day -60 to -10): After providing signed informed consent/assent (as applicable), patients will complete all screening assessments outlined in Table 3. At the start of screening, patients (or caregivers, as appropriate) will be given access to an app that is configured with patient-reported outcome (PRO) instruments (Hyperammonemia Indicator Questionnaire [HI Q], OTC Deficiency Impact Questionnaire [OTC D IQ], Patient Global Impression of Disease Frequency [PGIF], and Patient Global Impression of Disease Change [PGIC]) and an electronic diary (eDiary) for recording dietary intake, ammonia scavenger therapies, and OTC deficiency-related symptoms.
• Randomization (approximately Day -10): Patients must be randomized at least 10 days before the scheduled investigational product (IP) infusion to allow time for IP and the prophylactic oral prednisolone/placebo kit to be delivered to the site.
• Baseline (Day 0): On the day before IP administration, patients will be admitted to the hospital or research facility for baseline assessments.
• Day 1 IP Administration: On Day 1, patients randomized to the DTX301 arm will receive a single, blinded, peripheral intravenous (IV) infusion of DTX301. Patients randomized to the Placebo arm will receive a single, blinded, peripheral IV infusion of normal saline.
After completion of the baseline Ureagenesis Rate Test (URT) and 24-hour plasma ammonia assessment and prior to IP administration, patients in the DTX301 arm will start a prophylactic oral corticosteroid regimen (ie, prednisolone) to minimize or prevent potential vector-induced hepatic effects. Patients in the

Placebo arm will receive a matching oral placebo regimen at the same time to maintain the study blind.
• The Primary Efficacy Analysis Period (PEAP) (Day 1 to Week 64): The PEAP is the time from Day 1 postdose through the completion of the Week 64 predose assessments. The primary analysis will be conducted when all patients have completed the Week 64 Visit or discontinued the study.
• Week 64 IP Administration: At Week 64, patients will receive a second blinded infusion of IP. Patients in the DTX301 arm will receive Placebo at Week 64, while patients in the Placebo arm will receive a single, blinded, peripheral IV infusion of DTX301 at Week 64 after confirmation that the patient is still eligible for IP infusion.
Before the first patient reaches the Week 64 time point, an independent, unblinded statistician will review preliminary primary efficacy results and will confirm with Data Monitoring Committee (DMC) members that it is appropriate for patients in the Placebo arm to receive DTX301 (crossover treatment).
Patients will begin a prophylactic oral corticosteroid taper regimen (prednisolone or matching oral placebo) before the Week 64 IP administration (after completion of the Week 64 URT and 24-hour plasma ammonia assessment).
• The Follow-up Period (Week 64 postdose through Week 260 for the DTX301 arm, or Week 128 postdose through Week 324 for patients in the Placebo/DTX301 arm): Study assessments during the Follow-up Period will further characterize clinically meaningful ammonia control after DTX301 administration and will provide extended safety information (through 5 years from the time of DTX301 administration) to inform the overall risk-benefit profile.

Intervention

We will treat the patient once with the study drug. It will be given as a one-time infusion through the vein. The infusion will take approximately 30 minutes. The infusion cannot be reversed or undone. We cannot remove the vector or OTC gene from the body once we have given it to the patient.

For this study, we will have 2 groups:
• Group 1. The people in this group will get DTX301.
• Group 2. The people in this group will get placebo.

A draw will decide which treatment (DTX301 or placebo) the patient is given. There is a 50% chance that he/she will receive DTX301. The patient and the investigator do not know which group he/she in. But if it is important for his/her health, we can look this up.

If the patients joins the study, he/she will also receive medication to suppress inflammation (steroids or a placebo. This is intended to help the liver cells to stay normal.

Study burden and risks

DTX301
DTX301 may cause side effects. It is important that you tell your study doctor of all changes in your health after you receive DTX301 even if you think that some of the changes are not important or not caused by DTX301. Any experimental drug carries potential serious adverse complications, including a risk of death. You will be observed in the hospital after receiving the infusion of the gene transfer product to monitor for any side effects or discomforts. Several hundred people have been given AAV-based gene transfer, and no life threatening or irreversible side effects been reported in the immediate period after infusion.

: Potential risks related to use of DTX301, an AAV gene therapy vector delivered in the bloodstream (IV), may include but are not limited to the following:
• Liver damage
• Liver effects induced by the vector (transporter of the gene therapy) Immune response
• Allergic reaction
• Development of cancer
• Vector shedding

The medicinal product can also have side effects that we do not know about at the moment.
You can read more about this in appendix E of the ICF.

Sodium Acetate (used with the URT)
When you drink this mixture, you may experience a temporary unpleasant salty or acidic taste, nausea or increased belly sounds or flatulence.

Medication to suppress inflammation (steroids)
The follow side effects are common:
• Fluid retention
• Change in glucose
• High blood pressure
• Behaviour and mood changes
• Increased appetite and weight gain
• Increase of ammonia level
• Blurred vision
• Acne
These side effects are usually temporary and reverse when you stop taking the medication to suppress inflammation. You can read more about this in appendix E of the ICF.

Contacts

Public
Ultragenyx Pharmaceutical Inc.

Memorial Drive 840
Cambridge, MA 02139
US
Scientific
Ultragenyx Pharmaceutical Inc.

Memorial Drive 840
Cambridge, MA 02139
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)

Inclusion criteria

Eligible individuals must meet all of the following criteria:
1. Male or female patient 12 years of age or older at the time of signed informed consent.
2. Provide informed consent after the nature of the study has been explained, and prior to any research-related procedures. If a minor, willing and able (if possible) to provide assent and have a legally authorized representative provide informed consent after the nature of the study has been explained, and prior to any research-related procedures.
3. Confirmed clinical diagnosis of late-onset OTC deficiency with historical documentation by enzymatic (ie, liver biopsy), biochemical (ie,

hyperammonemia in the presence of elevated plasma glutamine, low citrulline, and elevated spot urine orotic acid), or molecular testing (ie, OTC analysis).
4. Documented history of >= 1 symptomatic hyperammonemia episode with ammonia level >= 100 µmol/L for confirmation of clinical disease.
5. Patient is currently receiving ammonia scavenger therapy and/or protein-restricted diet, is free from symptomatic hyperammonemia and has not required emergent active intervention for hyperammonemia within 4 weeks before screening/baseline.
6. Plasma 24-hour ammonia (AUC0-24) is <= 4800 µmol*h/L at screening. If the ammonia AUC0-24 is inconsistent with the patient's clinical status, the assessment may be repeated to ensure accurate results.
7. If on ongoing daily ammonia scavenger therapy, must be at stable daily dose(s) for >= 4 weeks prior to screening.
8. If on a protein-restricted diet, must be on a stable protein-restricted diet as evidenced by a stable amount of total protein intake (ie, daily protein intake in grams per day does not vary more than 20%) for >= 4 weeks prior to screening.
9. Willing and able to comply with study procedures and requirements, including periodic inpatient hospitalizations, frequent blood and urine collections, blood collections over a 24-hour period, questionnaires, cognitive assessments, and patient/caregiver reported outcome assessments. If a minor, must have a caregiver(s) willing and able to assist in all applicable study requirements.
10. From the time written informed consent is provided through Week 128, females of childbearing potential and fertile males must consent to use highly effective contraception as defined by the United States Food and Drug Administration (FDA) and Clinical Trial Facilitation Coordination Group (CTFG) Recommendations Related to Contraception and Pregnancy in Clinical Trials. If female, agree not to become pregnant. If male, agree to not father a child or donate sperm.

Exclusion criteria

Individuals who meet any of Exclusion Criteria 1 to 16 will not be eligible to participate in the study. Individuals who meet Exclusion Criteria 17 will not be eligible to undergo the URT:
1. Liver transplant, including hepatocyte cell therapy/transplant.
2. History of liver disease as evidenced by any of the following: portal hypertension, ascites, splenomegaly, esophageal varices, hepatic encephalopathy, or a liver biopsy with evidence of stage 3 fibrosis.
3. Significant hepatic inflammation or cirrhosis as evidenced by imaging or any of the following laboratory abnormalities: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1.5 ×

ULN, total bilirubin > 1.5 × ULN (except if patient has a diagnosis of Gilbert's syndrome), alkaline phosphatase > 2.5 × ULN. NOTE: Any of the LFTs may be retested.
4. Estimated glomerular filtration rate < 60 mL/min/1.73 m2 at screening by the CKD-EPI 2021 creatinine-based formula (Inker et al., 2021) for patients >= 18 years of age or the Schwartz bedside formula (Schwartz and Work, 2009) for patients < 18 years of age.
5. Evidence of active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, documented by current use of antiviral therapy for HBV or HCV or by hepatitis B surface antigen (HBsAg) or HCV RNA positivity. NOTE: Patients with a history of HCV infection must have documentation of 2 negative viral assays by polymerase chain reaction (PCR), collected at least 6 months apart, to be considered negative for HCV. Patients with a history of HCV infection who test positive for HCV RNA at screening can be rescreened once, after they have been treated and have documentation of at least 2 negative samples collected at least 6 months apart.
6. History of human immunodeficiency virus (HIV) infection AND any of the following: CD4+ cell count < 350 cells/mm3, change in antiretroviral therapy regimen within 6 months prior to Baseline (Day 0), or plasma viral load > 200 copies/mL, documented on 2 separate occasions, as measured by PCR.
7. Active infection (viral or bacterial).
8. Detectable pre-existing antibodies to the AAV8 capsid.
9. History of a malignancy for which the patient has received treatment in the past 2 years except for prostate cancer treated with watchful waiting or surgically removed nonmelanoma skin cancer.
10. Any of the following that, in the judgment of the Investigator, places the patient at increased risk for adverse effects:
• Known hypersensitivity to DTX301, its excipients, or its placebo
• Known hypersensitivity to prednisolone, its excipients, or its placebo
11. Chronic use of inhibitors of urea synthesis (eg, valproic acid) or drugs that significantly affect renal clearance (eg, probenecid).
12. Presence or history of any condition that, in the view of the Investigator, would interfere with participation, pose undue risk, or confound interpretation of results, including but not limited to:
• Underlying conditions that may require systemic corticosteroids if the condition worsens (eg, autoimmune disorders)
• Patient in a catabolic state (eg, due to current infection), or in whom a catabolic state may be reasonably foreseeable (eg, due to planned procedures)
• Patient is considered vulnerable by local regulations (eg, imprisoned or institutionalized)
13. Marked neurological deficit or compromise that, in the Investigator's opinion, would interfere with the patient's safety or ability to participate in the study.
14. Pregnant or breastfeeding or planning to become pregnant within 64

weeks after receiving DTX301 (ie, through Week 128 of this study).
15. Participation (current or previous) in another gene transfer study.
16. Use of any investigational product within 3 months prior to screening, or during the study.
17. Patient who meet any of the following criteria are not eligible to undergo the URT:
• Unable to fast safely for 12 hours
• History of hyperammonemic crisis (HAC) triggered by minimal vomiting
• Age < 18 years at screening
Note: Any patient < 18 years of age at screening will not undergo ureagenesis rate testing for the duration of study.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-01-2023
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	(1-13C) Sodium Acetate
Generic name:	Sodium Acetate

Ethics review

Approved WMO Date:	28-12-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-06-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-10-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-11-2022
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:	07-02-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-03-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	05-04-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-05-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-07-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-09-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-09-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-12-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-12-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-02-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	19-03-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-04-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-04-2024
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	CTIS2024-514337-38-00
EudraCT	EUCTR2020-003384-25-NL
CCMO	NL78036.000.21