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This lay summary is a brief summary of the main results from a clinical study. The study listed may include approved and non-approved uses, formulations or treatment regimens. It is not intended to promote any product or indication and is not intended to replace the advice of a health care professional. The results reported in any single clinical trial may not reflect the results obtained across the full clinical development program. Only a physician can determine if a specific product is the appropriate treatment for a particular patient. If you have questions, please consult a health care professional. Before prescribing any product, healthcare professionals should consult the regional approved product labeling for indications and proper use of the product.

Clinical study results

The safety of DTX401 in patients with glycogen storage disease type Ia (GSDIa)

Thank you!

Thank you to the patients who took part in the clinical study for DTX401, also called AAV8G6PC. Ultragenyx, the sponsor of this study, is grateful to those who participated and believes it is important to share the results.

By taking part in this study, the patients helped the researchers learn more about using DTX401 in people with glycogen storage disease type Ia, also called GSDIa.

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Why was this study needed?

Researchers designed this study, **401GSDIA01**, to learn about the safety of different doses of DTX401 in patients with glycogen storage disease type Ia (GSDIa). It was also designed to learn if patients who received DTX401 could go longer between meals and take less cornstarch before getting low blood sugar.

GSDIa is a rare, genetic condition that prevents the body from keeping normal blood sugar levels between meals. This leads to low blood sugar (hypoglycemia) that can be life-threatening.

GSDIa is caused by changes (mutations) in the gene *G6PC*, which makes G6Pase. In patients with GSDIa, *G6PC* creates a nonworking type of G6Pase that cannot turn glycogen into glucose. Glycogen can build up and damage certain organs, like the liver and kidneys.

How does the body usually keep normal blood sugar levels?

When the body doesn't need to use blood sugar **(glucose)** for energy right away, it stores glucose as **glycogen** in the muscles and liver.

When the body needs energy between meals, a protein called **G6Pase** turns glycogen back into glucose to use as energy and keep normal blood sugar levels.

There is no approved medicine for GSDIa. Currently, patients with GSDIa manage their symptoms by closely watching their blood sugar levels, following a special meal plan to avoid certain types of sugar, and taking cornstarch between meals.

What is DTX401?

DTX401, also called AAV8G6PC, is a gene therapy designed to treat GSDIa by adding a healthy copy of the *G6PC* gene to make a working type of G6Pase.

It is given through a vein as **one intravenous (IV) infusion** that delivers the copy of the gene mainly to the liver.

Who was in this study?

This study included **12 patients** with GSDIa from Canada, the Netherlands, Spain, and the United States.

The patients included men and women between 18 to 57 years old when they joined the study. Their average age was 32 years old.

All patients were tested to make sure they had no antibodies to DTX401 before joining the study.

What happened during this study?

Before treatment

The study doctors checked each patient's health to make sure they could join the study. The patients stayed at the study site overnight to measure how long they could go without eating before getting low blood sugar.

During treatment with DTX401

Each patient received one dose of DTX401 as an IV infusion:

- **Group 1** received a **lower dose** of DTX401
- **Groups 2, 3, and 4** received a **higher dose** of DTX401

Most patients were also given medicines, called **steroids**, to take by mouth.

After treatment

For 3 months after the patients received DTX401, study staff checked their health during visits at the study site or the patient's home.

Each patient visited the study site 3, 6, 9, and 12 months after receiving DTX401 for staff to check their health. For 2 or 3 of the visits, the patients stayed at the site overnight for staff to measure how long they could go without eating before getting low blood sugar.

The study started in May 2018 and ended in November 2021. The patients were in the study for up to 1 year. When this study ended, the patients were invited to join a 4-year safety follow-up study, 401GSDIA02.

Why were the patients given steroids?

When a gene therapy delivers the copy of a gene mainly to the liver, it can cause liver inflammation. **Inflammation** is part of the immune system's response to foreign things that may harm it. To reduce their immune system's response to the study treatment and lessen inflammation, most patients were given steroids.

To check for liver inflammation, patients had blood tests to measure levels of **alanine aminotransferase**, or **ALT**. High ALT blood levels can be a sign of liver inflammation.

Each treatment group took steroids at different times and different doses to learn which worked best to prevent or treat possible liver inflammation. The table below shows when patients were given steroids and the dose of steroids. Each patient's dose of steroids went down over time. A patient could take steroids for longer, if needed based on their ALT blood levels.

Group	DTX401 dose	When they were given steroids
1	Lower dose	• Started at 40 mg of steroids **after** receiving DTX401 **if their ALT blood levels went up** • Took for up to 6 weeks
2	Higher dose	• Started at 40 mg of steroids **after** receiving DTX401 **if their ALT blood levels went up** • Took for up to 6 weeks
3	Higher dose	• Started at 60 mg of steroids **after** receiving DTX401 **if their ALT blood levels went up** • Took for up to 7 weeks
4	Higher dose	• Started at 60 mg of steroids **before** receiving DTX401 **regardless of their ALT blood levels** • Took for up to 8 weeks

What were the results from this study?

This is a **summary** of the main results from the group of all patients in this study. Each patient's individual results might be different and are not shown in this summary. If you took part in this study and have questions about your results, please contact the study site.

The results from several studies are needed to decide which treatments work best and are safest. Other studies may give new information or different results. Always talk to a doctor before making any treatment changes.

This study was designed to answer **2 main questions:**

- How many patients had side effects during the study?
- What side effects happened that the doctors thought might be related to the study treatment?

This study was also designed to answer the question:

- Could patients go for longer between meals before getting low blood sugar?

How many patients had side effects during the study?

All of the patients in this study had side effects, and 4 patients reported serious side effects.

Overall, the safety results were about the same for each treatment group.

What is a side effect?

A **side effect** is an unwanted or unexpected sign or symptom that happens after taking the study treatment.

A lot of research is needed to know if a treatment causes a side effect. Side effects may or may not be related to the study treatment, to other drugs taken while in the study, to the patients' medical history, or to any of the tests performed in the study.

What is a serious side effect?

A side effect is considered **serious** when it:

- Is considered medically important by a doctor
- Requires hospital care
- Causes a disability or birth defect
- Is life-threatening
- Causes death

This section is a summary of **all side effects** that happened during the study, even if the doctors thought they might not be related to the study treatment.

The table below shows the number of patients who had side effects and serious side effects during the study.

Number of patients who	**Group 1** 3 patients	**Group 2** 3 patients	**Group 3** 3 patients	**Group 4** 3 patients
Had any side effect	**100%** (3 of 3 patients)	**100%** (3 of 3 patients)	**100%** (3 of 3 patients)	**100%** (3 of 3 patients)
Had any **serious** side effect	**67%** (2 of 3 patients)	**33%** (1 of 3 patients)	**33%** (1 of 3 patients)	**0%** (0 of 3 patients)

No patients had side effects that could have meant the treatment dose was too high.
No patients died during this study.

The next section is a summary of the side effects that happened during the study that the doctors thought **might be related** to the study treatment.

What side effects happened that the doctors thought might be related to study treatment?

The most common side effect thought to be related to the study treatment was possible liver inflammation (based on blood test results, including ALT blood levels that went up). Blood test results went back to healthy levels after the patients took steroids.

What serious side effects did patients have that were thought to be related to the study treatment?

No patients had serious side effects thought to be related to the study treatment.

What common side effects did patients have that were thought to be related to the study treatment?

Below are the common side effects thought to be related to the study treatment that happened in **at least 25%** (3 or more patients) of all the patients in the study. There were other side effects thought to be related to the study treatment that happened in fewer patients.

Possible liver inflammation
(Based on one or more blood tests such as: alanine aminotransferase [ALT] increased, liver function test increased, hepatic enzyme increased, and hypertransaminasaemia)
12 of 12 patients

Headache
3 of 12 patients

High blood sugar
(hyperglycemia)
3 of 12 patients

Could patients go for longer between meals before getting low blood sugar?

Yes, on average, patients could fast (go without eating or drinking anything but water) longer at 3, 6, and 12 months after receiving DTX401.

On average, patients could fast for 1.5-2 hours longer after receiving DTX401. During the study, the researchers changed the meal they gave patients before they fasted to help get accurate results. Because the meal changed, there was a range in the length of time patients could fast.

To answer this question, the patients did a fasting test overnight at a hospital. In this test:

1. The researchers gave each patient dinner, which included a dose of cornstarch, and the patients fasted for up to 15 hours overnight.
2. The researchers tested their blood sugar levels many times until the patient had low blood sugar or showed symptoms of low blood sugar. **Low blood sugar** was 60 or lower milligrams of glucose per deciliter of blood (mg/dL) or 3.3 or lower millimoles per liter (mmol/L).
3. If a patient had low blood sugar, or showed symptoms of low blood sugar, researchers ended the test and treated them with any of these:
   - Cornstarch
   - A meal
   - Glucose through a vein

How has this study helped patients and researchers?

The researchers found the most common side effect thought to be related to the study treatment was possible liver inflammation (based on blood test results, including ALT blood levels that went up). They also found that after treatment with DTX401, patients could fast for longer and take less cornstarch, less often compared to before treatment.

The results from several studies are needed to decide which treatments work best and are safest. Ultragenyx has an ongoing study of DTX401 in patients 8 years and older with GSDIa to confirm this study's results. Ultragenyx also has plans for more studies of DTX401 in patients with GSDIa.

Other studies may have new or different results. Always talk to a doctor before making any treatment changes.

Where can I learn more about this study?

You can find more information about this study, including a report with the study's results, on these websites:

- https://clinicaltrials.gov/ct2/show/NCT03517085
- https://www.clinicaltrialsregister.eu

Official Study Title: 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)

National Clinical Trial number: NCT03517085

EudraCT number: 2016-003023-30

If you have questions about the results, please speak with a doctor or staff at the study site.

Thank you!

At Ultragenyx, our focus is developing medicines for people who live with rare and ultra-rare diseases. But it takes more than scientific knowledge and research to develop medicines. Your involvement is essential and ensures that the research process moves forward. Thank you for your participation in this study and commitment to research.

Ultragenyx is a biopharmaceutical company committed to bringing to patients products for the treatment of rare and ultra-rare diseases, with a focus on serious, debilitating genetic diseases.

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