Clinical trial results:
A Long-Term Open-Label Treatment and Extension Study of UX003 rhGUS Enzyme Replacement Therapy in Subjects with MPS 7

Summary

EudraCT number	2015-001875-32
Trial protocol	Outside EU/EEA PT
Global end of trial date	14 January 2019

Results information

Result version number	v1 (current)
This version publication date	26 July 2019
First version publication date	26 July 2019

Trial information

Trial identification

Sponsor protocol code	UX003-CL202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02432144
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ultragenyx Pharmaceutical Inc.
Sponsor organisation address	60 Leveroni Court, Novato, United States, California 94949
Public contact	Medical Information, Ultragenyx Pharmaceutical Inc., +1 888-756-8567, medinfo@ultragenyx.com
Scientific contact	Medical Information, Ultragenyx Pharmaceutical Inc., +1 888-756-8567, medinfo@ultragenyx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001540-PIP01-13
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	14 January 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate long-term safety of UX003 in subjects with mucopolysaccharidosis type 7 (MPS 7).

Protection of trial subjects:

The trial was designed, conducted, recorded, and reported in accordance with the principles established by the 18th World Medical Association General Assembly (Helsinki, 1964) and subsequent amendments and clarifications adopted by the General Assemblies. The investigators made every effort to ensure that the study was conducted in full conformance with Helsinki principles, International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines, current Food and Drug Administration (FDA) regulations, EU Clinical Trial Directive 2001/20/EC, and local ethical and regulatory requirements. Each investigator was thoroughly familiar with the appropriate administration and potential risks of administration of the study drug, as described in the protocol and Investigator's Brochure, prior to the initiation of the study. The method of obtaining and documenting informed consent and the contents of the informed consent form (ICF) complied with ICH GCP guidelines, the requirements of 21 CFR Part 50, "Protection of Human Subjects," the Health Insurance Portability and Accountability Act regulations, and all other applicable regulatory requirements. Investigators were responsible for preparing the ICF and submitting it to the Sponsor for approval prior to submission to the Institutional Review Board (IRB). All ICFs were written in regional language and contained the minimum elements for consent as mandated by the ICH guidelines. An IRB-approved ICF was provided by the Sponsor prior to initiation of the study. Investigators obtained signed written informed consent from each potential study subject prior to the conduct of any study procedures and after the methods, objectives, requirements, and potential risks of the study were fully explained to each potential subject. Consent for participation could be withdrawn at any time for any reason by the subject.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 November 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 12
Worldwide total number of subjects	12
EEA total number of subjects	0

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)	3
Adolescents (12-17 years)	4
Adults (18-64 years)	5
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects with MPS 7 who were who were UX003 treatment-naïve or previously enrolled and treated in a prior clinical study of UX003 could enroll into this treatment and extension study provided all eligibility criteria had been met for a given subject.

All subjects enrolled in USA, but 3 subjects later transferred to sites outside of USA.

Pre-assignment

Screening details:

Ten of 12 subjects entered this extension study at study Week 0 with ongoing UX003 treatment for the prior 24 or 48 weeks in study UX003-CL301 [2014-005638-71]; 2 subjects had a large gap between studies (61 weeks between doses).

Period 1

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

Arms

Arm title	UX003

Arm description:

4 mg/kg UX003 every other week (QOW)

Arm type	Experimental
Investigational medicinal product name	UX003
Investigational medicinal product code	
Other name	recombinant human beta-glucoronidase, rhGUS, Mepsevii ™, vestronidase alfa, vestronidase alfa-vjbk
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

UX003 was administered QOW by slow IV infusion over approximately 4 hours.

Number of subjects in period 1	UX003
Started	12
Completed	11
Not completed	1
Subject non-compliance	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study
Reporting group description:	
4 mg/kg UX003 QOW	

Reporting group values	Overall Study	Total	
Number of subjects	12	12	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	16.56		
standard deviation	± 5.466	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	4	4	
Ethnicity Units: Subjects			
Hispanic or Latino	6	6	
Not Hispanic or Latino	6	6	
Unknown or Not Reported	0	0	
Race Units: Subjects			
White	9	9	
Other, not specified	3	3	
Urinary Glycosaminoglycans (uGAG) Units: g GAG/g creatinine			
arithmetic mean	1.54848		
standard deviation	± 0.413237	-	

End points

End points reporting groups

Reporting group title	UX003
Reporting group description:	
4 mg/kg UX003 every other week (QOW)	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
All enrolled subjects who received at least one dose of investigational product in this study.	

Primary: Number of Subjects With Treatment Emergent Adverse Events (TEAEs), Serious TEAEs, and TEAEs Leading to Discontinuation

End point title	Number of Subjects With Treatment Emergent Adverse Events (TEAEs), Serious TEAEs, and TEAEs Leading to Discontinuation[1]
End point description:	
An adverse event (AE) is defined as any untoward medical occurrence, whether or not considered drug related. A serious AE is an AE that at any dose, results in any of the following outcomes: death; a life-threatening AE; inpatient hospitalization or prolongation of existing hospitalization; persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; a congenital anomaly/birth defect; or is an important medical event. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), Grade 5 (death). TEAEs were defined as reported AEs with onset during the treatment.	
End point type	Primary
End point timeframe:	
From first dose of study drug until 30 days after the last dose of study drug. Mean duration of UX003 treatment was 100.5 weeks.	

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	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: subjects				
TEAEs	12			
Serious TEAEs	4			
Treatment-Related TEAEs	9			
Treatment-Related Serious TEAEs	1			
Grade 3 or 4 TEAEs	3			
TEAEs Leading to Treatment Discontinuation	0			
TEAEs Leading to Study Discontinuation	0			
TEAEs Leading to Death	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline Over Time in Urinary Glycosaminoglycan (uGAG) Excretion (Liquid Chromatography-Tandem Mass Spectrometry, Dermatan Sulfate)

End point title	Percent Change From Baseline Over Time in Urinary Glycosaminoglycan (uGAG) Excretion (Liquid Chromatography-Tandem Mass Spectrometry, Dermatan Sulfate)

End point description:

First morning void urine was evaluated for uGAG concentration and normalized to urinary creatinine concentration.

End point type	Secondary

End point timeframe:

(prior to the first dose of study drug in UX003-CL301), Weeks 0, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	12[2]			
Units: percentage change in uGAG excretion				
arithmetic mean (standard deviation)				
Week 0; n=12	-62.19 (± 16.133)			
Week 12; n=11	-67.31 (± 13.953)			
Week 24; n=12	-64.03 (± 14.669)			
Week 36; n=11	-60.58 (± 23.552)			
Week 48; n=10	-57.04 (± 23.611)			
Week 60; n=9	-72.25 (± 18.609)			
Week 72; n=9	-78.52 (± 10.367)			
Week 84; n=8	-80.89 (± 10.023)			
Week 96; n=8	-82.39 (± 6.011)			
Week 108; n=7	-82.19 (± 6.551)			
Week 120; n=5	-88.74 (± 4.023)			
Week 132; n=4	-89.22 (± 3.662)			
Week 144; n=4	-91.62 (± 1.827)			

Notes:

[2] - n=subjects with an assessment at given time point

Attachments (see zip file)	Percent Change from BL in uGAG Excretion Stat Analyses.docx

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug until 30 days after the last dose of study drug. Mean duration of UX003 treatment was 100.5 weeks.

Adverse event reporting additional description:

TEAEs, defined as reported AEs with onset during the treatment, are presented.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0.0

Reporting groups

Reporting group title	Total

Reporting group description:

PLACEHOLDER

Serious adverse events	Total		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 12 (33.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Head Injury			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Interstitial Lung Disease			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchospasm			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Asthmatic Crisis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Total		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acrochordon			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Skin Papilloma			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hypotension			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Chest Pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gait Disturbance			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Infusion Site Extravasation			
subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	17		
Infusion Site Swelling			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
Oedema Peripheral			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Immune system disorders			
Seasonal Allergy			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Asthma			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Cough			

subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	7		
Epistaxis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nasal Congestion			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Rhinitis Allergic			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
Rhinorrhoea			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	4		
Upper Respiratory Tract Congestion			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Sleep Apnoea Syndrome			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Sinus Congestion			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Somnambulism			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Arthropod Bite			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Fall			

subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Head Injury subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Laceration subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Ligament Sprain subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2		
Skin Abrasion subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 4		
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Pericardial Effusion subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Nervous system disorders Brain Compression subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Cervical Cord Compression subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Headache subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2		
Hydrocephalus subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Memory Impairment			

subjects affected / exposed occurrences (all) Lethargy subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) Sinus Headache subjects affected / exposed occurrences (all) Sensory Disturbance subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1 2 / 12 (16.67%) 3 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1		
Blood and lymphatic system disorders Eosinophilia subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1		
Ear and labyrinth disorders Ear Pain subjects affected / exposed occurrences (all) Otorrhoea subjects affected / exposed occurrences (all)	 2 / 12 (16.67%) 3 1 / 12 (8.33%) 1		
Eye disorders Conjunctivitis Allergic subjects affected / exposed occurrences (all) Eye Pruritus subjects affected / exposed occurrences (all) Lacrimation Increased subjects affected / exposed occurrences (all)	 2 / 12 (16.67%) 2 1 / 12 (8.33%) 3 1 / 12 (8.33%) 7		
Gastrointestinal disorders			

Dyspepsia				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Diarrhoea				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	2			
Aphthous Ulcer				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Gastrooesophageal Reflux Disease				
subjects affected / exposed	3 / 12 (25.00%)			
occurrences (all)	4			
Gingival Bleeding				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Haematochezia				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Lip Ulceration				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Nausea				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	4			
Oesophagitis				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Tooth Discolouration				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Toothache				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Tooth Loss				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			

Vomiting			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Dermatitis Atopic			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Macule			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	39		
Erythema			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Papule			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	4		
Rash			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Rash Maculo-Papular			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Rash Papular			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
Rash Pruritic			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	5		
Urticaria			

subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	6		
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Dactylitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Back Pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Arthralgia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	4		
Joint Range Of Motion Decreased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Joint Stiffness			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Joint Swelling			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Muscle Twitching			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Pain In Extremity			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Scoliosis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Spinal Instability			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Trigger Finger			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Infections and infestations			
Acarodermatitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Abscess Neck			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Ear Infection			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
Folliculitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Furuncle			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Impetigo			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Otitis Media			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Otitis Externa			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	4		

Otitis Media Acute			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Pharyngitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	4		
Rhinitis			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	4		
Root Canal Infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Soft Tissue Infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Tinea Pedis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Upper Respiratory Tract Infection			
subjects affected / exposed	7 / 12 (58.33%)		
occurrences (all)	17		
Tooth Infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Viral Infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 December 2015	1. Administrative and Contact Information: The protocol was updated to provide the EudraCT number (2015-001875-32) for the study. Contact information for the medical monitor and drug safety was updated. 2. Study Population: Inclusion criterion #7 was modified to clarify that for UX003 treatment naïve subjects the elevated uGAG excretion must have been a minimum of 2 fold over mean normal levels for age (at Week 0). Inclusion criteria # 7 and #8 were combined; UX003 naïve participants must have been at least 5 years of age at enrollment. 3. Study Visit Schedule: The Early Termination Visit was renamed the Termination Visit. Visit qualifiers were modified such that if a subject withdrew from the study, or if the study was terminated prior to Week 144, the termination visit should have been completed within 30 days of the last dose of study drug. Assessments performed within 30 days of the termination visit were not to be repeated unless clinically indicated. 4. Study Procedures and Assessments: Several updates were to clarify or remove procedures and the associated Schedule of Events. Language regarding the assessments to be performed throughout this extension study was broadened for applicability to subjects who enrolled from additional feeder trials with UX003. In general, efficacy assessments not performed during the primary trial were not required for this long-term treatment and extension study; safety assessments were to be conducted on all subjects as indicated in the protocol. Modifications to specific study procedures and assessments specified in the protocol text are summarized below: • Serum GAG was removed from the study. • Weight for drug preparation could be obtained up to 15 days prior to the indicated visit and was removed from the Termination Visit procedures
18 December 2015	(continued) • The frequency of serum biomarker assessments was reduced from 12-week intervals to 24-week intervals throughout the study. A qualifier was inserted to perform if indicated based on prior studies. • Physician Clinical Global Impression was removed as an assessment in the study. • The frequency of qualitative assessments of the liver and spleen was reduced from 12-week intervals to 48-week intervals except for naïve patients; the assessment was separated from physical examinations in the Schedule of Events. 5. Reporting and Follow-up of Adverse Drug Events: Additional guidance and alignment with AE reporting requirements was added, including text to clarify that hospitalizations planned prior to study enrollment were not considered SAEs, simplification of the categories for attributions of AE relatedness to study drug, and the addition of a new section to provide direction on the reporting requirements for suspected unexpected serious adverse reactions (SUSAR) to appropriate Regulatory Authorities (including Competent Authorities in all Member States concerned), IRBs/ECs, and Investigators as per local laws and regulations.

04 March 2016	1. Study Design and Methodology: The protocol was updated to remove reference to availability of commercial drug in the subject's territory as a reason for study termination. In addition "end of trial" was defined as the last visit of the last subject undergoing evaluation in the study. As the planned duration of treatment in this study was up to 144 weeks, the end of trial was defined as the Week 144 visit of the last subject. In the event the study was terminated by the Sponsor prior to Week 144, all subjects were to complete a termination visit and the date of the last termination visit of the last subject would define the end of the trial. 2. Study Population: Inclusion criterion #2 was updated to clarify that written informed consent by a legally authorized representative could be provided for subjects, including adult subjects, who are intellectually impaired. Inclusion criterion #4 was updated to specify that sexually active subjects must have been willing to use a highly effective method of contraception. In addition, the list of examples of highly effective methods of contraception was updated to remove barrier methods and include bilateral tubal occlusion. Inclusion criterion #5 was updated to remove tubal ligation as a reason that female subjects would be considered not of childbearing potential and to clarify the definition of those considered not of childbearing potential.
04 March 2016	(continued) 3. Pregnancy During Study. The study procedures were updated to indicate that female subjects who became pregnant during the study would be withdrawn from study drug. At the conclusion of the pregnancy, a decision would be made if the female subject could resume study drug based on study treatment risk-benefit evaluation and willingness of the subject to comply with the contraceptive requirements. In the event of a pregnancy in the partner of a male subject, the male subject could continue with study drug and, as previously stated in the protocol, the Investigator must have made every effort to follow the pregnancy of either subject or partner through resolution of the pregnancy (delivery or termination) and report the resolution to Ultragenyx or its designee. 4. Record Retention: Study procedures were updated to state that all study records must be retained for at least 25 years after the end of the clinical trial or in accordance with national law.
28 July 2016	1. Title Page. The Coordinating Investigator was updated. 2. Pregnancy Testing and Contraception. The description of highly effective methods of contraception was updated to clarify that hormonal contraceptives should be associated with the inhibition of ovulation. 3. Criteria for Evaluation: Measurement of Anti-Drug Antibody (ADA) Types. ADA testing, as one of the safety assessments (primary objective), was clarified to indicate that clinically significant changes from UX003 CL301 Baseline in levels of all anti-drug antibodies (ADAs), not only the immunoglobulin G (IgG) isotype, would be evaluated. 4. Serum Biomarkers of Inflammation. Blood for analysis of serum biomarkers of inflammation would not be collected after Week 48. 5. Bruininks-Oseretsky Test of Motor Proficiency (BOT-2). This test of motor proficiency would not be conducted after Week 48. 6. Childhood Health Assessment Questionnaire (CHAQ). The person responsible for completing the CHAQ was clarified as the subject's parent or caregiver. 7. Health Assessment Questionnaire (HAQ). The mode of administration of the HAQ and the persons permitted to complete the HAQ were clarified. 8. Record Retention. Updated to clarify the responsibilities of the Investigator, Institution, and Ultragenyx with regard to record retention.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported