



## Clinical trial results:

### An Open-Label Phase 1/2 Study to Assess the Safety, Efficacy and Dose of UX003 rhGUS Enzyme Replacement Therapy in Patients With MPS 7 Summary

EudraCT number	2013-001152-35
Trial protocol	GB ES
Global end of trial date	13 July 2016

#### Results information

Result version number	v2
This version publication date	21 November 2018
First version publication date	30 August 2017
Version creation reason	• Correction of full data set study start update

#### Trial information

##### Trial identification

Sponsor protocol code	UX003-CL201
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01856218
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, Ultragenyx Pharmaceutical Inc. , 1 4154838148, rhostutler@ultragenyx.com
Scientific contact	Christine Haller, MD, VP, Drug Safety and Pharmacovigilance, Ultragenyx Pharmaceutical Inc. , 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	13 July 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	13 July 2016
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objectives of the study are to evaluate safety and tolerability of UX003 exposure and efficacy in subjects with mucopolysaccharidosis 7 (MPS VII, Sly syndrome) as determined by the reduction of total urinary glycosaminoglycan (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	18 November 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Regulatory reason
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 Kingdom: 3
Worldwide total number of subjects	3
EEA total number of subjects	3

Notes:

<b>Subjects enrolled per age group</b>	
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)	2
Adolescents (12-17 years)	0
Adults (18-64 years)	1
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

In this study, the 3 subjects who were enrolled at Site 111 in the United Kingdom (UK), were also enrolled at local sites in their home countries (1 in Spain and 2 in Turkey) for infusions and blood/urine sample collection. All subjects continued to attend study visits at the UK site for designated major efficacy assessment visits with infusions.

### Pre-assignment

Screening details:

Subjects were evaluated for trial participation based on the protocol-specified inclusion and exclusion criteria. All 3 of the subjects who were screened also enrolled in the study.

### Period 1

Period 1 title	First Phase
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Arm title	UX003
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Arm description:

During the initial 14-week treatment period of the study, subjects received 2 mg/kg UX003 every other week (QOW) for 12 weeks. At Week 14, subjects continued on UX003 therapy and began a forced dose titration period for an additional 24 weeks at the dose sequence of 1, 4, and 2 mg/kg UX003 QOW as follows:

- 1 mg/kg UX003 for 8 weeks beginning on Week 14, then
- 4 mg/kg UX003 for 8 weeks beginning on Week 22, then
- 2 mg/kg UX003 for 8 weeks beginning on Week 30.

Following the 24 week forced dose titration period, subjects who continued on treatment (continuation period) received 2 mg/kg UX003 QOW beginning at Week 38 for up to an additional 36 weeks.

Arm type	Experimental
Investigational medicinal product name	Recombinant human beta-glucuronidase
Investigational medicinal product code	UX003
Other name	RHGUS, vestronidase alfa
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

UX003 requires weight-based dosing QOW intravenously by slow infusions over a period of approximately 4 hours. The dosage is designated per study period within first phase.

<b>Number of subjects in period 1</b>	UX003
Started	3
Completed	3

**Period 2**

Period 2 title	Long-Term Extension Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

**Arms**

<b>Arm title</b>	UX003
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Arm description:

After the first phase of the study, subjects who elected to continue drug treatment were transitioned to the long-term extension phase, where they were treated with UX003 at 4 mg/kg beginning at Week 74, for up to an additional 168 weeks.

Arm type	Experimental
Investigational medicinal product name	Recombinant human beta-glucuronidase
Investigational medicinal product code	UX003
Other name	RHGUS, vestronidase alfa
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

UX003 requires weight-based dosing QOW intravenously by slow infusions over a period of approximately 4 hours. The dosage is designated per study period within first phase.

<b>Number of subjects in period 2</b>	UX003
Started	3
Completed > 118 weeks on treatment	3
Completed	0
Not completed	3
Transitioned to compassionate use	3

## Baseline characteristics

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### Reporting groups

Reporting group title	First Phase
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Reporting group description: -

Reporting group values	First Phase	Total	
Number of subjects	3	3	
Age categorical			
Units: Subjects			
Children (2-11 years)	2	2	
Adults (18-64 years)	1	1	
Gender categorical			
Units: Subjects			
Female	1	1	
Male	2	2	

## End points

### End points reporting groups

Reporting group title	UX003
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Reporting group description:

During the initial 14-week treatment period of the study, subjects received 2 mg/kg UX003 every other week (QOW) for 12 weeks. At Week 14, subjects continued on UX003 therapy and began a forced dose titration period for an additional 24 weeks at the dose sequence of 1, 4, and 2 mg/kg UX003 QOW as follows:

- 1 mg/kg UX003 for 8 weeks beginning on Week 14, then
- 4 mg/kg UX003 for 8 weeks beginning on Week 22, then
- 2 mg/kg UX003 for 8 weeks beginning on Week 30.

Following the 24 week forced dose titration period, subjects who continued on treatment (continuation period) received 2 mg/kg UX003 QOW beginning at Week 38 for up to an additional 36 weeks.

Reporting group title	UX003
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Reporting group description:

After the first phase of the study, subjects who elected to continue drug treatment were transitioned to the long-term extension phase, where they were treated with UX003 at 4 mg/kg beginning at Week 74, for up to an additional 168 weeks.

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

During the initial 14-week treatment period of the study, subjects received 2 mg/kg UX003 QOW for 12 weeks. At Week 14, subjects continued on UX003 therapy and began a forced dose titration period for an additional 24 weeks at the dose sequence of 1, 4, and 2 mg/kg UX003 QOW as follows:

- 1 mg/kg UX003 for 8 weeks beginning on Week 14, then
- 4 mg/kg UX003 for 8 weeks beginning on Week 22, then
- 2 mg/kg UX003 for 8 weeks beginning on Week 30.

Following the 24 week forced dose titration period, subjects who continued on treatment (continuation period) received 2 mg/kg UX003 QOW beginning at Week 38 for up to an additional 36 weeks.

After the continuation period, subjects who elected to continue drug treatment were transitioned to the long-term extension period of the study where they were treated with UX003 at 4 mg/kg beginning at Week 74, for up to an additional 168 weeks.

### Primary: Percentage Change From Baseline in uGAG (Dermatan Sulfate)

End point title	Percentage Change From Baseline in uGAG (Dermatan
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End point description:

Percentage change from baseline in the concentration of uGAGs normalized to the urinary creatinine concentration as measured by liquid chromatography-mass spectrometry/mass spectrometry-dermatan sulfate.

End point type	Primary
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End point timeframe:

Week 14, Week 22, Week 30, Week 38, Week 72, and end of study (up to Week 132)

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: Mean (SD) statistics are presented, per protocol.

End point values	UX003			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: percentage change				
arithmetic mean (standard deviation)				
Initial treatment-Week 14	-50.41 ( $\pm$ 7.895)			

Forced dose titration-Week 22	-38.94 ( $\pm$ 7.137)			
Forced dose titration-Week 30	-63.49 ( $\pm$ 6.889)			
Forced dose titration-Week 38	-51.82 ( $\pm$ 9.033)			
Continuation-Week 72	-54.2 ( $\pm$ 8.442)			
Long term extension-end of study	-34.44 ( $\pm$ 48.56)			

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage Change From Baseline in uGAG (Chondroitin Sulfate)

End point title	Percentage Change From Baseline in uGAG (Chondroitin Sulfate) <sup>[2]</sup>
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End point description:

Percentage change from baseline in the concentration of uGAGs normalized to the urinary creatinine concentration as measured by liquid chromatography-mass spectrometry/mass spectrometry-chondroitin sulfate.

End point type	Primary
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End point timeframe:

Week 14, Week 22, Week 30, Week 38, Week 72, and end of study (up to Week 132)

Notes:

[2] - 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: Mean (SD) statistics are presented, per protocol.

End point values	UX003			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: percentage change				
arithmetic mean (standard deviation)				
Initial treatment-Week 14	-52.5 ( $\pm$ 13.726)			
Forced dose titration-Week 22	-47.58 ( $\pm$ 3.958)			
Forced dose titration-Week 30	-60.78 ( $\pm$ 7.207)			
Forced dose titration-Week 38	-52.08 ( $\pm$ 13.298)			
Continuation-Week 72	-56.96 ( $\pm$ 13.379)			
Long term extension-end of study	-30.83 ( $\pm$ 40.794)			

## Statistical analyses

No statistical analyses for this end point



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**Primary: Number of Subjects With Any  $\geq$  50% Decrease in uGAG**

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End point title	Number of Subjects With Any $\geq$ 50% Decrease in uGAG <sup>[3]</sup>
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End point description:

Subjects with a  $\geq$  50% decrease in the concentration of uGAGs normalized to the urinary creatinine concentration as measured by liquid chromatography-mass spectrometry/mass spectrometry-dermatan sulfate or chondroitin sulfate.

End point type	Primary
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End point timeframe:

up to Week 132

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	UX003			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: subjects	3			

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**Statistical analyses**

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No statistical analyses for this end point

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**Primary: Number of Subjects with Treatment Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs), Deaths, and Study/Treatment Discontinuations**

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End point title	Number of Subjects with Treatment Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs), Deaths, and Study/Treatment Discontinuations <sup>[4]</sup>
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End point description:

Adverse Event (AE): any untoward medical occurrence in a subject, whether or not considered drug related. SAE: 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
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End point timeframe:

Up to 242 weeks + 30 days. SAEs were recorded beginning at the time the subject signed the informed consent form through 30 days following the last study visit. Non-serious AEs were recorded from the time of signing the ICF through the last study visit.

Notes:

[4] - 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	UX003			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: subjects				
Any TEAE	3			
Treatment-related TEAE	2			
SAE	2			
Grade 3 or 4 TEAE	2			
TEAE leading to treatment discontinuation	1			
TEAE leading to study discontinuation	0			
Fatal TEAE	0			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Dose Selection for the Long-term Extension Phase

End point title	Dose Selection for the Long-term Extension Phase
End point description:	
The choice of the dose of UX003 QOW for the Long-Term Extension Phase was based on a preliminary efficacy analysis at Week 36 prior to all 3 subjects completing the Forced-dose Titration Period of the First Phase of the study.	
End point type	Secondary
End point timeframe:	
Week 36	

End point values	UX003			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: mg/kg				
number (not applicable)	4			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 242 weeks + 30 days. SAEs were recorded beginning at the time the subject signed the informed consent form through 30 days following the last study visit. Non-serious AEs were recorded from the time of signing the ICF through the last study visit.

Adverse event reporting additional description:

TEAEs are presented. 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.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

### Reporting groups

Reporting group title	UX003
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Reporting group description:

During the initial 14-week treatment period of the study, subjects received 2 mg/kg UX003 QOW for 12 weeks. At Week 14, subjects continued on UX003 therapy and began a forced dose titration period for an additional 24 weeks at the dose sequence of 1, 4, and 2 mg/kg UX003 QOW as follows:

- 1 mg/kg UX003 for 8 weeks beginning on Week 14, then
- 4 mg/kg UX003 for 8 weeks beginning on Week 22, then
- 2 mg/kg UX003 for 8 weeks beginning on Week 30.

Following the 24 week forced dose titration period, subjects who continued on treatment (continuation period) received 2 mg/kg UX003 QOW beginning at Week 38 for up to an additional 36 weeks.

After the continuation period, subjects who elected to continue drug treatment were transitioned to the long-term extension period of the study where they were treated with UX003 at 4 mg/kg beginning at Week 74, for up to an additional 168 weeks.

Serious adverse events	UX003		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
Inguinal hernia repair			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Spinal cord compression			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Cerebral ventricle dilatation subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 3 (33.33%) 0 / 1 0 / 0		
General disorders and administration site conditions Oedema peripheral subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 3 (33.33%) 0 / 1 0 / 0		
Gastrointestinal disorders Incarcerated inguinal hernia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 3 (33.33%) 0 / 4 0 / 0		
Musculoskeletal and connective tissue disorders Osteoarthritis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 3 (33.33%) 0 / 2 0 / 0		

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

<b>Non-serious adverse events</b>	UX003		
Total subjects affected by non-serious adverse events subjects affected / exposed	3 / 3 (100.00%)		
Investigations Body temperature increased subjects affected / exposed occurrences (all)  Weight increased subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 2  2 / 3 (66.67%) 2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Papilloma subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Injury, poisoning and procedural complications Ligament sprain subjects affected / exposed occurrences (all)  Skin abrasion subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1  1 / 3 (33.33%) 1		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)  Nystagmus subjects affected / exposed occurrences (all)  Reflexes abnormal subjects affected / exposed occurrences (all)  Visual field defect subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1  1 / 3 (33.33%) 1  1 / 3 (33.33%) 1  1 / 3 (33.33%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
General disorders and administration site conditions Discomfort subjects affected / exposed occurrences (all)  Gait disturbance subjects affected / exposed occurrences (all)  Infusion site extravasation	1 / 3 (33.33%) 1  1 / 3 (33.33%) 1		

subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 3		
Oedema peripheral subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Pyrexia subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 3		
Generalised Oedema subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Gastrointestinal disorders			
Constipation subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Diarrhoea subjects affected / exposed occurrences (all)	2 / 3 (66.67%) 2		
Oral mucosal erythema subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Toothache subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Vomiting subjects affected / exposed occurrences (all)	2 / 3 (66.67%) 3		
Respiratory, thoracic and mediastinal disorders			
Bronchospasm subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Cough subjects affected / exposed occurrences (all)	2 / 3 (66.67%) 2		
Increased viscosity of bronchial secretion			

subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	4		
Respiratory failure			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	3		
Rhinitis allergic			
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	2		
Rhinorrhoea			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Rash macular			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Seborrhoeic dermatitis			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 3 (100.00%)		
occurrences (all)	6		
Groin pain			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Musculoskeletal stiffness			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	2		
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Dermatitis infected			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Ear infection			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	2		
Molluscum contagiosum			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	2		
Nosocomial infection			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Otitis media			



subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	2		
Pharyngitis			
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	3		
Respiratory tract infection			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Tooth abscess			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	7		
Urinary tract infection			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	2		
Viral rash			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 November 2013	The most important changes included the change from a single-center study to a global multi-center study, a clarification that the normal uGAG reference range was the age-specific normal mean. The definition of relatedness for AEs was updated, and pregnancy language was updated to include acceptable forms of contraception and the required length of time after the last dose of study drug that subjects should continue to use an acceptable form of contraception.
01 December 2014	The addition of the Long-term Extension Phase with selection of 4 mg/kg dose to the study design, and addition of PK sampling time points.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This study was terminated due to business considerations unrelated to safety or efficacy concerns.

Notes: