



Clinical trial results:

A Randomized, Placebo-Controlled, Blind-Start, Single-Crossover Phase 3 Study to Assess the Efficacy and Safety of UX003 rhGUS Enzyme Replacement Therapy in Patients with MPS VII

Summary

EudraCT number	2014-005638-71
Trial protocol	Outside EU/EEA
Global end of trial date	04 May 2016

Results information

Result version number	v2 (current)
This version publication date	31 March 2019
First version publication date	23 July 2017
Version creation reason	<ul style="list-style-type: none">New data added to full data set Updates to subject disposition, baseline characteristics and endpoint descriptions

Trial information

Trial identification

Sponsor protocol code	UX003-CL301
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02230566
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ultragenyx Pharmaceutical Inc
Sponsor organisation address	60 Leveroni Court, Novato, United States, 94949
Public contact	Robert Hostutler, Sr. Clinical Program Manager, Clinical Operations, 1 4154838148, rhostutler@ultragenyx.com
Scientific contact	Christine Haller, MD, VP, Drug Safety and Pharmacovigilance, 1 4154838937, challer@ultragenyx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-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	04 May 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	04 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In the European Union (EU) and rest of world, efficacy of UX003 in mucopolysaccharidosis VII MPS VII subjects is determined by the percent reduction of urinary glycosaminoglycan (uGAG) excretion after 24 weeks of treatment relative to the pre-treatment baseline. In the United States (US) only, efficacy of UX003 in MPS VII subjects is based on the totality of the clinical data on a per subject basis.

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	02 December 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Regulatory reason, Scientific research
Long term follow-up duration	36 Months
Independent data monitoring committee (IDMC) involvement?	Yes

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

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were evaluated for trial participation based on the protocol-specified inclusion and exclusion criteria. There were 14 subjects screened, of which 12 enrolled and completed the study. Two subjects withdrew consent prior to enrollment.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The study was conducted as a randomized, double-blind, blind start, single crossover, placebo-controlled study. Double-blind conditions were established so that neither the sponsor, subject, or site personnel involved in study conduct knew the identity of a subject's treatment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A: 4 mg/kg UX003

Arm description:

4 mg/kg UX003 every other week (QOW) through Week 46

Arm type	Experimental
Investigational medicinal product name	UX003
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

UX003 is a sterile liquid buffered saline formulation of recombinant human betaglucuronidase (rhGUS) at a concentration of 2 mg/mL filled to allow the withdrawal of a 5.0 mL deliverable volume and supplied in a 10 mL glass vial. Dosage of UX003 is 4 mg/kg body weight administered QOW by slow intravenous (IV) infusion over a period of approximately 4 hours.

Arm title	Group B: 8 Weeks Placebo Then 4 mg/kg UX003
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Arm description:

Placebo QOW for the first 8 weeks followed by 4 mg/kg UX003 QOW through Week 46

Arm type	Experimental
Investigational medicinal product name	UX003
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

UX003 is a sterile liquid buffered saline formulation of recombinant human betaglucuronidase (rhGUS) at a concentration of 2 mg/mL filled to allow the withdrawal of a 5.0 mL deliverable volume and supplied in a 10 mL glass vial. Dosage of UX003 is 4 mg/kg body weight administered QOW by slow intravenous (IV) infusion over a period of approximately 4 hours.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A placebo consisting of the UX003 formulation buffer (without rhGUS) will be administered IV QOW to Groups B-D over a period of approximately 4 hours during the respective placebo treatment portion of the Blinded Period.

Arm title	Group C: 16 Weeks Placebo Then 4 mg/kg UX003
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Arm description:

Placebo QOW for the first 16 weeks followed by 4 mg/kg UX003 QOW through Week 46

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A placebo consisting of the UX003 formulation buffer (without rhGUS) will be administered IV QOW to Groups B-D over a period of approximately 4 hours during the respective placebo treatment portion of the Blinded Period.

Investigational medicinal product name	UX003
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

UX003 is a sterile liquid buffered saline formulation of recombinant human betaglucuronidase (rhGUS) at a concentration of 2 mg/mL filled to allow the withdrawal of a 5.0 mL deliverable volume and supplied in a 10 mL glass vial. Dosage of UX003 is 4 mg/kg body weight administered QOW by slow intravenous (IV) infusion over a period of approximately 4 hours.

Arm title	Group D: 24 Weeks Placebo Then 4 mg/kg UX003
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Arm description:

Placebo QOW for the first 24 weeks followed by 4 mg/kg UX003 QOW through Week 46

Arm type	Experimental
Investigational medicinal product name	UX003
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

UX003 is a sterile liquid buffered saline formulation of recombinant human betaglucuronidase (rhGUS) at a concentration of 2 mg/mL filled to allow the withdrawal of a 5.0 mL deliverable volume and supplied in a 10 mL glass vial. Dosage of UX003 is 4 mg/kg body weight administered QOW by slow intravenous (IV) infusion over a period of approximately 4 hours.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A placebo consisting of the UX003 formulation buffer (without rhGUS) will be administered IV QOW to Groups B-D over a period of approximately 4 hours during the respective placebo treatment portion of

the Blinded Period.

Number of subjects in period 1	Group A: 4 mg/kg UX003	Group B: 8 Weeks Placebo Then 4 mg/kg UX003	Group C: 16 Weeks Placebo Then 4 mg/kg UX003
Started	3	3	3
Completed	3	3	3

Number of subjects in period 1	Group D: 24 Weeks Placebo Then 4 mg/kg UX003
Started	3
Completed	3

Baseline characteristics

Reporting groups

Reporting group title	Group A: 4 mg/kg UX003
Reporting group description:	4 mg/kg UX003 every other week (QOW) through Week 46
Reporting group title	Group B: 8 Weeks Placebo Then 4 mg/kg UX003
Reporting group description:	Placebo QOW for the first 8 weeks followed by 4 mg/kg UX003 QOW through Week 46
Reporting group title	Group C: 16 Weeks Placebo Then 4 mg/kg UX003
Reporting group description:	Placebo QOW for the first 16 weeks followed by 4 mg/kg UX003 QOW through Week 46
Reporting group title	Group D: 24 Weeks Placebo Then 4 mg/kg UX003
Reporting group description:	Placebo QOW for the first 24 weeks followed by 4 mg/kg UX003 QOW through Week 46

Reporting group values	Group A: 4 mg/kg UX003	Group B: 8 Weeks Placebo Then 4 mg/kg UX003	Group C: 16 Weeks Placebo Then 4 mg/kg UX003
Number of subjects	3	3	3
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	13.13	12.50	20.77
standard deviation	± 1.656	± 4.004	± 3.004
Gender categorical			
Units: Subjects			
Female	3	2	3
Male	0	1	0

Reporting group values	Group D: 24 Weeks Placebo Then 4 mg/kg UX003	Total	
Number of subjects	3	12	
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	15.23		
standard deviation	± 8.633	-	
Gender categorical			
Units: Subjects			
Female	0	8	
Male	3	4	

End points

End points reporting groups

Reporting group title	Group A: 4 mg/kg UX003
Reporting group description:	4 mg/kg UX003 every other week (QOW) through Week 46
Reporting group title	Group B: 8 Weeks Placebo Then 4 mg/kg UX003
Reporting group description:	Placebo QOW for the first 8 weeks followed by 4 mg/kg UX003 QOW through Week 46
Reporting group title	Group C: 16 Weeks Placebo Then 4 mg/kg UX003
Reporting group description:	Placebo QOW for the first 16 weeks followed by 4 mg/kg UX003 QOW through Week 46
Reporting group title	Group D: 24 Weeks Placebo Then 4 mg/kg UX003
Reporting group description:	Placebo QOW for the first 24 weeks followed by 4 mg/kg UX003 QOW through Week 46
Subject analysis set title	Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	Subjects received placebo for the first 8 weeks (Group B), 16 weeks (Group C) or 24 weeks (Group D) of the study, based on the blind-start design.
Subject analysis set title	UX003 Active Treatment
Subject analysis set type	Safety analysis
Subject analysis set description:	Subjects received 4 mg/kg UX003 QOW per group assignment (based on the blind-start design) and were dosed through Week 46. All groups received a minimum of 24 weeks of treatment with UX003.
Subject analysis set title	UX003 4 mg/kg
Subject analysis set type	Full analysis
Subject analysis set description:	Subjects were randomized 1:1:1:1 to 1 of 4 treatment sequence groups to either start treatment with 4 mg/kg UX003 (Group A), or placebo for the first 8 weeks (Group B), 16 weeks (Group C) or 24 weeks (Group D) of the study and cross over to 4 mg/kg UX003. Subjects were dosed QOW through Week 46. All groups received a minimum of 24 weeks of treatment with 4 mg/kg UX003 QOW.

Primary: European Union (EU) and Rest of World: Percentage Change From Baseline in Urinary Glycosaminoglycan (uGAG) Dermatan Sulfate (DS) at UX003 Treatment Week 24

End point title	European Union (EU) and Rest of World: Percentage Change From Baseline in Urinary Glycosaminoglycan (uGAG) Dermatan Sulfate (DS) at UX003 Treatment Week 24 ^[1]
End point description:	<p>Baseline was defined as the average of all assessments prior to or on the date of cross-over to active treatment with UX003. (This provides the valid assessment, as placebo effect was subtracted from the treatment effect estimate providing a more conservative assessment of the true treatment effect.) Percent change from baseline in uGAG DS was analyzed by generalized estimating equation (GEE) modeling based on observed data. The GEE model included baseline value, and the UX003 treatment week as a categorical variable. The covariance structure within subjects was assumed to be exchangeable.</p> <p>In the United States (US), this was considered a secondary outcome measure. Per guidance from the Food and Drug Administration (FDA), no primary efficacy variable was declared in the US. Efficacy was to be based on the totality of the clinical data on a per subject basis.</p>
End point type	Primary
End point timeframe:	Baseline (defined as the average of all assessments prior to or on the date of cross-over to active treatment with UX003) to 24 weeks of UX003 study drug treatment

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: Statistical analysis data are included in the attachments section (see zip file).

End point values	UX003 4 mg/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	12 ^[2]			
Units: percentage change				
least squares mean (standard error)	-64.82 (± 2.468)			

Notes:

[2] - subjects who had non-missing baseline and ≥1 post-baseline value during 24 weeks of UX003 treatment

Attachments (see zip file)	uGAG excretion statistical analysis.docx
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Statistical analyses

No statistical analyses for this end point

Secondary: Multi-Domain Responder Index (MDRI) Score at UX003 Treatment Week 24

End point title	Multi-Domain Responder Index (MDRI) Score at UX003 Treatment Week 24
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End point description:

MDRI score, calculated as the total response score at UX003 Treatment Week 24 across 6 domains: 6-Minute Walk Test, forced vital capacity predicted value, shoulder flexion, visual acuity, and Bruininks-Oseretsky Test of Motor Proficiency fine motor and gross motor capacity. For each domain, a minimally important difference (MID) was prespecified. Changes from before treatment (baseline) to 24 weeks after treatment in each domain variable were scored against pre-specified MIDs. (This provides the valid assessment, as placebo effect would be subtracted from the treatment effect estimate providing a more conservative assessment of the true treatment effect.) An improvement or decline ≥ MID was scored either as a +1 or -1, respectively, and a change <MID was scored as 0. The integration of benefit occurred by summing the responses (-1, +1, 0) across all 6 domain variables to derive the MDRI score, with a range of -6 (greatest possible decline) to +6 (greatest possible improvement).

End point type	Secondary
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End point timeframe:

Baseline (defined as the last assessment prior to or on the date of cross-over to active treatment with UX003) to 24 weeks of UX003 study drug treatment

End point values	UX003 4 mg/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: units on a scale				
arithmetic mean (standard deviation)	0.5 (± 0.8)			

Attachments (see zip file)	MDRI statistical analysis.docx
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Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in 6MWT at UX003 Treatment Week 24

End point title	Change From Baseline in 6MWT at UX003 Treatment Week 24
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End point description:

The total distance walked (in meters) in a 6-minute period was measured. Baseline was defined as the last assessment prior to or on the date of cross-over to active treatment with UX003. (This provides the valid assessment, as placebo effect would be subtracted from the treatment effect estimate providing a more conservative assessment of the true treatment effect.) A positive change from Baseline indicates improvement. Change from baseline in 6MWT was analyzed by GEE modeling based on observed data. The GEE model included all subjects who had non-missing baseline and at least one post-baseline value during the 24 weeks of UX003 treatment. The model included baseline value, and the UX003 treatment week as a categorical variable. The covariance structure within subjects was assumed to be exchangeable.

End point type	Secondary
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End point timeframe:

Baseline (defined as the last assessment prior to or on the date of cross-over to active treatment with UX003) to 24 weeks of UX003 study drug treatment

End point values	UX003 4 mg/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	9 ^[3]			
Units: meters				
least squares mean (standard error)	20.8 (± 16.75)			

Notes:

[3] - subjects who had non-missing baseline and ≥1 post-baseline value during 24 weeks of UX003 treatment

Attachments (see zip file)	6MWT statistical analysis.docx
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Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pulmonary Function Testing: FVC%pred at UX003 Treatment Week 24

End point title	Change From Baseline in Pulmonary Function Testing: FVC%pred at UX003 Treatment Week 24
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End point description:

Spirometry was administered to subjects who did not require invasive ventilatory support or have a tracheostomy and measured percentage of predicted FVC. The percent predicted values were calculated after testing using published normative data. Baseline was defined as the last assessment prior to or on the date of cross-over to active treatment with UX003. (This provides the valid assessment, as placebo effect would be subtracted from the treatment effect estimate providing a more conservative assessment of the true treatment effect.) No GEE analysis was performed for FVC due to the limitation of the sample size.

End point type	Secondary
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End point timeframe:

Baseline (defined as the last assessment prior to or on the date of cross-over to active treatment with UX003) to 24 weeks of UX003 study drug treatment

End point values	UX003 4 mg/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	1 ^[4]			
Units: percentage predicted FVC				
arithmetic mean (standard deviation)	0 (± 99999)			

Notes:

[4] - 99999=not applicable (1 subject had non-missing change from baseline at UX003 Treatment Week 24).

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pulmonary Function Testing: Maximum Ventilatory Ventilation (MVV) at UX003 Treatment Week 24

End point title	Change From Baseline in Pulmonary Function Testing: Maximum Ventilatory Ventilation (MVV) at UX003 Treatment Week 24
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End point description:

Spirometry was administered to subjects who did not require invasive ventilatory support or have a tracheostomy to measure MVV. The percent predicted values were calculated after testing using published normative data. Baseline was defined as the last assessment prior to or on the date of cross-over to active treatment with UX003. (This provides the valid assessment, as placebo effect would be subtracted from the treatment effect estimate providing a more conservative assessment of the true treatment effect.)

End point type	Secondary
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End point timeframe:

Baseline (defined as the last assessment prior to or on the date of cross-over to active treatment with UX003) to 24 weeks of UX003 study drug treatment

End point values	UX003 4 mg/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	0 ^[5]			
Units: L/m				
arithmetic mean (standard deviation)	()			

Notes:

[5] - no change from baseline calculated due to lack of data at baseline and/or UX003 Treatment Week 24

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Shoulder Flexion and Extension Maximum Range of Motion at UX003 Treatment Week 24

End point title	Change From Baseline in Shoulder Flexion and Extension Maximum Range of Motion at UX003 Treatment Week 24
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End point description:

Goniometry was used to measure (in degrees) the maximum passive shoulder range of motion in both flexion and extension. Baseline was defined as the last assessment prior to or on the date of cross-over to active treatment with UX003. (This provides the valid assessment, as placebo effect would be subtracted from the treatment effect estimate providing a more conservative assessment of the true treatment effect.) Change from baseline in shoulder flexion left was analyzed by GEE modeling based on observed data. The GEE model included all subjects who had nonmissing baseline and at least one post-baseline value during the 24 weeks of UX003 treatment. The model included baseline value, and the UX003 treatment week as a categorical variable. The covariance structure within subjects was assumed to be exchangeable.

End point type	Secondary
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End point timeframe:

Baseline (defined as the last assessment prior to or on the date of cross-over to active treatment with UX003) to 24 weeks of UX003 study drug treatment

End point values	UX003 4 mg/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	12 ^[6]			
Units: degrees				
least squares mean (standard error)				
Shoulder flexion - left; n=12	-6.5 (± 4.86)			
Shoulder extension - left; n=11	-1.5 (± 4.83)			
Shoulder flexion - right; n=12	-1.8 (± 3.54)			
Shoulder extension - right; n=11	-3.4 (± 3.48)			
Tighter shoulder flexion; n=12	-9.4 (± 4.6)			
Tighter shoulder extension; n=11	-6.7 (± 3.53)			

Notes:

[6] - subjects who had non-missing baseline and ≥1 post-baseline value during 24 weeks of UX003 treatment

Attachments (see zip file)	shoulder flexion_extension statistical analyses.docx
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Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Uncorrected Visual Acuity at UX003 Treatment Week 24

End point title	Change From Baseline in Uncorrected Visual Acuity at UX003 Treatment Week 24
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End point description:

Visual acuity was measured (corrected and uncorrected) using a standard eye chart and recorded for each eye independently. Baseline was defined as the last assessment prior to or on the date of cross-over to active treatment with UX003. The change in the number of lines from pre-treatment baseline to 24 weeks of treatment was evaluated. (This provides the valid assessment, as placebo effect would be subtracted from the treatment effect estimate providing a more conservative assessment of the true treatment effect.) A positive change from baseline indicates improvement. Change from baseline in uncorrected visual acuity was analyzed by GEE modeling based on observed data. The GEE model included all subjects who had non-missing baseline and at least one post-baseline value during the 24 weeks of UX003 treatment. The model included baseline value, and the UX003 treatment week as a categorical variable. The covariance structure within subjects was assumed to be exchangeable.

End point type	Secondary
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End point timeframe:

Baseline (defined as the last assessment prior to or on the date of cross-over to active treatment with

End point values	UX003 4 mg/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	7 ^[7]			
Units: lines				
least squares mean (standard error)				
Left eye	1 (± 0.63)			
Right eye	0.9 (± 0.51)			

Notes:

[7] - subjects who had non-missing baseline and ≥1 post-baseline value during 24 weeks of UX003 treatment

Attachments (see zip file)	visual acuity statistical analyses.docx
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Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in BOT-2 Scores at UX003 Treatment Week 24

End point title	Change From Baseline in BOT-2 Scores at UX003 Treatment Week 24
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End point description:

BOT-2 was administered to evaluate treatment-related changes in 4 domains assessing both fine and gross motor function: balance (score 0 to 37), fine motor precision (score 0 to 41), manual dexterity (score 0 to 45), and running speed/agility (score 0 to 52). Higher scores indicate more motor proficiency; a positive change from baseline indicates improvement. Baseline was defined as the last assessment prior to or on the date of cross-over to active treatment with UX003. (This provides the valid assessment, as placebo effect would be subtracted from the treatment effect estimate providing a more conservative assessment of the true treatment effect.) Change from baseline in BOT-2 was analyzed by GEE modeling based on observed data. The GEE model included baseline value, and the UX003 treatment week as a categorical variable. The covariance structure within subjects was assumed to be exchangeable.

End point type	Secondary
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End point timeframe:

Baseline (defined as the last assessment prior to or on the date of cross-over to active treatment with UX003) to 24 weeks of UX003 study drug treatment

End point values	UX003 4 mg/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	11 ^[8]			
Units: units on a scale				
least squares mean (standard error)				
Balance; n=6	0.8 (± 0.46)			
Fine motor precision; n=11	-0.2 (± 0.23)			
Manual dexterity; n=11	0.2 (± 0.21)			
Running speed and agility; n=5	0.2 (± 0.12)			

Notes:

[8] - subjects who had non-missing baseline and ≥ 1 post-baseline value during 24 weeks of UX003 treatment

Attachments (see zip file)	BOT-2 statistical analyses.docx
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Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pediatric Quality of Life (PedsQL) Multidimensional Fatigue Scale at UX003 Treatment Week 24

End point title	Change From Baseline in Pediatric Quality of Life (PedsQL) Multidimensional Fatigue Scale at UX003 Treatment Week 24
End point description: The PedsQL 18-item scale is comprised of 3 dimensions: general fatigue (6 items), sleep/rest fatigue (6 items) and cognitive fatigue (6 items). Each item has a 5-point Likert response scale that is reverse scored and transformed to a 0 to 100 scale with higher scores indicating less fatigue. Baseline was defined as the last assessment prior to or on the date of cross-over to active treatment with UX003. (This provides the valid assessment, as placebo effect would be subtracted from the treatment effect estimate providing a more conservative assessment of the true treatment effect.) Change from baseline in PedsQL total fatigue score was analyzed by GEE modeling based on observed data. The GEE model included all subjects who had non-missing baseline and ≥ 1 post-baseline value during the 24 weeks of UX003 treatment. The model included baseline value, and the UX003 treatment week as a categorical variable. The covariance structure within subjects was assumed to be exchangeable.	
End point type	Secondary
End point timeframe: Baseline (defined as the last assessment prior to or on the date of cross-over to active treatment with UX003) to 24 weeks of UX003 study drug treatment	

End point values	UX003 4 mg/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: units on a scale				
least squares mean (standard error)	3.4 (\pm 2.64)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Individual Clinical Response (ICR) Responders at UX003 Treatment Week 24

End point title	Percentage of Individual Clinical Response (ICR) Responders at UX003 Treatment Week 24
End point description: Percentage of subjects who were ICR responders based on MID criteria at Week 24. At the Randomization visit, the physician queried the subject or parent/caregiver about signs and symptoms of	

MPS VII that interfered most with the subject's daily life. Answers were mapped to an appropriate clinical outcome measure (e.g., difficulty walking could map to the 6MWT; breathing problems to FVC). The clinical outcome ranked with the highest impact on daily life that could be reliably completed by the subject and met a threshold level of impairment was selected as the ICR for that subject. ICR response was assessed based on a positive change (according to pre-specified MID criteria) of each subject's ICR. Agresti-Coull confidence interval with nominal coverage $\geq 95\%$.

End point type	Secondary
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End point timeframe:

Baseline (defined as the last assessment prior to or on the date of cross-over to active treatment with UX003) to 24 weeks of UX003 study drug treatment

End point values	UX003 4 mg/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: percentage of responders				
number (confidence interval 95%)	25 (8.3 to 53.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Impactful Clinical Problem Total Score at UX003 Treatment Week 24

End point title	Change From Baseline in Impactful Clinical Problem Total Score at UX003 Treatment Week 24
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End point description:

The 3 most impactful clinical problems as reported by the subject/parent/caregiver during the Clinical Problem Evaluation were scored on a Likert scale from 1 (very little problem) to 7 (an extreme amount) at randomization and post-randomization visits. At post-randomization visits, each clinical problem was again scored for impact on daily activities. Total scores ranged from 3 to 21; lower scores reflect less impact on daily life. Baseline was defined as the last assessment prior to or on the date of cross-over to active treatment with UX003. (This provides the valid assessment, as placebo effect would be subtracted from the treatment effect estimate providing a more conservative assessment of the true treatment effect.) The change from baseline up to UX003 Treatment Week 24 were analyzed by GEE modeling, including baseline value, and the post-UX003 initiation treatment week as a categorical variable. The covariance structure within subjects is assumed to be exchangeable.

End point type	Secondary
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End point timeframe:

Baseline (defined as the last assessment prior to or on the date of cross-over to active treatment with UX003) to 24 weeks of UX003 study drug treatment

End point values	UX003 4 mg/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: units on a scale				
least squares mean (standard error)	-1.2 (\pm 0.92)			

Attachments (see zip file)	impactful clinical problems statistical analysis.docx
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Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Safety information was collected for all subjects who received any study drug from signing the informed consent form through 30 days after last dose of study drug. Mean treatment duration for UX003 was 36.0 weeks, and for placebo was 15.8 weeks.

Adverse event reporting additional description:

Treatment-emergent adverse events (TEAEs) are presented. Given that the study has only has 12 subjects, and a by arm/group analysis would include no more than 3 subjects per arm/group, the TEAE summary was planned to present data by treatment only.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Subjects received placebo for the first 8 weeks (Group B), 16 weeks (Group C) or 24 weeks (Group D) of the study, based on the blind-start design.

Reporting group title	UX003 Active Treatment
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Reporting group description:

Subjects received 4 mg/kg UX003 QOW per group assignment (based on the blind-start design) and were dosed through Week 46. All groups received a minimum of 24 weeks of treatment with UX003.

Serious adverse events	Placebo	UX003 Active Treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	2 / 12 (16.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Craniocerebral injury	Additional description: CTCAE grade 2 non-related craniocerebral injury as a result of falling off the bed. Computed tomography scan of the head did not show intracranial bleeding nor acute intracranial injury.		
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactoid reaction	Additional description: CTCAE grade 3 treatment-related anaphylactoid reaction secondary to an infusion rate error occurring during the first hour of UX003 administration.		
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	UX003 Active Treatment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)	12 / 12 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Infusion site extravasation			
subjects affected / exposed	1 / 9 (11.11%)	4 / 12 (33.33%)	
occurrences (all)	1	4	
Oedema			
subjects affected / exposed	1 / 9 (11.11%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Pyrexia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Catheter site bruise			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	3	
Chills			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Infusion site bruising			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Infusion site swelling			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	

Peripheral swelling subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 12 (8.33%) 1	
Infusion site discomfort subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 12 (0.00%) 0	
Immune system disorders			
Anaphylactoid reaction subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 12 (8.33%) 1	
Seasonal allergy subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	1 / 12 (8.33%) 1	
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2	3 / 12 (25.00%) 3	
Dyspnoea exertional subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 12 (8.33%) 1	
Nasal obstruction subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 12 (8.33%) 1	
Productive cough subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 12 (8.33%) 1	
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 12 (8.33%) 1	
Epistaxis subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 12 (0.00%) 0	
Psychiatric disorders			
Post-traumatic stress disorder subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 12 (8.33%) 1	

Depression subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 12 (0.00%) 0	
Insomnia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 12 (0.00%) 0	
Investigations Body temperature increased subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 12 (0.00%) 0	
Injury, poisoning and procedural complications Excoriation subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 2	1 / 12 (8.33%) 2	
Contusion subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 12 (8.33%) 1	
Post-traumatic neck syndrome subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 12 (8.33%) 1	
Tooth fracture subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 12 (8.33%) 1	
Fall subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 12 (0.00%) 0	
Craniocerebral injury subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 12 (8.33%) 1	
Nervous system disorders Ataxia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 12 (8.33%) 1	
Clonus subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 12 (8.33%) 1	

Dysstasia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 12 (8.33%) 1	
Headache subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 12 (8.33%) 1	
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 12 (0.00%) 0	
Eye disorders Eye pain subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 12 (0.00%) 0	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	3 / 12 (25.00%) 3	
Vomiting subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 3	3 / 12 (25.00%) 3	
Abdominal pain subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	1 / 12 (8.33%) 1	
Abdominal pain lower subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 12 (8.33%) 1	
abdominal pain upper subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 12 (8.33%) 1	
Abnormal faeces subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 12 (8.33%) 2	
Rectal haemorrhage subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 12 (8.33%) 1	
cheilosis			

subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 12 (0.00%) 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 9 (11.11%)	3 / 12 (25.00%)	
occurrences (all)	2	3	
Urticaria			
subjects affected / exposed	1 / 9 (11.11%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Pruritus			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Rash macular			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Rash papular			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Skin ulcer			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	3 / 9 (33.33%)	4 / 12 (33.33%)	
occurrences (all)	3	5	
Arthralgia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Arthritis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Joint range of motion decreased			

subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Musculoskeletal stiffness			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	2	
Joint swelling			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	3 / 9 (33.33%)	5 / 12 (41.67%)	
occurrences (all)	3	6	
Ear infection			
subjects affected / exposed	1 / 9 (11.11%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Cellulitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Conjunctivitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Gastrointestinal viral infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Oral herpes			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Rash pustular			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Otitis media acute			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	
occurrences (all)	1	0	

Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Decreased appetite			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 September 2013	The following parts of the protocol were updated: primary efficacy hypothesis and study objectives, investigational plan, efficacy measures, APRG safety reporting, statistical methodology, inclusion criteria, description of study drug. This amendment was made prior to the first patient consenting to the study.
18 September 2014	Dose selection was updated. This amendment was made prior to the first patient consenting to the study.
07 October 2014	The primary efficacy hypothesis and study objectives, efficacy measures and statistical analysis were updated. This amendment was made prior to the first patient consenting to the study.
15 December 2014	The drug concentration measurements, assessment of anti-drug antibodies, timing of assessments, relationship of adverse events to study drug and safety contact information were updated. This amendment was made after the first patient consented to the study.
18 April 2016	The urinary and serum GAG methodologies, record retention, complement level measurements, end of study definition, unblinding information and adverse event reporting were updated. This amendment was made after the first patient consented to the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported