The Cyprus^{2+} Study

You may be able to help shape the future of Wilson disease treatment.

Your disease is rare, but you are not alone. At Ultragenyx, we are committed to bringing patients new treatments for rare and ultra-rare diseases.

Cyprus^{2+}™

Gene Therapy for the
Treatment of Wilson Disease

What is a clinical study?

Clinical studies (also called clinical trials) are a big part of developing new medicines and treatments. They are how we find out if a treatment can help people and if it is safe. People who take part in studies are at the center of this process.

Each clinical study has a written plan and follows a set of rules. This is to protect the people who take part in the study. It also helps ensure that the results are accurate and fair.

Why are we doing this research?

Currently there are no treatments that address the root causes of Wilson disease. Managing symptoms is the only thing patients can do right now.

The Cyprus^{2+} study is testing an investigational treatment called UX701. Investigational means UX701 is not approved to treat Wilson disease. It is approved for use in research studies like this one. UX701 is a kind of treatment called gene therapy. This study is designed to:

- Assess three dose levels of UX701 to find the best dose
- Help us learn if UX701 is an effective and safe treatment for adults with Wilson disease
- Evaluate a laboratory test designed to help identify people who are eligible for treatment with UX701

Institutional Review Boards (IRBs) and Ethics Committees have approved this study. These groups review all studies before they start. The role of these groups is to protect the rights and welfare of people who take part in research studies.

Thank you for taking the time to learn about this study. In this brochure, "you" refers to the person living with Wilson disease.

What is gene therapy?

Genes have specific instructions, like a cookbook recipe, for making proteins in your body. Proteins help your body work the way it should. Changes to genes, called variants, can cause problems in how a cell makes proteins. Wilson disease is caused by variants in a single gene known as *ATP7B*.

The goal of gene therapy is to deliver fully functioning copies of a gene to a cell. If this works, the cell should be able to read the new gene and produce a protein properly.

Gene therapy has been studied for decades, and the science continues to evolve. Studies like this one help us build on previous learnings. We are working to understand the effects of gene therapy and its "long-term durability." In other words, we want to find out how long the effects might last.

What is UX701?

UX701 has the potential to restore *ATP7B* protein function. This investigational gene therapy product is:

- A one-time intravenous (IV) infusion
- Delivered directly into the bloodstream through a vein
- Being developed with the goal of restoring your body's ability to transport copper so that it does not collect inside your organs

Who can be in this study?

You may be eligible to take part in this study if you:

- Have been diagnosed with Wilson disease
- Are 18 years of age or older
- Have been on copper chelator and/or zinc therapy for at least 12 months with no medication changes in the past 6 months
- Have not had a liver transplant
- Limit your intake of high copper-containing foods

You will also need to meet some additional requirements. The study doctor will explain these to you.

Why consider joining this study?

You may be able to help us find a way to address the root causes of Wilson disease. In this study, you will provide information that can help us learn more about UX701. We hope this will lead to a better future for people living with Wilson disease.

How do I join this study?

You may want to talk with your doctor, friends, and family about the Cyprus^{2+} study. They can help you decide if this study could be right for you. Feel free to contact us if you want to:

- Learn more about the study
- Find out if you can join the study

You can contact us by sending an email to:

TrialRecruitment@Ultragenyx.com

You can also reach out to your health care provider directly.

How long will I be in the study?

If you are eligible and choose to take part, you will be in the study for approximately 5 or 6 years. This will depend on when you receive UX701. This length of time is needed to find out if UX701 is helping study participants.

While you are in the study, you will have the full support of the study team. Members of the team are experts in the treatment of Wilson disease. They will monitor your health and your Wilson disease throughout the study.

You will be a volunteer in this study. You may choose to stop being in the study at any time, for any reason. Your decision will not affect the medical care you receive outside this study.

What will I need to do if I join this study?

Taking part in this study will be much like going to your doctor. However, there are some key differences. For example, in this study you will:

- Receive UX701 and oral steroids*
- Have frequent health assessments
- Complete some procedures at home

You will continue your current medications for Wilson disease (copper chelator and/or zinc therapy). These will not be provided as part of the study.

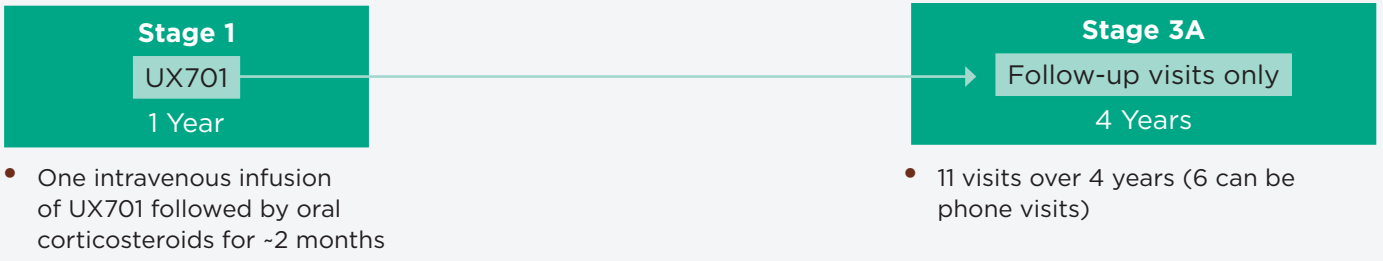
* Depending on when you enter the study, you may receive placebo at some point during your participation.

What study treatment will I receive?

This study consists of three stages. You will enter the study in either Stage 1 or Stage 2, depending on when you enroll. You will take part in only two of the stages: either Stage 1 and Stage 3A OR Stage 2 and Stage 3B. If you enroll in Stage 1, you will receive UX701 as a single IV infusion. If you enroll in Stage 2, you will receive either UX701 or placebo. You will then receive the opposite study treatment assignment in Stage 3B. The diagram on the right outlines the progression between stages.

Notes

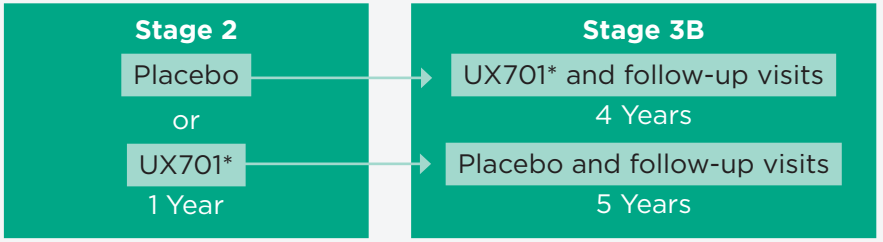
- Stage 2 will not begin until Stage 1 is completely enrolled.
- The exact dose of UX701 may vary depending on when you enter the study. If you enter the study in Stage 2, the dose will have already been determined from Stage 1.



- One intravenous infusion of UX701 followed by oral corticosteroids for ~2 months
- 11 visits over 4 years (6 can be phone visits)

Additional Stage 1 and Stage 2 Information

- 3-4 Screening visits (1 can be a home-health visit)
- Once eligible, 2 clinic visits on consecutive days (Baseline visit then Dosing Day)
- After Dosing, 19 follow-up visits over 1 year (14 can be home-health visits)



- One intravenous infusion of either UX701 or placebo followed by oral corticosteroids (or placebo) for ~2 months

**Dose selected in Stage 1*

- If you received placebo in Stage 2, you will receive UX701 in Stage 3B, if still eligible, followed by ~2 months of oral corticosteroids.
- If you received UX701 in Stage 2, you will receive placebo in Stage 3B, followed by ~2 months of placebo oral corticosteroids.
- Ongoing clinic and home-health visits to evaluate the long-term safety and efficacy of UX701.

What is a placebo? (Applies to Stage 2 only)

The placebo infusion looks like UX701; the oral placebo looks like an oral steroid. The placebos do not contain active ingredients. This means they should not have any true physical effects. Clinical studies often include placebos. This is so that results from different study groups can be compared. Comparing results can help us learn more about the drug or therapy being studied. In this study, if you receive placebo in Stage 2, you will have the opportunity to receive UX701 in Stage 3B, if eligible.

Why do we use steroids with AAV gene therapy?

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 your immune system's response to the study treatment and lessen inflammation, you will be given steroids.

You will take these steroids (or placebo) starting on the day of your infusion with the study treatment. You will be monitored while you are on the steroid (or placebo). The dosage will gradually be reduced over the course of a few weeks.

What will happen at study visits?

You will have frequent study visits for:

- Copper assessments
- 24-hour urine collections
- Blood draws for laboratory assessments. If enrolled in stage 1, additional blood, saliva, stool, and urine lab collections
- Other evaluations

For safety, it is important that you have these visits. You may need to stay overnight in the clinical site or a nearby hotel for some visits. In Stage 1 or Stage 2, you will have 24 visits over a period of 1 year. If you complete Stage 1, you will have 11 visits over 4 years in Stage 3A. If you complete Stage 2, you will have either:

- 27 visits over 4 years in Stage 3B (if dosed with UX701 in Stage 2)

  or

- 29 visits over 5 years in Stage 3B (if dosed with placebo in Stage 2 and eligible based on the results of a blood test at your Week 52 visit)

Home visits

You may have the option to complete some study visits at home instead of going to the clinical site. This will depend on where you live and if it is allowed by local laws. If you consent to have home visits, your clinical site will work with the home health provider to arrange the visits and provide you with the details of each visit. Specifically:

- **Stage 1 or Stage 2 – 14 visits can be home visits**
- **Stage 3A – 6 can be at home visits via a phone call**
- **Stage 3B – 17 can be at home visits (out of the 27 visits) OR 18 can be home visits (out of the 29), depending on which path or sequence of dosing you receive**

Travel support

You will have the option for the study travel vendor to arrange travel for you and a caregiver to and from study visits at no cost to you. You will need to provide written consent before they can do this. This vendor will also reimburse you for some costs related to coming to visits. If allowed by local laws, the vendor will pay you a stipend for each visit.

Visit schedule

We value your time and commitment to the study. The study doctor and team will do their best to stick to the noted length for each visit; please keep in mind these are estimates. Visits not shaded in green will NEED to be conducted at the study site. **Visits shaded in green may be conducted at the study site or as home health, telephone, or video visits. This will depend on where you live and if you consent to Home Health Nurse services. Some home visits may be longer so that the nurse can process and pack samples for shipment before leaving.**

STAGE 1 AND STAGE 2

Visit Name	Visit Timing	Expected Visit Duration
Screening (SCR1)	Up to 84 days prior to dosing	5-6 hours
Screening (SCR2)	Approximately 4 weeks after SCR1	30-60 min
Screening (SCR3)	Before dosing, after all assessments from SCR1 and SCR2 are completed, and your eligibility is confirmed	3-4 hours (additional 2-3 hours if completing optional liver biopsy)
Unscheduled (as needed)	For any assessments from screening that may need to be repeated	30-60 min
Pre-Dose 1	The day prior to dosing Day -1	5-6 hours
Dosing/Post-Dose 1	Day 0*	8-10 hours
W1-W4	Follow up 1, 2, 3, and 4 weeks after dosing	30-60 min
W6	Follow up 6 weeks after dosing	2-3 hours
W8	Follow up 8 weeks after dosing	30-60 min
W12	Follow up 12 weeks after dosing	2-3 hours
W14	Follow up 14 weeks after dosing	30-60 min
W16	Follow up 16 weeks after dosing	30-60 min
W18	Follow up 18 weeks after dosing	30-60 min
W20	Follow up 20 weeks after dosing	30-60 min
W24	Follow up 24 weeks after dosing	2-3 hours
W28	Follow up 28 weeks after dosing	30-60 min
W32	Follow up 32 weeks after dosing	30-60 min
W36	Follow up 36 weeks after dosing	2-3 hours
W40	Follow up 40 weeks after dosing	30-60 min
W44	Follow up 44 weeks after dosing	30-60 min
W48	Follow up 48 weeks after dosing	30-60 min
W52	Follow up 52 weeks after dosing	5-7 hours (additional 2-3 hours if completing optional liver biopsy)

* Day 0 is the day when you will receive study treatment Dose 1.

Continued >

Visit schedule *Continued*

If you enter the study in Stage 1, you will receive UX701, and you will move on to Stage 3A after the Stage 1 Week 52 visit.

If you entered the study in Stage 2, you will move on to Stage 3B after the Stage 2 Week 52 visit to undergo a second dosing. If you received Placebo in Stage 2, samples drawn at the Week 52 visit will be tested to find out if you can receive UX701 in Stage 3B.

STAGE 3A

Visit Name	Visit Timing	Expected Visit Duration
W60	Follow up 60 weeks after dosing in Stage 1	15 min
W68	Follow up 68 weeks after dosing in Stage 1	15 min
W78	Follow up 78 weeks after dosing in Stage 1	5-7 hours
W91	Follow up 91 weeks after dosing in Stage 1	15 min
W104/Y2	Follow up 104 weeks / 2 years after dosing in Stage 1	5-7 hours
W130	Follow up 130 weeks after dosing in Stage 1	15 min
W156/Y3	Follow up 156 weeks / 3 years after dosing in Stage 1	5-7 hours
W182	Follow up 182 weeks after dosing in Stage 1	15 min
W208/Y4	Follow up 208 weeks / 4 years after dosing in Stage 1	5-7 hours
W234	Follow up 234 weeks after dosing in Stage 1	15 min
W260/Y5/ EOS	Follow up 260 weeks / 5 years after dosing – End of Study for Subjects dosed with UX701 in Stage 1	5-7 hours

STAGE 3B

Visit Name	Visit Timing	Expected Visit Duration
Pre-Dose 2	The day prior to second dosing, after completion of Stage 2	5-6 hours
Dosing/Post-Dose 2	Day of second Dosing	8-10 hours
W53-W56	Follow up 53, 54, 55, 56 weeks after Stage 2 dosing	30-60 min
W58	Follow up 58 weeks after Stage 2 dosing	2-3 hours
W60	Follow up 60 weeks after Stage 2 dosing	30-60 min
W64	Follow up 64 weeks after Stage 2 dosing	2-3 hours
W66	Follow up 66 weeks after Stage 2 dosing	30-60 min
W68	Follow up 68 weeks after Stage 2 dosing	30-60 min
W70	Follow up 70 weeks after Stage 2 dosing	30-60 min
W72	Follow up 72 weeks after Stage 2 dosing	30-60 min
W76	Follow up 76 weeks after Stage 2 dosing	2-3 hours
W80	Follow up 80 weeks after Stage 2 dosing	30-60 min
W84	Follow up 84 weeks after Stage 2 dosing	30-60 min
W88	Follow up 88 weeks after Stage 2 dosing	2-3 hours
W92	Follow up 92 weeks after Stage 2 dosing	30-60 min
W96	Follow up 96 weeks after Stage 2 dosing	30-60 min
W100	Follow up 100 weeks after Stage 2 dosing	30-60 min
W104	Follow up 104 weeks after Stage 2 dosing	5-7 hours
W130	Follow up 130 weeks after Stage 2 dosing	15 min
W156/Y3	Follow up 156 weeks / 3 years after Stage 2 dosing	5-7 hours
W182	Follow up 182 weeks after Stage 2 dosing	15 min
W208/Y4	Follow up 208 weeks / 4 years after Stage 2 dosing	5-7 hours
W234	Follow up 234 weeks after Stage 2 dosing	15 min
W260/Y5/ EOS**	Follow up 260 weeks / 5 years after Stage 2 dosing – End of Study for subjects dosed with UX701 in Stage 2	5-7 hours
W286	Follow up 286 weeks after Stage 2 dosing	15 min
W312/Y6/ EOS**	Follow up 312 weeks / 6 years after Stage 2 dosing – End of Study for subjects dosed with Placebo in Stage 2	5-7 hours

** If you receive UX701 in Stage 2, your final visit will be at Week 260 (Year 5). If you receive UX701 in Stage 3B, your final visit will be at Week 312 (Year 6).

What will I need to do between visits?

You will receive instructions for all activities that need to be done at home. These activities will help the study doctor watch your health between visits. It is important to complete them as instructed.

Electronic diary (eDiary)

The study team will provide a tablet for you to use as your eDiary. You will use this to complete assessments before study visits. You will rate your health, Wilson disease symptoms, impact on your life, and overall changes. The study doctor will tell you when you need to do this. It may be 14 days before a visit, 7 days before, or 1 day before.

Oral steroids or placebo

After each infusion (UX701 or placebo) you will take oral steroids or placebo at home for approximately 2 months. The study team will give you a schedule so you know when to take these pills. You will also use the schedule to keep track of the pills you take. The study doctor will review this with you at visits.

Stool sample collection

If you enter the study in Stage 1, you will need to collect stool samples at home before some study visits. You will receive written instructions to help you with this. They will tell you how to prepare for collecting the samples, how to collect the samples, and what to do with the samples.

24-hour urine collection

You will need to collect urine samples at home before some study visits. You will receive written instructions and a worksheet. You will use the worksheet to record dates, times, and amounts of urine. It is very important that you follow the instructions closely and record all data requested. You will need to return the worksheet to the study team.

Are there potential risks?

The study sponsor and study doctors have taken steps to minimize or avoid risks related to being in this study. Even so, you may still have problems or side effects. Everyone taking part in the study will be watched carefully for side effects. As with any clinical study, there may be unknown risks. The study doctor will discuss all known risks with you. You will also read about them in the Informed Consent Form, which you will need to sign if you want to join the study.

Will I have to pay anything?

You will not have to pay to take part in this study. Study treatment will be provided at no cost to you. Procedures that are required for the study will also be provided at no cost to you. However, you or your health insurance company will be responsible for costs related to your current standard of care for Wilson disease. This will include your standard medications (for example, zinc, trientine, and/or penicillamine). Also, as mentioned (see page 8), you will have the option for the study travel vendor to arrange travel for you and a caregiver to and from study visits at no cost to you.

Will my privacy be protected?

The study doctor and team will keep your study records secure. They will take appropriate steps to maintain your privacy at all times. Information that identifies you (such as your name) will be replaced with a study code. That way, you cannot be personally identified.

Notes

Notes

Thank you for learning about the Cyprus^{2+} study!
If you have questions, please contact us at:

TrialRecruitment@Ultragenyx.com

Cyprus^{2+}™
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MRCM-UX701-00115 02/23