Clinical trial results:
An Open-label Study of UX003 rhGUS Enzyme Replacement Therapy in MPS 7 Patients Less than 5 Years Old

Summary

EudraCT number	2015-000104-26
Trial protocol	Outside EU/EEA ES PT
Global end of trial date	26 March 2019

Results information

Result version number	v1 (current)
This version publication date	09 October 2019
First version publication date	09 October 2019

Trial information

Trial identification

Sponsor protocol code	UX003-CL203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02418455
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	Medical Information, Ultragenyx Pharmaceutical Inc., 1 8887568567, medinfo@ultragenyx.com
Scientific contact	Medical Information, Ultragenyx Pharmaceutical Inc., 1 8887568567, 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	26 March 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the effect of UX003 treatment in pediatric MPS 7 subjects less than 5 years of age on:
-Safety and tolerability
-Efficacy as determined by the reduction of uGAG excretion

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	21 July 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	Portugal: 1
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United States: 6
Worldwide total number of subjects	8
EEA total number of subjects	2

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)	1
Children (2-11 years)	7
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The Baseline (Week 0) visit took place within 30 days of the Screening visit. Screening assessments (physical exam and safety labs) performed within 7 days prior to the first dose of study drug were allowed for baseline assessments. Subjects were treated only after all inclusion/exclusion criteria were confirmed.

Period 1

Period 1 title	48-Week Treatment Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	UX003

Arm description:

UX003 4 mg/kg every other week (QOW). Initial treatment period 48 weeks. Continuation period up to 240 weeks.

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

Dosage and administration details:

Study drug (UX003) was administered QOW by slow IV infusion over a period of approximately 4 hours.

Number of subjects in period 1	UX003
Started	8
Previously treated under emergency IND	1 [1]
Completed	7
Not completed	1
Other, Not Specified	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This subject was previously treated with UX003 under an emergency Investigational New Drug (eIND) application.

Period 2

Period 2 title	Continuation Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	UX003

Arm description:

UX003 4 mg/kg every other week (QOW). Initial treatment period 48 weeks. Continuation period up to 240 weeks.

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

Dosage and administration details:

Study drug (UX003) was administered QOW by slow IV infusion over a period of approximately 4 hours.

Number of subjects in period 2	UX003
Started	7
Completed	0
Not completed	7
Sponsor decision	7

Baseline characteristics

Reporting groups	
Reporting group title	UX003
Reporting group description:	
UX003 4 mg/kg every other week (QOW). Initial treatment period 48 weeks. Continuation period up to 240 weeks.	

Reporting group values	UX003	Total	
Number of subjects	8	8	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	3.25		
standard deviation	± 1.197	-	
Gender categorical			
Units: Subjects			
Female	3	3	
Male	5	5	
Ethnicity			
Units: Subjects			
Hispanic or Latino	3	3	
Not Hispanic or Latino	4	4	
Unknown or Not Reported	1	1	
Race			
Units: Subjects			
Asian	2	2	
Black or African American	1	1	
White	3	3	
Other, Not Specified	2	2	
Urinary Glycosaminoglycans (uGAG) Excretion			
Liquid chromatography-mass spectrometry/mass spectrometry-dermatan sulfate (LS-MS/MS-DS) method.			
Units: g GAG/g creatinine			
arithmetic mean	2.092		
standard deviation	± 1.3307	-	
Standing Height			
For all subjects (including the subject previously treated with UX003 under an eIND), the last non-missing study assessment prior to the first dose in this study was used as baseline. eIND and non-eIND subjects were analyzed separately for this measure. 99999=not applicable (1 subject analyzed).			
Units: cm			
arithmetic mean			
standard deviation	±	-	
Standing Height Z-Score			
The Z-score indicates the number of standard deviations away from a reference population (from the Centers for Disease Control [CDC] growth charts) in the same age range and with the same sex. A Z-score of 0 is equal to the mean with negative numbers indicating values lower than the mean and			

positive values higher. Higher Z-scores indicate a better outcome.

eIND and non-eIND subjects were analyzed separately for this measure.

