Clinical trial results:
A Phase 1/2 First-in-human, 2-part Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single Ascending Doses (Part 1: Open-label) and Repeat Doses (Part 2: Randomized, Double-blind, Placebo-controlled) of UX053 in Patients with GSD III

Summary

EudraCT number	2021-000903-19
Trial protocol	FR IT ES
Global end of trial date	20 March 2023

Results information

Result version number	v1 (current)
This version publication date	03 April 2024
First version publication date	03 April 2024

Trial information

Trial identification

Sponsor protocol code	UX053-CL101

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04990388
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ultragenyx Pharmaceutical Inc.
Sponsor organisation address	60 Leveroni Court, Novato, California, United States, 94949
Public contact	Trial Recruitment, Ultragenyx Pharmaceutical Inc., 1 415 756-8657, Trialrecruitment@ultragenyx.com
Scientific contact	Medical Information, Ultragenyx Pharmaceutical, Inc., 1 888 756-8657, medinfo@ultragenyx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 March 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 March 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the safety of UX053 in adults with Glycogen Storage Disease Type III (GSD III).

Protection of trial subjects:

All parents and/or legal guardians of the participant will be provided with an Information Sheet and/or Consent Form describing this study and providing sufficient information for participants to make an informed decision about the participation of their represented participant in this study. Where required, consent will be sought from the parents and/or legal guardian of the participant. The Informed Consent Forms (ICFs) and Patient Informed Consent Forms (PICFs) will include all elements required by ICH, Good Clinical Practice (GCP) and applicable regulatory requirements.

The Information Sheet and/or Consent Form will be submitted with the protocol for review and approval by the relevant Ethical Review Board for the study in each country. The formal consent of a participant, using the Informed Consent Form approved by the relevant Ethical Review Board, must be obtained before that participant undergoes any study procedure. The consent form must be signed by the participant's parent/legal guardian, and the Investigator-designated research professional obtaining the consent. Where required by the relevant Ethical Review Board, a witness may sign the consent form.

Background therapy:

Participants will also receive premedication, consisting of oral paracetamol/acetaminophen or ibuprofen, an H2 blocker (famotidine), and an H1 blocker (cetirizine).

Evidence for comparator: -

Actual start date of recruitment	18 October 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 6
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Spain: 2
Worldwide total number of subjects	9
EEA total number of subjects	3

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	9
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 9 participants enrolled in this study; 1 withdrew consent prior to group assignment, did not receive study drug, and was not included in any data table.

Pre-assignment

Screening details:

Eight participants enrolled and were treated; all completed participation in the single ascending dose (SAD) cohorts and were included in the final analysis. None of these participants were randomized, as they were only in SAD cohorts, and none rolled into an open label-repeated dose cohort, as the study discontinued early.

Pre-assignment period milestones

Number of subjects started	9
Number of subjects completed	8

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 1

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	SAD Cohort 1: 0.05 mg/kg

Arm description:

Participants received a single, peripheral intravenous (IV) infusion of a 0.05 mg/kg dose of UX053.

Arm type	Experimental
Investigational medicinal product name	UX053
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Study drug was administered as an IV infusion over the course of at least 4 hours, with a slower rate of infusion for the first hour to minimize the risk of infusion reactions.

Arm title	SAD Cohort 2: 0.10 mg/kg

Arm description:

Participants received a single, peripheral IV infusion of a 0.10 mg/kg dose of UX053.

Arm type	Experimental
Investigational medicinal product name	UX053
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Study drug was administered as an IV infusion over the course of at least 4 hours, with a slower rate of

infusion for the first hour to minimize the risk of infusion reactions.

Number of subjects in period 1[1]	SAD Cohort 1: 0.05 mg/kg	SAD Cohort 2: 0.10 mg/kg
Started	4	4
Completed	4	4

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One participant withdrew prior to reporting group assignment, and is not included in any data table.

Baseline characteristics

Reporting groups	
Reporting group title	SAD Cohort 1: 0.05 mg/kg
Reporting group description:	
Participants received a single, peripheral intravenous (IV) infusion of a 0.05 mg/kg dose of UX053.	
Reporting group title	SAD Cohort 2: 0.10 mg/kg
Reporting group description:	
Participants received a single, peripheral IV infusion of a 0.10 mg/kg dose of UX053.	

Reporting group values	SAD Cohort 1: 0.05 mg/kg	SAD Cohort 2: 0.10 mg/kg	Total
Number of subjects	4	4	8
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	52.20	43.53	
standard deviation	± 5.21	± 10.10	-
Gender categorical Units: Subjects			
Female	2	2	4
Male	2	2	4
Ethnicity Units: Subjects			
Hispanic or Latino	0	1	1
Not Hispanic or Latino	4	3	7
Race Units: Subjects			
White	3	4	7
Black or African American	1	0	1

End points

End points reporting groups

Reporting group title	SAD Cohort 1: 0.05 mg/kg
Reporting group description:	
Participants received a single, peripheral intravenous (IV) infusion of a 0.05 mg/kg dose of UX053.	
Reporting group title	SAD Cohort 2: 0.10 mg/kg
Reporting group description:	
Participants received a single, peripheral IV infusion of a 0.10 mg/kg dose of UX053.	

Primary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs, Deaths, Discontinuations, and/or Dose Changes

End point title	Number of Participants With Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs, Deaths, Discontinuations, and/or Dose Changes[1]

End point description:

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A TEAE is defined as any AE not present prior to the initiation of the drug treatment or any AE already present that worsens in either intensity or frequency following exposure to the drug treatment. An SAE is an AE that meets any of the following criteria in the view of either the Investigator or Ultragenyx: death; life-threatening; inpatient hospitalization or prolongation of existing hospitalization; disability/Incapacity; congenital anomaly/birth defect not present at screening; other important medical events. Severity of events were graded as mild (grade1), moderate (grade 2), severe (grade 3), life-threatening (grade 4), or death (grade 5).

End point type	Primary

End point timeframe:

From first dose of study drug through the end of study (up to Day 90)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics are presented per protocol.

End point values	SAD Cohort 1: 0.05 mg/kg	SAD Cohort 2: 0.10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: participants				
Any TEAE	3	4		
Serious TEAE	0	0		
Related TEAE	0	0		
Serious Related TEAE	0	0		
TEAE With Maximum Severity Grade 5	0	0		
TEAE With Maximum Severity Grade 4	0	0		
TEAE With Maximum Severity Grade 3	0	0		
TEAE With Maximum Severity Grade 2	0	0		
TEAE With Maximum Severity Grade 1	3	4		
TEAE Leading to Study Discontinuation	0	0		
TEAE Leading to Treatment Discontinuation	0	0		
TEAE Leading to Death	0	0		
TEAE Leading to Dose Reduction	0	0		
TEAE Leading to Dose Interruption	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) of Amylo-α-1,6-glucosidase 4-alpha-glucanotransferase Messenger Ribonucleic Acid (AGL mRNA) and the Excipient ATX95: Maximum Blood/Plasma Concentration (Cmax)

End point title	Pharmacokinetics (PK) of Amylo-α-1,6-glucosidase 4-alpha-glucanotransferase Messenger Ribonucleic Acid (AGL mRNA) and the Excipient ATX95: Maximum Blood/Plasma Concentration (Cmax)

End point description:

End point type	Secondary

End point timeframe:

Pre-infusion; 1, 3, 4, 4.5, 5 hr (± 10 min), 6 hr (± 20 min), 8, 10 hr (± 30 min), 24 hr (± 2 hr), 96, 168 hr (± 24 hr), 336, 504, 672 hr (± 48 hr) post-start of infusion

End point values	SAD Cohort 1: 0.05 mg/kg	SAD Cohort 2: 0.10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: ng/mL				
arithmetic mean (standard deviation)				
AGL mRNA	56.00 (± 30.59)	72.15 (± 60.99)		
ATX95	7010.00 (± 1360.71)	8585.00 (± 4439.62)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK of AGL mRNA and the Excipient ATX95: Time to Peak Drug Concentration (Tmax)

End point title	PK of AGL mRNA and the Excipient ATX95: Time to Peak Drug Concentration (Tmax)

End point description:

End point type	Secondary

End point timeframe:

Pre-infusion; 1, 3, 4, 4.5, 5 hr (± 10 min), 6 hr (± 20 min), 8, 10 hr (± 30 min), 24 hr (± 2 hr), 96, 168 hr (± 24 hr), 336, 504, 672 hr (± 48 hr) post-start of infusion

End point values	SAD Cohort 1: 0.05 mg/kg	SAD Cohort 2: 0.10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: hours				
median (full range (min-max))				
AGL mRNA	6.10 (4.5 to 7.9)	6.15 (2.8 to 8.1)		
ATX95	4.20 (3.0 to 4.4)	3.90 (3.0 to 4.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK of AGL mRNA and the Excipient ATX95: Total Drug Exposure to the Last Measurable Concentration (AUC0-last)

End point title	PK of AGL mRNA and the Excipient ATX95: Total Drug Exposure to the Last Measurable Concentration (AUC0-last)

End point description:

End point type	Secondary

End point timeframe:

Pre-infusion; 1, 3, 4, 4.5, 5 hr (± 10 min), 6 hr (± 20 min), 8, 10 hr (± 30 min), 24 hr (± 2 hr), 96, 168 hr (± 24 hr), 336, 504, 672 hr (± 48 hr) post-start of infusion

End point values	SAD Cohort 1: 0.05 mg/kg	SAD Cohort 2: 0.10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: ng*h/mL				
arithmetic mean (standard deviation)				
AGL mRNA	2567.5 (± 956.4)	3931.0 (± 4191.2)		
ATX95	25350.0 (± 3087.1)	31350.0 (± 20738.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK of AGL mRNA and the Excipient ATX95: Total Drug Exposure to Infinity (AUC0-inf)

End point title	PK of AGL mRNA and the Excipient ATX95: Total Drug Exposure to Infinity (AUC0-inf)

End point description:

End point type	Secondary

End point timeframe:

Pre-infusion; 1, 3, 4, 4.5, 5 hr (± 10 min), 6 hr (± 20 min), 8, 10 hr (± 30 min), 24 hr (± 2 hr), 96, 168 hr (± 24 hr), 336, 504, 672 hr (± 48 hr) post-start of infusion

End point values	SAD Cohort 1: 0.05 mg/kg	SAD Cohort 2: 0.10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: ng*h/mL				
arithmetic mean (standard deviation)				
AGL mRNA	2572.5 (± 958.0)	3948.5 (± 4178.7)		
ATX95	25375.0 (± 3055.5)	31425.0 (± 20758.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK of AGL mRNA and the Excipient ATX95: Elimination Half-life (t½)

End point title	PK of AGL mRNA and the Excipient ATX95: Elimination Half-life (t½)

End point description:

End point type	Secondary

End point timeframe:

Pre-infusion; 1, 3, 4, 4.5, 5 hr (± 10 min), 6 hr (± 20 min), 8, 10 hr (± 30 min), 24 hr (± 2 hr), 96, 168 hr (± 24 hr), 336, 504, 672 hr (± 48 hr) post-start of infusion

End point values	SAD Cohort 1: 0.05 mg/kg	SAD Cohort 2: 0.10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: hours				
arithmetic mean (standard deviation)				
AGL mRNA	53.8 (± 4.3)	44.8 (± 11.6)		
ATX95	18.0 (± 7.5)	32.3 (± 32.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK of AGL mRNA and the Excipient ATX95: Clearance (CL)

End point title	PK of AGL mRNA and the Excipient ATX95: Clearance (CL)

End point description:

End point type	Secondary

End point timeframe:

Pre-infusion; 1, 3, 4, 4.5, 5 hr (± 10 min), 6 hr (± 20 min), 8, 10 hr (± 30 min), 24 hr (± 2 hr), 96, 168 hr (± 24 hr), 336, 504, 672 hr (± 48 hr) post-start of infusion

End point values	SAD Cohort 1: 0.05 mg/kg	SAD Cohort 2: 0.10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: mL/h/kg				
arithmetic mean (standard deviation)				
AGL mRNA	21.42 (± 7.16)	55.51 (± 52.36)		
ATX95	39.80 (± 4.62)	94.73 (± 69.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK of AGL mRNA and the Excipient ATX95: Volume of Distribution at Steady State (Vss)

End point title	PK of AGL mRNA and the Excipient ATX95: Volume of Distribution at Steady State (Vss)

End point description:

End point type	Secondary

End point timeframe:

Pre-infusion; 1, 3, 4, 4.5, 5 hr (± 10 min), 6 hr (± 20 min), 8, 10 hr (± 30 min), 24 hr (± 2 hr), 96, 168 hr (± 24 hr), 336, 504, 672 hr (± 48 hr) post-start of infusion

End point values	SAD Cohort 1: 0.05 mg/kg	SAD Cohort 2: 0.10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: mL/kg				
arithmetic mean (standard deviation)				

AGL mRNA ATX95	1638.8 (± 722.4) 167.8 (± 76.0)	3993.3 (± 3546.5) 741.5 (± 874.0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to 90 days after dosing.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0
Reporting groups	
Reporting group title	SAD Cohort 1: 0.05 mg/kg
Reporting group description: Participants received a single, peripheral intravenous (IV) infusion of a 0.05 mg/kg dose of UX053.	
Reporting group title	SAD Cohort 2: 0.10 mg/kg
Reporting group description: Participants received a single, peripheral IV infusion of a 0.10 mg/kg dose of UX053.	
Reporting group title	Total
Reporting group description: Participants received a single, peripheral IV infusion of a 0.05 or 0.10 mg/kg dose of UX053.	

Serious adverse events	SAD Cohort 1: 0.05 mg/kg	SAD Cohort 2: 0.10 mg/kg	Total
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 8 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	SAD Cohort 1: 0.05 mg/kg	SAD Cohort 2: 0.10 mg/kg	Total
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 4 (75.00%)	4 / 4 (100.00%)	7 / 8 (87.50%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Joint Injury			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 8 (12.50%)
occurrences (all)	0	1	1

Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Hypertension			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Immune system disorders			
Seasonal Allergy			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Infections and infestations			
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Ear infection bacterial			

subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0	1 / 8 (12.50%) 1
Metabolism and nutrition disorders Hypoglycaemia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	1 / 4 (25.00%) 1	2 / 8 (25.00%) 2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 March 2021	• Vital signs was added as an assessment at the home health Week 1 visit for repeat dose (RD) cohorts. • Home health visits were added at Weeks 3, 5, and 7 for RD cohorts that included the following assessments: AEs, concomitant medications, hematology, chemistry, urinalysis, serum C-reactive protein (CRP), nutrition diary, and continuous glucose monitor (CGM). • Sample collection for anti-drug antibody (ADA) analysis was added at Weeks 2 and 6 for RD cohorts • An optional vital sign assessment was added at the time of discharge for all subjects • The SAD cohort data review was updated from an internal review to a review by the independent data monitoring committee (DMC). • The interval between dosing of individual subjects within SAD cohorts was updated from a minimum of 48 hours to a minimum of 72 hours. • Coronavirus 2019 (COVID-19) testing by real time – polymerase chain reaction (RT-PCR) was added to the Initial Screening Visit. • Hemoglobin A1C was added to the Initial Screening Visit for both the SAD and RD cohorts, as well as the Week 12 and Week 48/EOS Visit for the RD cohorts • Criteria for discharge 24 hours after the end of study drug administration were added. • Guidance on communication and seeking immediate medical attention was added. • The following inclusion criterion were added: o Criteria to ensure enrolled subjects have clinically significant disease manifestations that are likely to be improved by UX053 treatment. o "alanine aminotransferase (ALT) ≤ 5x upper limit of normal (ULN) during the 3 months prior to the Baseline Visit."
24 March 2021	(con't) • The following exclusion criteria was added: o "Receipt of only 1 of 2 planned doses of a coronavirus disease 2019 (COVID-19) vaccine. Subjects who have not received a COVID-19 vaccine, and those who have completed COVID-19 vaccination are eligible" and "Symptomatic COVID-19 infection." Additionally, guidance around the ability and timing to receive the COVID-19 vaccine and measures taken to minimize risk to COVID-19 exposure were added o "Severe renal impairment defined as a defined as a glomerular filtration rate (GFR) ≤ 29 mL/min (Levey et al., 2005)." o "Poorly controlled hypothyroidism, based on the judgement of the Investigator or Ultragenyx, whichever is most conservative" o "History of chronic coagulopathy, thrombophilia, or disorder of complement activation" o "Use of concomitant medications that alter PT/INR, including warfarin and direct oral anticoagulants (eg, rivaroxaban, apixaban, and edoxaban). Patients who receive medications that affect platelet function, such as aspirin or clopidogrel, are allowed unless they have comorbidities that in the judgment of the Investigator place them at undue risk to participate in the study." o "Current treatment with long-term immunosuppressive medications. This includes subjects with autoimmune conditions managed with immunosuppressive medications and solid organ transplant recipients." o "Active tuberculosis requiring treatment in the past 3 years." o "History of active alcohol and/or drug abuse that in the Investigator's assessment would impair the subject's ability to comply with the protocol." o "Females of childbearing potential with hepatocellular adenoma who are unwilling to use nonhormonal contraception." o Poorly controlled diabetes and its definitions o Resistant hypertension

24 March 2021	(con't) • The exclusion criterion "Presence or history of any hypersensitivity reactions to UX053 or its excipients that, in the judgment of the Investigator, places the subject at increased risk for adverse effects" was updated to "Presence or history of any hypersensitivity requiring medical evaluation and management (including injection/infusion associated reactions, such as lymphadenopathy) to UX053, its excipients, or any drug products that contain polysorbate or polyethyleneglycol (PEG). This may include mRNA-based vaccines that contain PEG or polysorbate." • If dexamethasone (or equivalent) was used as a rescue medication, premedication with dexamethasone (or equivalent) should be considered for all subjects' subsequent infusions. • Text was added to indicate that Ultragenyx would no longer reserve the right to discontinue subjects or the study for administrative reasons. Subjects only eligible for removal from the study due to withdrawal of consent. • Subject-level Redosing and Stopping Criteria was added, including requirements for redosing study drug, criteria that exclude subjects from redosing (eg, developing new or worsening symptoms of liver disease, receipt of blood products for treatment of consumptive coagulopathy, and specific elevations in ALT levels), and action required in the event that an IRR occurs, as specified by Common Terminology Criteria for Adverse Events (CTCAE) severity. Additionally, text was added to indicate that Ultragenyx would notify the DMC immediately if any subject experienced an event that satisfied subject-level or study-level stopping criteria.
24 March 2021	(con't) • The following were added as a study stopping criteria: o Anaphylaxis o "Any TEAE with a severity ≥ Grade 3 (CTCAE version 5.0) affecting the cardiopulmonary, renal, or neurological systems, regardless of relationship to study drug, pending a DMC safety review" o "3 subjects develop platelet counts < 50,000 per mm^3 (or thrombocytopenia ≥ Grade 3 in severity)" o "3 subjects develop international normalized ratio (INR) > 1.5 (or INR increase ≥ Grade 2 in severity)" • The following study stopping criterion was modified from "Increases in serum concentrations of ALT or aspartate aminotransferase (AST) > 2x from Baseline and > 3x theULN, accompanied by increases in serum concentrations of total bilirubin > 2x ULN or INR > 1.5, without any other underlying cause that may account for such changes" to "Increases in ALT or AST > 2x from Baseline and > 3x the ULN, accompanied by total bilirubin > 2x ULN or INR > 1.5, without findings of cholestasis (defined as serum alkaline phosphatase (ALP) activity < 2x ULN) and in the absence of a plausible alternate explanation." • The following text was added: "Regulatory authorities will be notified immediately if the study stopping criteria are met and study enrollment or dosing is halted." • Text was added to indicate that subjects will not be replaced if they have received any study drug. • Oxygen saturation was added to the list of vital sign assessments. • R-R was added to the list of measurements calculated for the electrocardiogram assessment. • In addition to glycogen content, muscle fat fraction in the calf was added during the calf 13C Magnetic Resonance Spectroscopy (MRS) assessment. • Text was added to reflect that the AE Cytokine Release Syndrome (CRS) will be graded by the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading for CRS (Lee et al., 2019).
24 March 2021	(con't) • The end of the safety reporting period was updated to 28 days following the final dose of study drug or the EOS I (SAD cohorts) and EOS II (RD cohorts) final study visit, whichever occurs later. Additionally, suspected related SAEs could have been reported at any time following the EOS I/II visit. • Magnesium and bicarbonate were added to the list of assessments included in the standard chemistry panel. • The text "plus 90 days for a full sperm cycle" was removed from the following statement: "The time period required is generally determined by the pharmacokinetic properties of the study product and non-clinical reproductive toxicity data, plus 90 days for a full sperm cycle."

01 October 2021	• The following inclusion criterion was removed: o "History of any of the following: a) Severe hypoglycemia, defined as neuroglycopenia (eg, altered mental status, seizure, dizziness, slurred speech, blurry vision, abnormal behavior, perioral paresthesia, requiring intervention by a caregiver) or blood glucose < 54 mg/dL (3 mmol/L) within the last year; b) ≥ 2 incidents of symptomatic hypoglycemia (defined as blood glucose < 70 mg/dL [3.9 mmol/L] if measured at the time of symptoms) within the last year, despite nutrition management c) Ongoing liver injury, defined as alanine aminotransferase (ALT) > 2.5x the ULN within the last year" • The liver MRI, MRS, Fibroscan/ultrasound elastrography, and calf MRS occurring during screening was moved from the Stablization Visit (STV) to the Initial Screening Visit (ISV). • At the discretion of the Investigator, with input from Ultragenyx and the DMC, and based on the emerging safety profile of UX053, additional premedications and rescue medications were allowed to reduce the risk and severity of immune reactions in RD cohorts. Premedication and rescue medication selection were based on the nature of the reactions being observed and the risks of such medications in patients with GSD III. • A row was added to the schedule of events table to indicate the visit windows. • Edits were made to reflect that handheld glucometer (HHG) and CGM data went from being entered by the site in the case report form (CRF) to being uploaded weekly by subjects on a study-provided laptop • Appendix 3 was updated to include all laboratory assessments instead of only safety laboratory assessments. Related to this change, creatine kinase was removed from the chemistry panel in Appendix 3, as it is already collected under Skeletal Muscle & Strength Assessments
01 October 2021	(con't) • Text clarified that for the SAD cohorts, a complete physical exam was required at the Screening, Baseline, and End of Study/Early Termination Visits. A targeted physical exam was performed at the Day 1 Visit. • The PROMIS questionnaires, SF-36v2, and GNE Myopathy Functional Activities Scale (GNEM-FAS) were removed from the Screening Visit for SAD cohorts. • Serum B-type natriuretic peptide (BNP) was updated to plasma BNP. • Magnetic resonance spectroscopy (MRS) was no longer limited to 13C MRS.
14 July 2022	• Peripheral blood mononuclear cell (PBMC) collection for the assessment of glycogen debranching enzyme (GDE) enzyme activity was removed • RD cohorts were separated into 2 types: double blind (DB)-RD and open label (OL)-RD, as subjects who complete participation in SAD cohorts could be rescreened and enrolled into OL-RD cohorts, receiving 4 additional doses of UX053 Q4W. DB-RD cohorts still receive 5 total doses of UX053 Q2W. Initiation of OL-RD cohorts was designed to run in parallel with initiation of DB-RD cohorts, guided by DMC review. During rescreening for OL-RD cohorts, subjects would have been assessed for status of diet optimization and stability based on nutrition data collected during participation in SAD cohorts and rescreening for OL-RD cohorts. A schematic was added to illustrate nutrition optimization and stabilization requirements during screening. • Reflecting the addition of a Q4W dosing regimen, the secondary endpoint was updated to "PK parameters of AGL mRNA and ATX95, which may include Tmax, Cmax, AUClast, AUCinf, AUCtau (RD cohorts only), accumulation ratio (RAUC; RD cohorts only), Tlast, T1/2, CL, Vss" • One new inclusion criterion and 1 new exclusion criterion were added to allow rescreening of subjects from the SAD cohorts as they enter the OL-RD cohorts (noted above). Existing eligibility criteria that referred to RD cohorts were edited to specify how the criteria apply to the new OL-RD cohorts. The newly added inclusion criterion is: For subjects rescreening into OL-RD cohorts, after treatment with UX053 in a SAD cohort, subjects must meet the following criteria: a) If a significant rise in ALT occurs after the prior dose, ALT should show a decreasing trend toward the subject's baseline value; b) Total bilirubin is within normal limits; c) Platelets are within normal limits; d) INR is within normal limits.

14 July 2022	(con't) The additional exclusion criterion is: For subjects rescreening into OL-RD cohorts, any of the following after treatment with UX053 in a SAD cohort [are excluded]: a) New or worsening symptoms of liver disease (including new or worseninghepatomegaly) along with any increase in transaminase levels; b) Receipt of any blood product administration (eg, packed red blood cells, platelet, fresh frozen plasma) for management of consumptive coagulopathy; c) An ALT level that is ≥ 8x ULN and > 2x the subject's baseline value in the absence of an alternative explanation. • An optional controlled fasting challenge (CFC) was added for subjects in RD cohorts. • SAD cohorts 3S and 4S were updated to comprise of 2 subjects instead of 3 subjects. • Dose escalation plans were clarified, with an aim to test at least 3 dose levels of UX053. Text was added to indicate that dose levels for each cohort may be altered depending on safety, PK, and pharmacodynamic (PD) findings from prior cohorts, with a maximum dose of 0.30 mg/kg. Cohorts 4S and 4R, in which subjects were to receive single or multiple doses of UX053 at 0.30 mg/kg, respectively, were made optional. • The total number of subjects included in the study was updated to approximately 18, reflecting 6 planned subjects in Cohorts 1S, 2S, and 3S and 12 planned subjects in Cohorts DB-1R, DB-2R, and DB-3R. Text was added to clarify that additional subjects may be added to SAD or RD cohorts for further characterization of safety. • Reference to the Pharmacy Manual regarding guidance on dose reductions was removed. If a subject in a RD cohort (either DB or OL) developed a TEAE/serious TEAE ≥ Grade 3 that was considered by the Investigator to be related to study drug or an intolerable TEAE in a RD cohort, any further study drug administration and any subject-level dose reductions should have been discussed with the Medical Monitor.
14 July 2022	(con't) • Text was edited to clarify that telephone calls regarding the use of CGM andHHG devices will occur as needed, outside of scheduled study visits. • Text was added to clarify that subjects within a given RD cohort can be dosed simultaneously. After initiation of repeat dosing, subjects will follow a Q2W (DB-RD cohorts) or Q4W (OL-RD cohorts) dosing regimen. • The italicized text was added to the following inclusion criterion "Willing and able to provide access to medical records surrounding medical treatment that occurred prior to enrollment and during the study." • The exclusion criterion "Planned surgery, including dental surgeries, during the SAD Period for subjects in Part 1 or prior to Week 10 of the RD Period for subjects in Part 2" was updated to "Planned surgery, including dental surgeries, during the study." This text was also updated in the section regarding restricted procedures. • For all cohorts, nutrition diary recordings were changed to be recorded at least 3 consecutive days per week through Screening and for the 3 consecutive days in the week leading up to each subsequent visit • Assessments for serum CK – muscle/brain (CK-M/B), troponin I, and CK, and plasma B-type natriuretic peptide (BNP) were added at Weeks 2, 4, 6, and 8 for the DB-RD cohorts. The assessment for plasma BNP was removed from Initial Screening Visit (ISV). • Assessments for urine beta hydroxybutyrate and whole blood for RNA analysis were removed for all cohorts. • The physical exam and weight assessment was removed from Week 12, 24, and 36 for the DB-RD cohorts. • The Day 42 Visit was removed for the SAD cohort. • Assessment of serum ketones was removed at Week 9 for the DB-RD cohorts. Serum ketones was also changed to capillary ketones for DB-RD cohorts. Also for the DB-RD cohorts, ketones are no longer assessed at the Nutrition Optimization Visit (NOV; previously optional per discretion of the Investigator) and Weeks 1, 12, 24, and 36.

14 July 2022	(con't) • The schedule of events tables for the RD cohorts reflects that the imaging assessments (liver MRI, MRS, FibroScan or ultrasound elastography) can occur throughout rescreening (OL-RD) or screening (DB-RD). Imaging assessments were also removed for the DB-RD EOS III W48/ET Visit. • PT/INR was changed to be assessed at all scheduled study visits in the Treatment and Follow-up Period for the DB-RD cohorts. • Plasma glucose tetrasaccharide (Glc4) assessment was removed from the study, and assessments for urine Glc4 were added at Weeks 3, 4, 5, 6, 7, and 9 for DB-RD cohorts. • White blood cell (WBC) and red blood cell (RBC) collection was added for future use. • Additional safety language was added noting that epinephrine should be administered if a subject develops an infusion-related reaction (IRR) that meets diagnostic criteria for anaphylaxis. For all other hypersensitivity reactions ≥ Grade 2 in severity suspected to be due to immune activation, dexamethasone should be the initial rescue medication. Additional text was added to account for rescue medications in the event of severe consumptive coagulopathy and profound complement activation. • The terminology regarding the analyses sets, Safety, Per Protocol, and PK, was updated. • Footnote a in the SAD cohort's schedule of events table was updated to indicate that there must be a minimum of 10 days between any assessments that are measured at both the Screening and the Baseline Visit • When feasible, quantitation of glycogen using nuclear overhauser enhancement (glycoNOE) (Zhou et al., 2020) of the liver, was added to be collected at the time of the liver MRI/MRS. • Text was added to clarify modification of infusion rate, including "If the total infusion time is extended beyond 4 hours, a blood sample should be collected at the new end of infusion (EOI) time. If the new EOI time overlaps with a prespecified time point, sampling should continue at the next scheduled time point"
14 July 2022	(con't) • Text was added defining a stable diet as remaining within the nutritional guidelines for adults with GSD III based on expert recommendations. Additionally, text providing examples of how deviating from a stable diet could have been a protocol deviation was removed. • Scoring of the GNEM-FAS was changed from the clinician, who administers the assessment, to Ultragenyx. • Text was added indicating that a future amendment may occur to add an open-label extension after an interim review of safety, PK, and PD data • In exclusion criterion 9, the text "mRNA-based" was removed from the following sentence "This may include mRNA-based vaccines that contain PEG or polysorbate." • In the following sentence within exclusion criterion 10, "asymptomatic cardiomyopathy" was updated to "mild cardiomyopathy:" "Asymptomatic cardiomyopathy and left ventricular hypertrophy (LVH) are allowed. • A brief study title was added to the title page. The study title was also edited. • The sentence "If dexamethasone (or equivalent) is used as a rescue medication, premedication with dexamethasone (or equivalent) should be considered for all subjects' subsequent infusions" was updated to "If dexamethasone (or equivalent) is used as a rescue medication, premedication with dexamethasone (or equivalent) should be considered for that subject's subsequent infusions after discussion with the Medical Monitor." • Serum myoglobin, serum biotinidase, and calf MRS were removed from the study for all cohorts. • The Week 12, 24, and 36 Visits for DB-RD cohorts were changed to be conducted at home. As a result, Fibroscan or ultrasound elastography will be conducted at Week 10 instead of Week 12; and GNEM-FAS, Patient-reported Outcomes Measurement Information System (PROMIS), and HHD will be assessed at Week 10, and not at Weeks 12, 24, and 36.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported