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Clinical study results

The safety of DTX301 in patients with ornithine transcarbamylase (OTC) deficiency

Thank you!

Thank you to the patients who took part in the clinical study for DTX301, also called scAAV8OTC and avalotcagene ontaparvovec. Ultragenyx, the sponsor of this study, is grateful to those who participated and believes it is important to share the results with the patients.

By taking part in this study, the patients helped the researchers learn more about using DTX301 to help people with ornithine transcarbamylase deficiency, also called OTC deficiency.

Contents

Why was this study needed?

Researchers designed this study, **301OTC01**, to learn about the safety of different doses of DTX301 in patients with ornithine transcarbamylase (OTC) deficiency. It was also designed to learn if the body could turn more ammonia into urea after treatment with DTX301.

OTC deficiency is a rare, genetic condition that prevents the body from removing ammonia in the blood. This leads to high levels of **ammonia** in the blood, which can be toxic.

OTC deficiency is caused by changes (mutations) in the gene that makes the OTC protein. Genes carry instructions that tell the body how to make proteins. In patients with OTC deficiency, the gene creates a nonworking type of OTC protein that cannot turn ammonia into urea. Ammonia can then build up to high levels in the blood.

What is ammonia?

Ammonia is a waste product that the body makes when it breaks down protein.

How does the body usually remove ammonia?

Usually, a protein in the liver called **OTC** turns ammonia into **urea**, which leaves the body in urine.

In adults, symptoms of high ammonia levels include feeling very sleepy, migraines, blurry vision, feeling confused, and trouble moving and speaking.

Currently, patients with OTC deficiency manage their symptoms with a low-protein meal plan and medicines to remove ammonia from the blood (called **ammonia scavenger medicines** or nitrogen scavengers).

What is DTX301?

DTX301, also called scAAV8OTC and avalotcagene ontaparvovec, is a gene therapy designed to be a treatment for OTC deficiency by adding a healthy copy of the OTC gene to make a working type of OTC protein.

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 **11 patients** from Canada, Spain, the United Kingdom, and the United States. All patients had **late onset OTC deficiency**, in which symptoms start at 1 month of age or older.

All patients were tested to make sure they had no antibodies to DTX301 before joining the study.

The patients included men and women between 19 to 44 years old when they joined the study. Their average age was 29 years old.

What happened during this study?

Before treatment

The study doctors checked each patient's health to make sure they could join the study. The study staff measured the levels of urea and ammonia in patients' blood.

During treatment with DTX301

Each patient received one dose of DTX301 as one IV infusion:

- **Group 1** received a **lower dose** of DTX301
- **Group 2** received a **medium dose** of DTX301
- **Groups 3 and 4** received a **higher dose** of DTX301

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

After treatment

Each patient visited the study site every 4 days for the first 3 months of the study. They also returned at months 4, 5, 6, 9, and 12 for the staff to check their health.

The study started in July 2017 and ended in December 2021. Each patient was in the study for a little over 1 year. When this study ended, the patients were invited to join a 4-year follow-up study, 301OTC02, to learn more about the long-term effects and safety of DTX301.

Why were patients given steroids?

When a gene therapy deliveries 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, the 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 started to take steroids at different times to learn which worked best to prevent or treat possible liver inflammation. The table below shows when patients started steroids. Each patient's dose of steroids started at 60 mg per day and went down over time. They stopped taking steroids after about 5 weeks. A patient could take steroids for longer, if needed based on their ALT blood levels.

Group	DTX301 dose	When they were given steroids
1	Lower dose	Started steroids **after** receiving DTX301 **if their ALT blood levels went up**
2	Medium dose	Started steroids **after** receiving DTX301 **if their ALT blood levels went up**
3	Higher dose	Started steroids **after** receiving DTX301 i**f their ALT blood levels went up**
4	Higher dose	Started steroids **before** receiving DTX301 **regardless of their ALT blood levels**

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 your study site.

The results from several studies are needed to decide if treatments are safe and work. Other studies may provide 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 doctors thought might be related to the study treatment?

This study was also designed to answer the question:

- Could the body turn more ammonia into urea after treatment?

How many patients had side effects during the study?

All of the patients in this study had side effects, and 1 patient had 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** 2 patients
Had any side effect	**100%** (3 of 3 patients)	**100%** (3 of 3 patients)	**100%** (3 of 3 patients)	**100%** (2 of 2 patients)
Had any **serious** side effect	**0%** (0 of 3 patients)	**0%** (0 of 3 patients)	**0%** (0 of 3 patients)	**50%** (1 of 2 patients)

No patients died during this study.

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

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

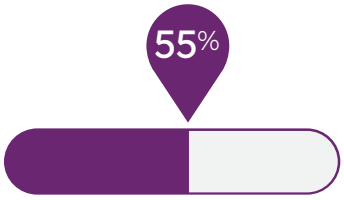
The most common side effects thought to be related to the study treatment were high blood pressure and possible liver inflammation (based on blood test results, including ALT levels that went up). Both side effects went away by the end of the study.

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

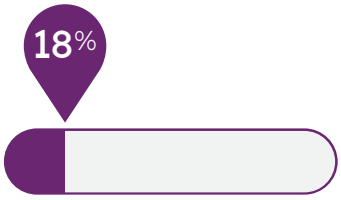
No patients had serious side effects thought to be related to the study treatment.

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 18%** of all the patients (2 or more patients) in this study. There were other side effects thought to be related to the study treatment that happened in fewer patients.



Possible liver inflammation
(based on these blood test results: hepatic enzyme increased, liver function test abnormal or increased, and hepatitis)
6 of 11 patients



High blood pressure
(hypertension)
2 of 11 patients

Could the body turn more ammonia into urea after treatment?

After treatment, patients began to make urea more quickly and the level of ammonia in their blood went down on average, regardless of the dose of DTX301 they received.

To learn about the levels of urea and ammonia in patients' blood, the researchers took blood samples from the patients throughout the year after they received DTX301. During this time, some patients received a lower dose or stopped receiving ammonia scavenger medicines.

On average, during the year after treatment, patients' bodies began to make urea **more quickly**, regardless of the dose of DTX301.

On average, during the year after treatment, some patients' blood levels of ammonia **went down**, regardless of the dose of DTX301.

How has this study helped patients and researchers?

The researchers found that the most common side effects thought to be related to DTX301 were signs of liver inflammation and high blood pressure. They also found that on average, during the year after treatment with any of the doses of DTX301, patients began to make urea more quickly and some patients' ammonia blood levels were lower.

Ultragenyx has a larger, ongoing study of DTX301 in patients with OTC deficiency. Ultragenyx also has plans for more studies of DTX301 in patients with OTC deficiency.

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:

- www.clinicaltrials.gov/ct2/show/NCT02991144
- www.clinicaltrialsregister.eu/ctr-search/search?query=2016-001057-40

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 Human Ornithine Transcarbamylase (OTC) in Adults with Late-onset OTC Deficiency

National Clinical Trial number: NCT02991144

EudraCT number: 2016-001057-40

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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