99999=not applicable (1 subject analyzed)

Units: Z-score			
arithmetic mean			
standard deviation	±	-	
Head Circumference			

For all subjects (including the subject previously treated with UX003 under an eIND), the last non-missing study assessment prior to the first dose in this study was used as baseline.
eIND and non-eIND subjects were analyzed separately for this measure.
99999=not applicable (1 subject analyzed)

Units: cm			
arithmetic mean			
standard deviation	±	-	
Head Circumference Z-Score			

The Z-score indicates the number of standard deviations away from a reference population (from the CDC growth charts) in the same age range and with the same sex. A Z-score of 0 is equal to the mean with negative numbers indicating values lower than the mean and positive values higher. Higher Z-scores indicate a better outcome.

eIND and non-eIND subjects were analyzed separately for this measure. Subjects with a non-missing baseline assessment are presented (n=5 for the non-eIND group).
99999=not applicable (1 subject analyzed)

Units: Z-score			
arithmetic mean			
standard deviation	±	-	
Weight			

For all subjects (including the subject previously treated with UX003 under an eIND), the last non-missing study assessment prior to the first dose in this study was used as baseline.
eIND and non-eIND subjects were analyzed separately for this measure.
99999=not applicable (1 subject analyzed)

Units: kg			
arithmetic mean			
standard deviation	±	-	
Historical Pre-Treatment (Within 2 Years) Growth Velocity			

Pre-treatment data include baseline and pre-treatment data (within 2 years). For the eIND participant, the growth velocity was calculated for pre initial UX003 treatment.
All enrolled subjects who received at least one dose of UX003 during the study with a non-missing assessment at baseline were included (n=5).

Units: cm/year			
arithmetic mean	5.06		
standard deviation	± 1.885	-	
Pre-Treatment (Within 2 Years) Growth Velocity Z-Score			

The Z-score indicates the number of standard deviations away from a reference population (based on Tanner's standard [Tanner et al. 1985]) in the same age range and with the same sex. A Z-score of 0 is equal to the mean with negative numbers indicating values lower than the mean and positive values higher. Higher Z-scores indicate a better outcome.

All enrolled subjects who received at least one dose of UX003 during the study with a non-missing assessment at baseline included. Calculated only for subjects ≥ 2.25 years (n=4)

Units: Z-score			
arithmetic mean	-2.587		
standard deviation	± 1.4860	-	
Liver Measurement			

For all subjects (including the subject previously treated with UX003 under an eIND), the last non-missing study assessment prior to the first dose in this study was used as baseline.

eIND and non-eIND subjects were analyzed separately for this measure. One subject in the non-eIND group (n=6) did not have a baseline measurement. 99999=not applicable (1 subject analyzed)			
Units: cm arithmetic mean standard deviation	±	-	
Spleen Measurement			
For all subjects (including the subject previously treated with UX003 under an eIND), the last non-missing study assessment prior to the first dose in this study was used as baseline. eIND and non-eIND subjects were analyzed separately for this measure. 99999=not applicable (1 subject analyzed)			
Units: cm arithmetic mean standard deviation	±	-	

Subject analysis sets

Subject analysis set title	UX003: eIND
Subject analysis set type	Full analysis

Subject analysis set description:

UX003 4 mg/kg QOW. Initial treatment period 48 weeks. Continuation period up to 240 weeks. Participant previously treated with UX003 under an emergency Investigational New Drug (eIND) application.

Subject analysis set title	UX003: Non-eIND
Subject analysis set type	Full analysis

Subject analysis set description:

UX003 4 mg/kg QOW. Initial treatment period 48 weeks. Continuation period up to 240 weeks.

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 UX003 during the study and had a non-missing baseline and Week 48 assessment.

Reporting group values	UX003: eIND	UX003: Non-eIND	Full Analysis Set
Number of subjects	1	7	8
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	±	±	±
Gender categorical Units: Subjects			
Female Male			
Ethnicity Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported			

Race Units: Subjects			
Asian Black or African American White Other, Not Specified			
Urinary Glycosaminoglycans (uGAG) Excretion			
Liquid chromatography-mass spectrometry/mass spectrometry-dermatan sulfate (LS-MS/MS-DS) method.			
Units: g GAG/g creatinine arithmetic mean standard deviation	±	±	±
Standing Height			
For all subjects (including the subject previously treated with UX003 under an eIND), the last non-missing study assessment prior to the first dose in this study was used as baseline. eIND and non-eIND subjects were analyzed separately for this measure. 99999=not applicable (1 subject analyzed).			
Units: cm arithmetic mean standard deviation	52.20 ± 99999	89.34 ± 7.198	±
Standing Height Z-Score			
The Z-score indicates the number of standard deviations away from a reference population (from the Centers for Disease Control [CDC] growth charts) in the same age range and with the same sex. A Z-score of 0 is equal to the mean with negative numbers indicating values lower than the mean and positive values higher. Higher Z-scores indicate a better outcome. eIND and non-eIND subjects were analyzed separately for this measure. 99999=not applicable (1 subject analyzed)			
Units: Z-score arithmetic mean standard deviation	-5.352 ± 99999	-2.241 ± 0.4327	±
Head Circumference			
For all subjects (including the subject previously treated with UX003 under an eIND), the last non-missing study assessment prior to the first dose in this study was used as baseline. eIND and non-eIND subjects were analyzed separately for this measure. 99999=not applicable (1 subject analyzed)			
Units: cm arithmetic mean standard deviation	37.00 ± 99999	51.57 ± 2.130	±
Head Circumference Z-Score			
The Z-score indicates the number of standard deviations away from a reference population (from the CDC growth charts) in the same age range and with the same sex. A Z-score of 0 is equal to the mean with negative numbers indicating values lower than the mean and positive values higher. Higher Z-scores indicate a better outcome. eIND and non-eIND subjects were analyzed separately for this measure. Subjects with a non-missing baseline assessment are presented (n=5 for the non-eIND group). 99999=not applicable (1 subject analyzed)			
Units: Z-score arithmetic mean standard deviation	-3.329 ± 99999	1.465 ± 1.3186	±
Weight			
For all subjects (including the subject previously treated with UX003 under an eIND), the last non-missing study assessment prior to the first dose in this study was used as baseline. eIND and non-eIND subjects were analyzed separately for this measure. 99999=not applicable (1 subject analyzed)			
Units: kg			

arithmetic mean	4.26	13.99	
standard deviation	± 99999	± 2.274	±
Historical Pre-Treatment (Within 2 Years) Growth Velocity			
Pre-treatment data include baseline and pre-treatment data (within 2 years). For the eIND participant, the growth velocity was calculated for pre initial UX003 treatment. All enrolled subjects who received at least one dose of UX003 during the study with a non-missing assessment at baseline were included (n=5).			
Units: cm/year			
arithmetic mean			
standard deviation	±	±	±
Pre-Treatment (Within 2 Years) Growth Velocity Z-Score			
The Z-score indicates the number of standard deviations away from a reference population (based on Tanner's standard [Tanner et al. 1985]) in the same age range and with the same sex. A Z-score of 0 is equal to the mean with negative numbers indicating values lower than the mean and positive values higher. Higher Z-scores indicate a better outcome. All enrolled subjects who received at least one dose of UX003 during the study with a non-missing assessment at baseline included. Calculated only for subjects ≥ 2.25 years (n=4)			
Units: Z-score			
arithmetic mean			
standard deviation	±	±	±
Liver Measurement			
For all subjects (including the subject previously treated with UX003 under an eIND), the last non-missing study assessment prior to the first dose in this study was used as baseline. eIND and non-eIND subjects were analyzed separately for this measure. One subject in the non-eIND group (n=6) did not have a baseline measurement. 99999=not applicable (1 subject analyzed)			
Units: cm			
arithmetic mean	7.60	10.70	
standard deviation	± 99999	± 1.138	±
Spleen Measurement			
For all subjects (including the subject previously treated with UX003 under an eIND), the last non-missing study assessment prior to the first dose in this study was used as baseline. eIND and non-eIND subjects were analyzed separately for this measure. 99999=not applicable (1 subject analyzed)			
Units: cm			
arithmetic mean	6.40	8.17	
standard deviation	± 99999	± 1.115	±

End points

End points reporting groups

Reporting group title	UX003
Reporting group description:	
UX003 4 mg/kg every other week (QOW). Initial treatment period 48 weeks. Continuation period up to 240 weeks.	
Reporting group title	UX003
Reporting group description:	
UX003 4 mg/kg every other week (QOW). Initial treatment period 48 weeks. Continuation period up to 240 weeks.	
Subject analysis set title	UX003: eIND
Subject analysis set type	Full analysis
Subject analysis set description:	
UX003 4 mg/kg QOW. Initial treatment period 48 weeks. Continuation period up to 240 weeks. Participant previously treated with UX003 under an emergency Investigational New Drug (eIND) application.	
Subject analysis set title	UX003: Non-eIND
Subject analysis set type	Full analysis
Subject analysis set description:	
UX003 4 mg/kg QOW. Initial treatment period 48 weeks. Continuation period up to 240 weeks.	
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 UX003 during the study and had a non-missing baseline and Week 48 assessment.	

Primary: Percent Change From Baseline in uGAG Excretion at Week 48

End point title	Percent Change From Baseline in uGAG Excretion at Week 48[1]
End point description:	
Liquid chromatography-mass spectrometry/mass spectrometry-dermatan sulfate (LS-MS/MS-DS) method. For the subject previously treated with UX003 under an eIND, percent change from initial baseline was used.	
End point type	Primary
End point timeframe:	
Baseline (Week 0), Week 48	

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 analyses are presented in the attachment.

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	7[2]			
Units: percentage change in uGAG Excretion				
arithmetic mean (standard deviation)	-58.17 (± 16.915)			

Notes:

[2] - Subjects who had a non-missing baseline and Week 48 assessment.

Attachments (see zip file)	statistical analysis uGAG.docx

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Treatment Emergent Adverse Events (TEAEs), Serious TEAEs, and Discontinuations Due to TEAEs

End point title	Number of Subjects with Treatment Emergent Adverse Events (TEAEs), Serious TEAEs, and Discontinuations Due to TEAEs[3]

End point description:

Adverse event (AE): any untoward medical occurrence in a subject, whether or not considered drug related. Serious AE: an AE or suspected adverse reaction 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. Other important medical events may also, in the opinion of the Investigator, be considered SAEs. An AE was considered a TEAE if it occurred on or after the first dose, and was not present prior to the first dose, or it was present at the first dose but increased in severity during the study. Events recorded as either possibly, probably, or definitely related to treatment were categorized as related. AE severity was graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events, Version 4.03.

End point type	Primary

End point timeframe:

From first dose of study drug until 30 days after the last dose of study drug. Mean (SD) treatment duration was 98.11 (29.02) weeks

Notes:

[3] - 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	8			
Units: subjects				
TEAEs	8			
Serious TEAEs	3			
Treatment-Related TEAEs	5			
Treatment-Related Serious TEAEs	1			
Grade 3 or 4 TEAEs	2			
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: Change From Baseline Over Time in Standing Height

End point title	Change From Baseline Over Time in Standing Height

End point description:

For all subjects (including the subject previously treated with UX003 under an eIND), the last non-

missing study assessment prior to the first dose in this study was used as baseline.

n=subjects with a non-missing assessment at baseline and given time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132

End point values	UX003: eIND	UX003: Non-eIND		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1[4]	7[5]		
Units: cm				
arithmetic mean (standard deviation)				
Change at Week 12; n=0,7	99999 (± 99999)	1.94 (± 1.927)		
Change at Week 24; n=1,7	15.00 (± 999999)	3.71 (± 0.994)		
Change at Week 36; n=1,7	20.00 (± 999999)	5.64 (± 1.725)		
Change at Week 48; n=0,7	99999 (± 99999)	6.57 (± 1.058)		
Change at Week 60; n=0,7	99999 (± 99999)	8.59 (± 1.318)		
Change at Week 72; n=0,6	99999 (± 99999)	9.63 (± 1.451)		
Change at Week 84; n=0,6	99999 (± 99999)	10.93 (± 2.095)		
Change at Week 96; n=0,5	99999 (± 99999)	11.86 (± 3.146)		
Change at Week 108; n=0,3	99999 (± 99999)	12.17 (± 3.329)		
Change at Week 120; n=0,3	99999 (± 99999)	12.67 (± 3.617)		
Change at Week 132; n=0,1	99999 (± 99999)	14.80 (± 999999)		

Notes:

[4] - 99999=not applicable (0 subjects analyzed); 999999=not applicable (1 subject analyzed)

[5] - 999999=not applicable (1 subject analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in Standing Height Z-Score

End point title	Change From Baseline Over Time in Standing Height Z-Score

End point description:

The Z-score indicates the number of standard deviations away from a reference population (from the CDC growth charts) in the same age range and with the same sex. A Z-score of 0 is equal to the mean with negative numbers indicating values lower than the mean and positive values higher. Higher Z-scores indicate a better outcome.

For all subjects (including the subject previously treated with UX003 under an eIND), the last non-missing study assessment prior to the first dose in this study was used as baseline. n=subjects with a non-missing assessment at baseline and given time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132

End point values	UX003: eIND	UX003: Non-eIND		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1[6]	7[7]		
Units: Z-Score				
arithmetic mean (standard deviation)				
Change at Week 12; n=0,7	99999 (± 99999)	0.106 (± 0.4938)		
Change at Week 24; n=1,7	-0.481 (± 999999)	0.188 (± 0.3013)		
Change at Week 36; n=1,7	0.314 (± 999999)	0.314 (± 0.4103)		
Change at Week 48; n=0,7	99999 (± 99999)	0.196 (± 0.3012)		
Change at Week 60; n=0,7	99999 (± 99999)	0.333 (± 0.3883)		
Change at Week 72; n=0,6	99999 (± 99999)	0.246 (± 0.3299)		
Change at Week 84; n=0,6	99999 (± 99999)	0.203 (± 0.3973)		
Change at Week 96; n=0,5	99999 (± 99999)	0.237 (± 0.5312)		
Change at Week 108; n=0,3	99999 (± 99999)	-0.035 (± 0.4531)		
Change at Week 120; n=0,3	99999 (± 99999)	-0.176 (± 0.4915)		
Change at Week 132; n=0,1	99999 (± 99999)	-0.147 (± 999999)		

Notes:

[6] - 99999=not applicable (0 subjects analyzed); 999999=not applicable (1 subject analyzed)

[7] - 999999=not applicable (1 subject analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in Head Circumference

End point title	Change From Baseline Over Time in Head Circumference

End point description:

For all subjects (including the subject previously treated with UX003 under an eIND), the last non-missing study assessment prior to the first dose in this study was used as baseline.

n=subjects with a non-missing assessment at baseline and given time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132

End point values	UX003: eIND	UX003: Non-eIND		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1[8]	7[9]		
Units: cm				
arithmetic mean (standard deviation)				
Change at Week 12; n=0,7	99999 (± 99999)	0.36 (± 0.378)		
Change at Week 24; n=1,7	12.50 (± 999999)	0.54 (± 0.360)		
Change at Week 36; n=1,7	12.00 (± 999999)	-0.27 (± 1.732)		
Change at Week 48; n=0,7	99999 (± 99999)	0.79 (± 0.267)		
Change at Week 60; n=0,7	99999 (± 99999)	0.86 (± 0.378)		
Change at Week 72; n=0,5	99999 (± 99999)	1.10 (± 0.224)		
Change at Week 84; n=0,6	99999 (± 99999)	0.70 (± 0.837)		
Change at Week 96; n=0,5	99999 (± 99999)	0.84 (± 1.108)		
Change at Week 108; n=0,3	99999 (± 99999)	1.07 (± 1.793)		
Change at Week 120; n=0,3	99999 (± 99999)	1.33 (± 2.082)		
Change at Week 132; n=0,1	99999 (± 99999)	2.00 (± 99999)		

Notes:

[8] - 99999=not applicable (0 subjects analyzed); 999999=not applicable (1 subject analyzed)

[9] - 999999=not applicable (1 subject analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in Head Circumference Z-Score

End point title	Change From Baseline Over Time in Head Circumference Z-Score

End point description:

The Z-score indicates the number of standard deviations away from a reference population (from the CDC growth charts) in the same age range and with the same sex. A Z-score of 0 is equal to the mean with negative numbers indicating values lower than the mean and positive values higher. Higher Z-scores indicate a better outcome.

For all subjects (including the subject previously treated with UX003 under an eIND), the last non-missing study assessment prior to the first dose in this study was used as baseline. n=subjects with a non-missing assessment at baseline and given time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36, 48

End point values	UX003: eIND	UX003: Non-eIND		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1[10]	1[11]		
Units: Z-score				
arithmetic mean (standard deviation)				
Change at Week 12; n=0,1	99999 (± 99999)	0.052 (± 999999)		
Change at Week 24; n=1,1	3.804 (± 999999)	0.177 (± 999999)		
Change at Week 36; n=1,1	3.263 (± 999999)	-0.733 (± 999999)		
Change at Week 48; n=0,1	99999 (± 99999)	-0.218 (± 999999)		

Notes:

[10] - 99999=not applicable (0 subjects analyzed); 999999=not applicable (1 subject analyzed)

[11] - 999999=not applicable (1 subject analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in Weight

End point title	Change From Baseline Over Time in Weight

End point description:

For all subjects (including the subject previously treated with UX003 under an eIND), the last non-missing study assessment prior to the first dose in this study was used as baseline.

n=subjects with a non-missing assessment at baseline and given time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132

End point values	UX003: eIND	UX003: Non-eIND		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1[12]	7[13]		
Units: kg				
arithmetic mean (standard deviation)				
Change at Week 12; n=1,7	5.54 (± 99999)	0.69 (± 0.626)		
Change at Week 24; n=1,7	5.94 (± 99999)	1.21 (± 0.904)		
Change at Week 36; n=1,7	5.94 (± 99999)	1.46 (± 1.416)		
Change at Week 48; n=1,7	6.34 (± 99999)	2.11 (± 1.110)		
Change at Week 60; n=0,7	999999 (± 999999)	2.91 (± 1.447)		
Change at Week 72; n=0,7	999999 (± 999999)	3.49 (± 2.084)		
Change at Week 84; n=0,7	999999 (± 999999)	3.63 (± 2.170)		
Change at Week 96; n=0,5	999999 (± 999999)	5.06 (± 2.889)		
Change at Week 108; n=0,3	999999 (± 999999)	4.53 (± 3.415)		

Change at Week 120; n=0,3	999999 (± 999999)	5.17 (± 3.968)		
Change at Week 132; n=0,1	999999 (± 999999)	5.70 (± 99999)		

Notes:

[12] - 99999=not applicable (0 subjects analyzed); 999999=not applicable (1 subject analyzed)

[13] - 999999=not applicable (1 subject analyzed)

Statistical analyses

No statistical analyses for this end point

Secondary: Post-UX003 Growth Velocity (cm/yr) for Participants With Both Historical Pre-UX003 (Within 2 Years) and Post-UX003 Data

End point title	Post-UX003 Growth Velocity (cm/yr) for Participants With Both Historical Pre-UX003 (Within 2 Years) and Post-UX003 Data

End point description:

The growth velocity for pre-treatment is based on standing height within 2 years prior to treatment. The growth velocity for post-treatment is based on all standing height data during the study period. For the subject previously treated with UX003 under an eIND, the growth velocity was calculated for pre initial UX003 treatment and post initial UX003 treatment.

End point type	Secondary

End point timeframe:

Pre-treatment (based on standing height within 2 years prior to treatment), Post-treatment (based on all standing height data during the study period up to 240 weeks)

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	5[14]			
Units: cm/year				
arithmetic mean (standard deviation)	6.20 (± 1.954)			

Notes:

[14] - Subjects with both historical pre-treatment (within 2 years) and post-treatment data.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Pre-Treatment (Within 2 Years) to Post-Treatment Growth Velocity Z-Score

End point title	Change From Pre-Treatment (Within 2 Years) to Post-Treatment Growth Velocity Z-Score

End point description:

The Z-score indicates the number of standard deviations away from a reference population (based on the Tanner's standard [Tanner et al. 1985]) in the same age range and with the same sex. A Z-score of 0 is equal to the mean with negative numbers indicating values lower than the mean and positive values higher. Higher Z-scores indicate a better outcome.
The growth velocity for pre-treatment is based on standing height within 2 years prior to treatment. The growth velocity for post-treatment is based on all standing height data during the study period. For the subject previously treated with UX003 under an eIND, the growth velocity was calculated for pre initial UX003 treatment and post initial UX003 treatment. Growth velocity Z-score was only calculated for subjects ≥ 2.25 years.

End point type	Secondary

End point timeframe:

Pre-treatment (based on standing height within 2 years prior to treatment), Post-treatment (based on all standing height data during the study period up to Week 48)

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	4[15]			
Units: Z-score				
arithmetic mean (standard deviation)	2.291 (± 3.3555)			

Notes:

[15] - Subjects ≥ 2.25 years with both historical pre-treatment (within 2 years) and post-treatment data.

Attachments (see zip file)	statistical analysis growth velocity z-score.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in Liver Measurement

End point title	Change From Baseline Over Time in Liver Measurement

End point description:

For all subjects (including the subject previously treated with UX003 under an eIND), the last non-missing study assessment prior to the first dose in this study was used as baseline.

n=subjects with a non-missing assessment at baseline and given time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 48, 96, 144

End point values	UX003: eIND	UX003: Non-eIND		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1[16]	6		
Units: cm				
arithmetic mean (standard deviation)				
Change at Week 12; n=1,6	-0.30 (± 999999)	-0.87 (± 1.873)		
Change at Week 24; n=1,5	0.70 (± 999999)	-1.16 (± 2.701)		
Change at Week 48; n=1,6	-0.40 (± 999999)	-0.85 (± 2.160)		
Change at Week 96; n=0,6	99999 (± 99999)	-0.45 (± 1.868)		
Change at Week 144; n=0,2	99999 (± 99999)	-1.50 (± 3.394)		

Notes:

[16] - 99999=not applicable (0 subjects analyzed); 999999=not applicable (1 subject analyzed)

Attachments (see zip file)	statistical analysis liver measurement.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in Spleen Measurement

End point title	Change From Baseline Over Time in Spleen Measurement

End point description:

For all subjects (including the subject previously treated with UX003 under an eIND), the last non-missing study assessment prior to the first dose in this study was used as baseline.

n=subjects with a non-missing assessment at baseline and given time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 48, 96, 144

End point values	UX003: eIND	UX003: Non-eIND		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1[17]	7		
Units: cm				
arithmetic mean (standard deviation)				
Change at Week 12; n=1,7	0.00 (± 999999)	-0.37 (± 0.624)		
Change at Week 24; n=1,7	-0.10 (± 999999)	-0.03 (± 1.493)		
Change at Week 48; n=1,7	-1.60 (± 999999)	-0.16 (± 1.128)		
Change at Week 96; n=0,7	99999 (± 99999)	0.21 (± 1.056)		
Change at Week 144; n=0,2	99999 (± 99999)	-1.12 (± 0.686)		

Notes:

[17] - 99999=not applicable (0 subjects analyzed); 999999=not applicable (1 subject analyzed)

Attachments (see zip file)	statistical analysis spleen measurement.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 until 30 days after the last dose of study drug (treatment emergent events). Mean (SD) treatment duration was 98.11 (29.02) weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	UX003

Reporting group description:

UX003 4 mg/kg QOW. Initial treatment period 48 weeks. Continuation period up to 240 weeks.

Serious adverse events	UX003		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 8 (37.50%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Oxygen Saturation Decreased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cervical Cord Compression			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile Convulsion			

subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Device Fastener Issue			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Adenoidal Hypertrophy			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Cervical Spinal Stenosis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal Column Stenosis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal Instability			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Otitis Media			
subjects affected / exposed	1 / 8 (12.50%)		
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	UX003		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
General disorders and administration site conditions			
Device Defective			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Device Malfunction			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	4		
Discomfort			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Extravasation			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	3		
Inflammation			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Infusion Site Extravasation			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	5 / 8 (62.50%)		
occurrences (all)	13		
Secretion Discharge			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Tenderness			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Immune system disorders			

Anaphylactoid Reaction			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	3		
Cough			
subjects affected / exposed	3 / 8 (37.50%)		
occurrences (all)	11		
Hypoxia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Nasal Congestion			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	3		
Nasal Mucosal Disorder			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Oropharyngeal Pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Pneumonia Aspiration			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Rhinitis Allergic			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	3 / 8 (37.50%)		
occurrences (all)	7		
Tonsillar Hypertrophy			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Upper Respiratory Tract Congestion			

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Wheezing			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	4		
Psychiatric disorders			
Attention Deficit/Hyperactivity Disorder			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Irritability			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Sleep Disorder			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Blood Calcium Decreased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Blood Creatinine Decreased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Blood Pressure Increased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Body Temperature Increased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Body temperature abnormal			

subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Hepatic Enzyme Increased				
subjects affected / exposed	2 / 8 (25.00%)			
occurrences (all)	3			
Oxygen Saturation Decreased				
subjects affected / exposed	2 / 8 (25.00%)			
occurrences (all)	3			
Right Ventricular Systolic Pressure Increased				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Vitamin D Decreased				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Injury, poisoning and procedural complications				
Contusion				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	2			
Fall				
subjects affected / exposed	2 / 8 (25.00%)			
occurrences (all)	10			
Gastrostomy Tube Site Complication				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Limb Injury				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Procedural Pain				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Scar				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	2			
Scratch				

subjects affected / exposed occurrences (all) Skin Abrasion subjects affected / exposed occurrences (all) Sunburn subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 6 2 / 8 (25.00%) 7 1 / 8 (12.50%) 1		
Congenital, familial and genetic disorders Mucopolysaccharidosis Vii subjects affected / exposed occurrences (all) Pectus Carinatum subjects affected / exposed occurrences (all)	 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1		
Cardiac disorders Bradycardia subjects affected / exposed occurrences (all) Pulmonary Valve Stenosis subjects affected / exposed occurrences (all) Right Ventricular Hypertension subjects affected / exposed occurrences (all) Supraventricular Extrasystoles subjects affected / exposed occurrences (all) Tachycardia subjects affected / exposed occurrences (all)	 1 / 8 (12.50%) 4 1 / 8 (12.50%) 1 1 / 8 (12.50%) 2 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1		
Nervous system disorders Cerebellar Microhaemorrhage subjects affected / exposed occurrences (all) Enlarged Cerebral Perivascular Spaces	 1 / 8 (12.50%) 1		

subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Myelopathy subjects affected / exposed occurrences (all) Lethargy subjects affected / exposed occurrences (all) Periodic Limb Movement Disorder subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1 1 / 8 (12.50%) 6 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Lymphadenitis subjects affected / exposed occurrences (all) Microcytosis subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1		
Ear and labyrinth disorders Cerumen Impaction subjects affected / exposed occurrences (all) Ear Pain subjects affected / exposed occurrences (all)	 1 / 8 (12.50%) 2 2 / 8 (25.00%) 5		
Eye disorders			

Corneal Deposits			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Myopia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Strabismus			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Abdominal Pain Upper			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	4 / 8 (50.00%)		
occurrences (all)	9		
Gingival Pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Gingival Bleeding			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Lip Haemorrhage			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	3		
Oral Papule			

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	4 / 8 (50.00%)		
occurrences (all)	20		
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Blood Blister			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Dermatitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Ecchymosis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Intertrigo			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Keloid Scar			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	3		
Papule			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Rash Papular			

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Rash Pruritic			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	7		
Urticaria			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	16		
Skin Irritation			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Renal and urinary disorders			
Bladder Disorder			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Haematuria			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	11		
Bone Deformity			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Muscle Spasms			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Muscular Weakness			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Musculoskeletal Pain			

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Pain In Extremity			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	12		
Spinal Deformity			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Infections and infestations			
Adenoiditis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Bacterial Disease Carrier			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Device Related Infection			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Ear Infection			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	3		
Enterovirus Infection			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Eye Infection			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Fungal Infection			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Fungal Skin Infection			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Gastroenteritis			
subjects affected / exposed	4 / 8 (50.00%)		
occurrences (all)	8		

Gastroenteritis Viral				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Gastrointestinal Infection				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Gingival Abscess				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Nasopharyngitis				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	2			
Otitis Media				
subjects affected / exposed	3 / 8 (37.50%)			
occurrences (all)	3			
Otitis Media Acute				
subjects affected / exposed	2 / 8 (25.00%)			
occurrences (all)	5			
Otitis Media Chronic				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Pharyngitis				
subjects affected / exposed	2 / 8 (25.00%)			
occurrences (all)	3			
Pharyngitis Streptococcal				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	2			
Pharyngotonsillitis				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	2			
Pneumonia Viral				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			
Respiratory Tract Infection Viral				
subjects affected / exposed	1 / 8 (12.50%)			
occurrences (all)	1			

Rhinitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Rhinovirus Infection			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	3		
Tracheitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 8 (37.50%)		
occurrences (all)	9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 October 2015	• The study size was increased from up to seven subjects to approximately 15 subjects including approximately five infants with hydrops fetalis to provide a more robust assessment of safety and efficacy in this patient population. • Given the age of the study population and number of assessments, the study-specific Laboratory Manual was updated to provide details on prioritizing blood draws based on Maximum Allowable Blood Volume Guidelines for any subject on any given study visit; some assessments were not required if this limit was exceeded. • The Bayley-III would not be administered if the subject achieved the highest raw score on the instrument, or if, based on the clinical judgment of the Investigator, valid and reliable administration was not possible at the specified visit. • A Gross Motor Milestone checklist was included as a tertiary efficacy variable. The checklist was designed to allow for assessment of the functional status of the subject while limiting language interaction and physical handling. • Pulse oximetry measurements were added at 12-week intervals to provide continued monitoring of pulmonary function and potentially measure maintenance of efficacy. Procedures for the assessment of vital signs were specified for young pediatric subjects. • Serum markers of bone formation and bone resorption including P1NP, CTX-I, BALP, and vitamin D, were added to follow the effects of UX003 on skeletal tissue. • Specific time points for the collection of PK samples were provided.
07 April 2016	• Remove reference to availability of commercial drug in the subject's territory as a reason for study termination. • Defined the end of trial as the Week 240 visit of the last subject. If study is terminated by the Sponsor prior to Week 240, all subjects should complete a termination visit and the date of the last termination visit of the last subject would define the end of the trial. • Allow for mutation analysis at any point during the study to characterize the disease manifestations, severity and progression of MPS VII. • Clarify procedures for vital sign measurements and the monitoring and management of spinal cord compression. • Remove serum GAG assessments during the Continuation Period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported