Clinical trial results:
An Open-Label, Phase 2 Study to Assess the Safety, Pharmacodynamics, and Efficacy of KRN23 in Children from 1 to 4 Years Old with X-linked Hypophosphatemia (XLH)

Summary

EudraCT number	2018-001983-49
Trial protocol	Outside EU/EEA
Global end of trial date	10 September 2019

Results information

Result version number	v1 (current)
This version publication date	22 March 2020
First version publication date	22 March 2020

Trial information

Trial identification

Sponsor protocol code	UX023-CL205

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02750618
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-001659-PIP01-15
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	10 September 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 September 2019
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:
• Establish the safety profile of KRN23 for the treatment of XLH in children between 1 and 4 years old
• Determine the pharmacodynamic (PD) effects of KRN23 treatment on serum phosphorus and other PD markers that reflect the status of phosphate homeostasis in children between 1 and 4 years old with XLH

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	05 May 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 13
Worldwide total number of subjects	13
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)	3
Children (2-11 years)	10
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 study enrolled approximately 10 pediatric subjects between 1 and 4 years old, inclusive, with clinical findings consistent with XLH including hypophosphatemia and radiographic evidence of rickets, and a confirmed PHEX mutation or variant of uncertain significance.

Period 1

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

Arms

Arm title	Burosumab Q2W

Arm description:

Burosumab subcutaneous (SC) injections every 2 weeks (Q2W) for a total of 160 weeks.

Arm type	Experimental
Investigational medicinal product name	burosumab
Investigational medicinal product code	UX023
Other name	KRN23, Crysvita®, UX023
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The amount of drug administered will be calculated based on a subject's weight. All subjects will receive KRN23 at a Q2W dosing regimen.

Number of subjects in period 1	Burosumab Q2W
Started	13
Completed Week 40	13
Completed Week 64	13
Completed	12
Not completed	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups	
Reporting group title	Burosumab Q2W
Reporting group description:	
Burosumab subcutaneous (SC) injections every 2 weeks (Q2W) for a total of 160 weeks.	

Reporting group values	Burosumab Q2W	Total	
Number of subjects	13	13	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 2.94 ± 1.146	 -	
Gender categorical Units: Subjects			
Female	4	4	
Male	9	9	
Ethnicity Units: Subjects			
Hispanic or Latino	2	2	
Not Hispanic or Latino	11	11	
Unknown or Not Reported	0	0	
Race Units: Subjects			
White	12	12	
Black or African American	1	1	
Serum Phosphorus Units: mg/dL arithmetic mean standard deviation	 2.51 ± 0.284	 -	
Rickets Severity Score (RSS) Total Score			
The RSS system is a 10-point radiographic scoring method that was developed to assess the severity of nutritional rickets in the wrists and knees based on the degree of metaphyseal fraying, cupping, and the proportion of the growth plate affected. Scores are assigned for the unilateral wrist and knee X-rays deemed by the rater to be the more severe of the bilateral images. The maximum total score on the RSS is 10 points and the minimum score is 0, with a total possible score of 4 points for the wrists and 6 points for the knees. Higher scores indicate greater rickets severity.			
Units: units on a scale arithmetic mean standard deviation	 2.92 ± 1.367	 -	
Recumbent length/ Standing height			
Growth is measured by recumbent length for subjects < 2 years of age or those unable or unwilling to stand for the measurement.			
Units: cm arithmetic mean standard deviation	 89.15 ± 7.597	 -	
Recumbent length/ Standing height (Z			

score)			
Recumbent length/Standing height z scores are measures of height adjusted for a child's age and sex. 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.			
Units: Z score			
arithmetic mean	-1.378		
standard deviation	± 1.1947	-	
Recumbent length/ Standing height (percentile)			
Units: percentile			
arithmetic mean	18.044		
standard deviation	± 25.2644	-	
Serum Alkaline Phosphatase (ALP)			
Units: U/L			
arithmetic mean	548.5		
standard deviation	± 193.80	-	

End points

End points reporting groups

Reporting group title	Burosumab Q2W
Reporting group description:	
Burosumab subcutaneous (SC) injections every 2 weeks (Q2W) for a total of 160 weeks.	

Primary: Change From Baseline at Week 40 in Serum Phosphorus

End point title	Change From Baseline at Week 40 in Serum Phosphorus[1]
End point description:	
The Generalized Estimation Equation (GEE) model includes the change from baseline as the dependent variable, time as the categorical variable and adjusted for baseline measurement, with exchangeable covariance structure. Pharmacokinetic/Pharmacodynamic (PK/PD) Analysis Set: all participants who received at least one dose of study drug and had evaluable blood samples.	
End point type	Primary
End point timeframe:	
Baseline, Week 40	
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: GEE statistical analysis is presented in the data table.	

End point values	Burosumab Q2W			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: mg/dL				
least squares mean (standard error)	0.96 (± 0.117)			

Attachments (see zip file)	Statistical Analysis 1 for Change From Baseline at Week 40 in

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Participants With Adverse Events (AEs), Treatment Emergent AEs (TEAEs), Serious TEAEs, and TEAEs Leading to Discontinuation[2]
End point description:	
An AE was defined as any untoward medical occurrence associated with the use of a drug, whether or not considered drug related. A serious AE was defined as an AE that at any dose, in the view of either the Investigator or Sponsor, results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant incapacity or disability, a congenital anomaly/birth defect, or other important medical events (according to the investigator). 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 prior to the first dose but increased in severity during the study.	

Events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0: grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (life-threatening), grade 5 (death).

End point type	Primary

End point timeframe:

From first dose of study drug through the end of the study (at Week 160). Maximum duration of exposure to study drug was 160 weeks.

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: Descriptive statistics are presented per protocol.

End point values	Burosumab Q2W			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: participants				
Adverse Event Starting during Screening Period	5			
TEAEs	13			
Related TEAEs	5			
Serious TEAEs	1			
Serious Related TEAEs	0			
Grade 3 or 4 TEAEs	2			
TEAE Leading to Study Discontinuation	0			
TEAE Leading to Treatment Discontinuation	0			
TEAE Leading to Death	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Radiographic Global Impression of Change (RGI-C) Score at Week 40

End point title	Radiographic Global Impression of Change (RGI-C) Score at Week 40

End point description:

Changes in the severity of rickets and bowing were assessed centrally by three independent pediatric radiologists contracted by a central imaging facility using a disease specific qualitative RGI-C scoring system. The RGI-C is a seven point ordinal scale with possible values: +3 = very much better (complete or near complete healing of rickets), +2 = much better (substantial healing of rickets), +1 = minimally better (i.e., minimal healing of rickets), 0 = unchanged, -1 = minimally worse (minimal worsening of rickets), -2 = much worse (moderate worsening of rickets), -3 = very much worse (severe worsening of rickets). The Analysis of Covariance (ANCOVA) model includes the RGI-C score as the dependent variable, age and RSS at baseline as covariates.

End point type	Secondary

End point timeframe:

Week 40

End point values	Burosumab Q2W			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: units on a scale				
least squares mean (standard error)	2.21 (± 0.071)			

Attachments (see zip file)	Statistical Analysis 1 for Radiographic Global Impression of

Statistical analyses

No statistical analyses for this end point

Secondary: RGI-C Score at Week 64

End point title	RGI-C Score at Week 64

End point description:

Changes in the severity of rickets and bowing were assessed centrally by three independent pediatric radiologists contracted by a central imaging facility using a disease specific qualitative RGI-C scoring system. The RGI-C is a seven point ordinal scale with possible values: +3 = very much better (complete or near complete healing of rickets), +2 = much better (substantial healing of rickets), +1 = minimally better (i.e., minimal healing of rickets), 0 = unchanged, -1 = minimally worse (minimal worsening of rickets), -2 = much worse (moderate worsening of rickets), -3 = very much worse (severe worsening of rickets). The GEE model includes the RGI-C score as the dependent variable, visit as a factor, age and RSS at baseline as covariates, with exchangeable covariance structure.

Efficacy Analysis Set: all participants who received at least one dose of study drug and had at least one post-study drug measurement.

End point type	Secondary

End point timeframe:

Week 64

End point values	Burosumab Q2W			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: units on a scale				
least squares mean (standard error)	2.23 (± 0.111)			

Attachments (see zip file)	Statistical Analysis 1 for RGI-C Score at Week 64.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Rickets at Week 40 as Assessed by the RSS Total Score

End point title	Change From Baseline in Rickets at Week 40 as Assessed by

	the RSS Total Score

End point description:

The RSS system is a 10-point radiographic scoring method that was developed to assess the severity of nutritional rickets in the wrists and knees based on the degree of metaphyseal fraying, cupping, and the proportion of the growth plate affected. Scores are assigned for the unilateral wrist and knee X-rays deemed by the rater to be the more severe of the bilateral images. The maximum total score on the RSS is 10 points and the minimum score is 0, with a total possible score of 4 points for the wrists and 6 points for the knees. Higher scores indicate greater rickets severity. The ANCOVA model includes the RGI-C score as the dependent variable, age and RSS at baseline as covariates.

Efficacy Analysis Set: all participants who received at least one dose of study drug and had at least one post-study drug measurement.

End point type	Secondary

End point timeframe:

Baseline, Week 40

End point values	Burosumab Q2W			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: units on a scale				
least squares mean (standard error)	-1.75 (± 0.116)			

Attachments (see zip file)	Statistical Analysis 1 for Change From Baseline in Rickets at

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Rickets at Week 64 as Assessed by the RSS Total Score

End point title	Change From Baseline in Rickets at Week 64 as Assessed by the RSS Total Score

End point description:

The RSS system is a 10-point radiographic scoring method that was developed to assess the severity of nutritional rickets in the wrists and knees based on the degree of metaphyseal fraying, cupping, and the proportion of the growth plate affected. Scores are assigned for the unilateral wrist and knee X-rays deemed by the rater to be the more severe of the bilateral images. The maximum total score on the RSS is 10 points, with a total possible score of 4 points for the wrists and 6 points for the knees. Higher scores indicate greater rickets severity. The GEE model includes the change from baseline in RSS as the dependent variable, visit as a factor, age and RSS at baseline as covariates, with exchangeable covariance structure.

End point type	Secondary

End point timeframe:

Baseline, Week 64

End point values	Burosumab Q2W			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: units on a scale				
least squares mean (standard error)	-2.02 (± 0.115)			

Attachments (see zip file)	Change From Baseline in Rickets at Week 64 as Assessed by

Statistical analyses

No statistical analyses for this end point

Secondary: RGI-C Lower Limb Deformity Score at Week 40

End point title	RGI-C Lower Limb Deformity Score at Week 40

End point description:

Changes in the severity of lower extremity skeletal abnormalities were assessed centrally by three independent pediatric radiologists contracted by a central imaging facility using a disease specific qualitative RGI-C scoring system. The RGI-C is a seven point ordinal scale with possible values: +3 = very much better (complete or near complete healing of rickets), +2 = much better (substantial healing of rickets), +1 = minimally better (i.e., minimal healing of rickets), 0 = unchanged, -1 = minimally worse (minimal worsening of rickets), -2 = much worse (moderate worsening of rickets), -3 = very much worse (severe worsening of rickets). The ANCOVA model includes the RGI-C score as the dependent variable, age and RSS at baseline as covariates.

Efficacy Analysis Set: all participants who received at least one dose of study drug and had at least one post-study drug measurement.

End point type	Secondary

End point timeframe:

Week 40

End point values	Burosumab Q2W			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: units on a scale				
least squares mean (standard error)	1.21 (± 0.155)			

Attachments (see zip file)	Statistical Analysis 1 for RGI-C Lower Limb Deformity Score at

Statistical analyses

No statistical analyses for this end point

Secondary: RGI-C Lower Limb Deformity Score at Week 64

End point title	RGI-C Lower Limb Deformity Score at Week 64

End point description:

Changes in the severity of lower extremity skeletal abnormalities were assessed centrally by three independent pediatric radiologists contracted by a central imaging facility using a disease specific qualitative RGI-C scoring system. The RGI-C is a seven point ordinal scale with possible values: +3 = very much better (complete or near complete healing of rickets), +2 = much better (substantial healing of rickets), +1 = minimally better (i.e., minimal healing of rickets), 0 = unchanged, -1 = minimally worse (minimal worsening of rickets), -2 = much worse (moderate worsening of rickets), -3 = very much worse (severe worsening of rickets). The GEE model includes the RGI-C score as the dependent variable, visit as a factor, age and RSS at baseline as covariates, with exchangeable covariance structure.

Efficacy Analysis Set: all participants who received at least one dose of study drug and had at least one post-study drug measurement.

End point type	Secondary

End point timeframe:

Week 64

End point values	Burosumab Q2W			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: units on a scale				
least squares mean (standard error)	1.51 (± 0.123)			

Attachments (see zip file)	Statistical Analysis 1 for RGI-C Lower Limb Deformity Score at

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in Recumbent Length/Standing Height

End point title	Change From Baseline Over Time in Recumbent Length/Standing Height

End point description:

Efficacy Analysis Set: all participants who received at least one dose of study drug and had at least one post-study drug measurement at given time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 40, 64, 88, 112, 136, 160

End point values	Burosumab Q2W			
Subject group type	Reporting group			
Number of subjects analysed	13[3]			
Units: cm				
arithmetic mean (standard deviation)				
Week 12; n=13	1.44 (± 2.009)			

Week 24; n=13	2.52 (± 1.518)			
Week 40; n=13	4.29 (± 2.451)			
Week 64; n=13	7.22 (± 3.157)			
Week 88; n=13	10.30 (± 3.400)			
Week 112; n=13	13.25 (± 3.724)			
Week 136; n=11	15.41 (± 3.699)			
Week 160; n=12	18.96 (± 4.206)			

Notes:

[3] - n=participants with an assessment at given time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline Over Time in Recumbent Length/Standing Height as Assessed by Height-for-Age Z-Scores

End point title	Change from Baseline Over Time in Recumbent Length/Standing Height as Assessed by Height-for-Age Z-Scores

End point description:

Recumbent length/Standing height z scores are measures of height adjusted for a child's age and sex. 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.

Efficacy Analysis Set: all participants who received at least one dose of study drug and had at least one post-study drug measurement at given time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 40, 64, 88, 112, 136, 160

End point values	Burosumab Q2W			
Subject group type	Reporting group			
Number of subjects analysed	13[4]			
Units: Z score				
arithmetic mean (standard deviation)				
Week 12; n=13	-0.082 (± 0.4964)			
Week 24; n=13	-0.208 (± 0.4540)			
Week 40; n=13	-0.276 (± 0.6647)			
Week 64; n=13	-0.264 (± 0.8755)			
Week 88; n=13	-0.212 (± 0.9115)			
Week 112; n=13	-0.174 (± 0.9273)			

Week 136; n=11	-0.321 (± 0.9123)			
Week 160; n=12	-0.172 (± 0.9048)			

Notes:

[4] - n=participants with an assessment at given time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in Recumbent Length/Standing Height as Assessed by Percentiles

End point title	Change From Baseline Over Time in Recumbent Length/Standing Height as Assessed by Percentiles

End point description:

Efficacy Analysis Set: all participants who received at least one dose of study drug and had at least one post-study drug measurement at given time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 40, 64, 88, 112, 136, 160

End point values	Burosumab Q2W			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: percentiles				
arithmetic mean (standard deviation)				
Week 12; n=13	-0.006 (± 11.6149)			
Week 24; n=13	-4.940 (± 13.1323)			
Week 40; n=13	-5.283 (± 20.1675)			
Week 64; n=13	-4.980 (± 23.4412)			
Week 88; n=13	-4.155 (± 23.9126)			
Week 112; n=13	-3.000 (± 24.7569)			
Week 136; n=11	-7.026 (± 24.8583)			
Week 160; n=12	-3.628 (± 25.5113)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in Serum Alkaline Phosphatase (ALP)

End point title	Change From Baseline Over Time in Serum Alkaline Phosphatase (ALP)

End point description:

The GEE model includes the change from baseline as the dependent variable, time as the categorical variable and adjusted for baseline measurement, with exchangeable covariance structure.

PK/PD Analysis Set: all participants who received at least one dose of study drug and had evaluable blood samples at given time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 12, 20, 40, 48, 56, 64, 76, 88, 100, 112, 124, 136, 148, 160

End point values	Burosumab Q2W			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: U/L				
least squares mean (standard error)				
Week 4; n=13	-82.91 (± 23.348)			
Week 12; n=13	-83.84 (± 45.263)			
Week 20; n=13	-161.38 (± 12.924)			
Week 40; n=13	-214.99 (± 13.628)			
Week 48; n=12	-226.58 (± 11.491)			
Week 56; n=13	-216.45 (± 16.165)			
Week 64; n=13	-216.76 (± 12.705)			
Week 76; n=13	-231.22 (± 15.964)			
Week 88; n=12	-237.78 (± 12.837)			
Week 100; n=13	-218.14 (± 15.340)			
Week 112; n=13	-233.91 (± 11.098)			
Week 124; n=12	-252.22 (± 8.312)			
Week 136; n=12	-267.89 (± 13.124)			
Week 148; n=12	-248.05 (± 12.653)			
Week 160; n=12	-248.47 (± 10.990)			

Attachments (see zip file)	Statistical Analysis 15 for Change From Baseline Over Time in

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline Over Time in Serum ALP

End point title	Percent Change From Baseline Over Time in Serum ALP

End point description:

PK/PD Analysis Set: all participants who received at least one dose of study drug and had evaluable blood samples at given time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 12, 20, 40, 48, 56, 64, 76, 88, 100, 112, 124, 136, 148, 160

End point values	Burosumab Q2W			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: percent change				
arithmetic mean (standard deviation)				
Week 4; n=13	-12.47 (± 16.620)			
Week 12; n=13	-5.00 (± 60.124)			
Week 20; n=13	-24.76 (± 18.883)			
Week 40; n=13	-36.25 (± 12.787)			
Week 48; n=13	-37.29 (± 13.936)			
Week 56; n=13	-35.80 (± 16.568)			
Week 64; n=13	-35.95 (± 14.851)			
Week 76; n=13	-38.36 (± 15.621)			
Week 88; n=12	-39.08 (± 12.987)			
Week 100; n=13	-37.42 (± 12.466)			
Week 112; n=13	-39.05 (± 13.808)			
Week 124; n=12	-43.11 (± 12.493)			
Week 136; n=12	-47.01 (± 11.752)			
Week 148; n=12	-43.47 (± 11.321)			
Week 160; n=12	-42.35 (± 13.574)			

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 through the end of the study (at Week 160). Maximum duration of exposure to study drug was 160 weeks.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Burosumab Q2W
Reporting group description: Burosumab SC injections Q2W for a total of 160 weeks.	

Serious adverse events	Burosumab Q2W		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 13 (7.69%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Infections and infestations			
Tooth Abscess			
subjects affected / exposed	1 / 13 (7.69%)		
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	Burosumab Q2W		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 13 (100.00%)		
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Haematoma			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
General disorders and administration			

site conditions			
Fatigue			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Injection Site Bruising			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	3		
Injection Site Erythema			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	4		
Injection Site Pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	2		
Injection Site Pruritus			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Injection Site Reaction			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	11 / 13 (84.62%)		
occurrences (all)	54		
Vaccination Site Reaction			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	2		
Immune system disorders			
Food Allergy			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Hypersensitivity			

subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	4		
Reproductive system and breast disorders			
Penile Erythema			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Penile Pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Adenoidal Disorder			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Chronic Throat Clearing			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	11 / 13 (84.62%)		
occurrences (all)	40		
Epistaxis			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	11		
Nasal Congestion			
subjects affected / exposed	8 / 13 (61.54%)		
occurrences (all)	9		
Nasal Discharge Discolouration			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Oropharyngeal Pain			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	10		
Productive Cough			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	4		
Respiratory Tract Congestion			

subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	4		
Rhinorrhoea			
subjects affected / exposed	7 / 13 (53.85%)		
occurrences (all)	35		
Sinus Congestion			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	2		
Sneezing			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	3		
Throat Irritation			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Wheezing			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	7		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	2		
Investigations			
Amylase Increased			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Blood 25-Hydroxycholecalciferol Decreased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Blood Parathyroid Hormone Increased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Blood Phosphorus Decreased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Heart Rate Abnormal			

subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Lipase Increased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Vitamin D Decreased			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
White Blood Cell Count Increased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Arthropod Bite			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	8		
Contusion			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Fall			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	6		
Laceration			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Lip Injury			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Skin Abrasion			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	5		
Tooth Fracture			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Tooth Injury			

subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Traumatic Tooth Displacement			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Congenital, familial and genetic disorders			
Skull Malformation			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Syringomyelia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Dysarthria			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	6 / 13 (46.15%)		
occurrences (all)	15		
Hypersomnia			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Lethargy			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	4		
Periodic Limb Movement Disorder			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Deafness Unilateral			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Ear Haemorrhage			

subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Ear Pain			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	17		
Excessive Cerumen Production			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	2		
Hypoacusis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	2		
Motion Sickness			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	2		
Otorrhoea			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Tinnitus			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Eye disorders			
Ocular Hyperaemia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal Discomfort			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	4		
Abdominal Pain Upper			
subjects affected / exposed	5 / 13 (38.46%)		
occurrences (all)	12		
Aphthous Ulcer			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	5		
Constipation			

subjects affected / exposed	2 / 13 (15.38%)			
occurrences (all)	3			
Dental Caries				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Diarrhoea				
subjects affected / exposed	6 / 13 (46.15%)			
occurrences (all)	9			
Epigastric Discomfort				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Gingival Blister				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Gingival Erythema				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Gingival Pain				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Haematochezia				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	2			
Loose Tooth				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Nausea				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	2			
Oral Pain				
subjects affected / exposed	4 / 13 (30.77%)			
occurrences (all)	6			
Post-Tussive Vomiting				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Stomatitis				

subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Teething subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Toothache subjects affected / exposed occurrences (all)	3 / 13 (23.08%) 6		
Vomiting subjects affected / exposed occurrences (all)	7 / 13 (53.85%) 15		
Vomiting Projectile subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Skin and subcutaneous tissue disorders			
Dermatitis Contact subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Pruritus subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 2		
Rash subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 3		
Rash Papular subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Skin Disorder subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Swelling Face subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Urticaria subjects affected / exposed occurrences (all)	4 / 13 (30.77%) 8		

Urticaria Papular subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) Polyuria subjects affected / exposed occurrences (all) Urinary Incontinence subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back Pain subjects affected / exposed occurrences (all) Bone Pain subjects affected / exposed occurrences (all) Foot Deformity subjects affected / exposed occurrences (all) Knee Deformity subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Pain In Extremity subjects affected / exposed occurrences (all)	 4 / 13 (30.77%) 13 1 / 13 (7.69%) 1 3 / 13 (23.08%) 6 1 / 13 (7.69%) 1 3 / 13 (23.08%) 3 1 / 13 (7.69%) 2 9 / 13 (69.23%) 40		
Infections and infestations			

Atypical Pneumonia				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Conjunctivitis				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Croup Infectious				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Ear Infection				
subjects affected / exposed	6 / 13 (46.15%)			
occurrences (all)	7			
Enterobiasis				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Eye Infection				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	2			
Gastroenteritis				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Gastrointestinal Viral Infection				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	2			
Genital Candidiasis				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Gingival Abscess				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	2			
Hand-Foot-And-Mouth Disease				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Hordeolum				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			

Impetigo				
subjects affected / exposed	2 / 13 (15.38%)			
occurrences (all)	3			
Influenza				
subjects affected / exposed	3 / 13 (23.08%)			
occurrences (all)	3			
Molluscum Contagiosum				
subjects affected / exposed	3 / 13 (23.08%)			
occurrences (all)	3			
Nasopharyngitis				
subjects affected / exposed	3 / 13 (23.08%)			
occurrences (all)	5			
Otitis Media				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	2			
Pharyngitis Streptococcal				
subjects affected / exposed	8 / 13 (61.54%)			
occurrences (all)	22			
Pneumonia				
subjects affected / exposed	2 / 13 (15.38%)			
occurrences (all)	2			
Sinusitis				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Tooth Abscess				
subjects affected / exposed	10 / 13 (76.92%)			
occurrences (all)	24			
Upper Respiratory Tract Infection				
subjects affected / exposed	9 / 13 (69.23%)			
occurrences (all)	11			
Urinary Tract Infection				
subjects affected / exposed	1 / 13 (7.69%)			
occurrences (all)	1			
Viral Infection				
subjects affected / exposed	2 / 13 (15.38%)			
occurrences (all)	6			

Viral Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	3 / 13 (23.08%) 15		
Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all) Increased Appetite subjects affected / exposed occurrences (all) Polydipsia subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 March 2016	1. Burosumab dose and dose justification: As a result of additional clinical data available since the time the original protocol was written, the dose of burosumab was changed. The starting dose of burosumab was changed to 0.8 mg/kg Q2W. The dose may then be increased to 1.2 mg/kg at any time during the study if a subject met the following dose adjustment criteria: 1) 2 consecutive serum phosphorus measurements were below the normal range; 2) serum phosphorus had increased by < 0.5 mg/dL from Baseline; and 3) the subject had not missed a dose of study drug that would have accounted for the decrease in serum phosphorus. Previously the protocol had specified a starting dose of 0.3 mg/kg Q2W for the first 2 doses and a target dose of 0.6 mg/kg Q2W. 2. Study Population: The inclusion criteria were modified to add PHEX mutation or VUS in either the patient or in a directly related family member with appropriate X-linked inheritance to confirm presence of XLH and to avoid including patients with syndromes that have clinical and biochemical phenotypic overlap with XLH. The criterion of intact fibroblast growth factor 23 (iFGF23) level ≥ 30 pg/mL by Kainos assay was eliminated because it was unnecessary in addition to genetic confirmation. The exclusion criteria were modified to add presence of nephrocalcinosis grade 4 on renal ultrasound (ie, stone formation). Presence of stone formation was added as an exclusion criterion based on regulatory agency request.
28 March 2016	(continued) 3. Prohibited Medications: The washout period required for subjects receiving oral phosphate and active vitamin D standard therapy was reduced from 14 days to 7 days. Oral phosphate is typically given 4–5 times daily in XLH due to its rapid clearance from the body (Carpenter et al. 2011). Prescribing information for oral calcitriol notes a half life of 27.4 hours in children (Rocaltrol 2008); therefore, a 7-day washout was deemed sufficient to remove phosphate and active vitamin D from the body and minimizes the duration of time that a patient is off therapy. 4. Study Procedures and Assessments: a. Screening Visit 2 was removed from the Schedule of Events. Assessments previously indicated to be performed at Screening Visit 2 were rescheduled to be performed at the Baseline visit. This change was made to reduce the burden of multiple visits on subjects and their families. b. The Pediatric Orthopedic Society of North America Pediatric Outcomes Data Collection Instrument was removed as an assessment in the study because the questionnaire could be administered to subjects less than 2 years of age and most of the items were only relevant for subjects 5 years of age or older. Therefore, the amount of data to be collected from this instrument in this study of children 1 to 4 years old was likely minimal. c. The frequency and schedule of renal ultrasounds was modified. Renal ultrasounds were to be conducted at Screening, Week 40, and Week 64. Renal ultrasound assessment was moved from Baseline to Screening because renal stone formation had been added as an exclusion criterion. The Week 12 renal ultrasound was removed to minimize patient burden in these young patients. d. The frequency and schedule for measurement of FGF23 levels was modified to Baseline, Week 24, and Week 64. This change was made to minimize blood volumes collected and to align with the Phase 3 pediatric protocol.

28 March 2016	(continued) e. Assessment of ADA was added at the Baseline Visit. ADA assessment was needed both before and after burosumab administration to distinguish between background signal and ADAs induced by administration of burosumab. f. The instructions for the measurement of BP were updated. BP was to be measured only in subjects who were ≥ 3 years of age. Previously, PB was measured one time each at the beginning and end of site visits in all subjects. At the Screening Visit, BP was to be measured 3 times, 30 seconds apart at the beginning of each visit; 3 additional BP measurements, 30 seconds apart, were to be obtained at the end of the study visit after all procedures had been performed. Elevated BP measurements were noted in some subjects in the Phase 2 pediatric UX023-CL201 study prior to administration of burosumab and in some subjects post administration of burosumab. To help ensure accurate pre-treatment and post-treatment BP measurements in this study, multiple assessments of BP were to be obtained at each site visit. The United States Department of Health and Human Services guidelines for Blood Pressure Measurement in Children was used as a reference. 5. Safety Measurements: Assessment of serum lipase in addition to serum amylase was added for all subjects. Amylase is produced by several organs including the pancreas and salivary gland and so elevated amylase levels are not diagnostic in the absence of other information. In ongoing and completed burosumab studies at Baseline, mild elevations of amylase (<2x the upper limit of the reference range [ULRR]) have been noted. Post treatment mild shifts in amylase elevation (< 2xULRR) has been noted without association with GI symptoms. No AEs of pancreatitis have been observed. The additional testing of serum lipase were to aid in a determination of whether the elevations were from pancreatic or salivary gland sources.
28 March 2016	(continued) 6. Data Monitoring Committee: Details of the DMC were updated. Specifically, the amended protocol stated that the independent DMC was to include members with expertise in metabolic bone disease, cardiology, and nephrology and the conduct of clinical trials in children. The FDA requested the inclusion of DMC members with expertise in pediatric cardiology and nephrology in addition to metabolic bone disease. 7. Record Retention: The record retention language was updated to state that all study records must have been retained for at least 25 years after the end of the clinical trial or in accordance with national law. This administrative change was made to reflect changes to European Union clinical trial regulations and current regulations by other health authorities.
12 June 2017	1. Study Objectives: The additional study objective was modified from "Pre-dose KRN23 drug concentration levels" to "KRN23 drug concentration levels (PK)" to clarify that burosumab drug concentration levels were to be assessed throughout the study. 2. Overall Study Design and Plan: The provision to maintain gender balance was modified from "no more than 7 subjects" to "no more than 70% of subjects". The original protocol planned sample size was 10 subjects, therefore 7 subjects (ie, 70% of the study population) were originally selected. The change more accurately reflected the total enrollment of 13 subjects (9 male; 69%). 3. Study Duration: An Extension Period of 96 weeks was added for continued assessment of the long-term safety and efficacy of burosumab in younger children. 4. Removal of Subjects: Language was added to allow orthopedic surgery during the Extension Period if recommended by the investigator or consulting physician. In addition, subjects who developed hyperparathyroidism were allowed to remain on study, but use of medication to suppress parathyroid hormone (eg, Sensipar®, cinacalcet, calcimimetics) was not permitted at any time. Subjects were to be removed from study if treatment for hyperparathyroidism became medically necessary.

12 June 2017	(continued) 5. Treatment: Updates were made to allow for a parent or caregiver to administer burosumab to the subject after proper training by study personnel in SC injection technique and documentation of proficiency. Additional updates were made to describe the timing of dose adjustments during the Extension Period and to describe methods for monitoring treatment compliance in the home setting via telephone contact and physical inventory of empty vials at site visits for study drug accountability. Allowing subjects' parents or caregivers to administer burosumab in the home setting was expected to reduce the burden on the subjects. Instructions for Use (IFU) were thoughtfully developed with input from XLH patients and were used to guide parents and caregivers through the injection process. The IFU was provided to sites and IRBs for approval prior to the initiation of parent/caregiver administration. To avoid potential errors with any dose adjustments, dose changes during the Extension Period were to be initially implemented at the clinic visits. Site personnel collected information on treatment compliance in the home setting and monitored the home administration via telephone contact. 6. Study Procedures and Assessments: Changes to study procedures are described below; a new Schedule of Events table was included to describe visits and assessments during the Extension Period.
12 June 2017	(continued) a. During the Extension Period, clinic visits were to occur at approximately 12-week intervals (±5 days). Home health or telephone visits were to occur every 2 weeks. For telephone visits, study sites scheduled biweekly telephone calls with the subjects' parent/caregiver to confirm administration of study drug, and for collection of AEs and concomitant medication information. Site personnel initiated a safety follow-up telephone call 5 weeks (+5 days) after the Week 160 visit to determine if the subject was receiving burosumab therapy under commercial use or another mechanism and to collect information on any ongoing or new AEs, serious TEAEs, and concomitant medications for subjects not receiving burosumab. The additional safety visit (10 weeks ± 5 days after Week 160) applied to subjects who discontinued treatment early or chose not to continue burosumab therapy as commercial product or through another mechanism once the study ended. These additional clinic visits and telephone calls were included in the Extension Period to monitor long-term safety, compliance, and efficacy at an interval deemed appropriate for the age of the population and duration of treatment. b. As previously communicated by memorandum (20 October 2016), updates were made to remove TmP/GFR and TRP (tubular reabsorption of phosphate) as estimates of renal phosphate reabsorption due to the breadth of available data and burden of obtaining urine samples in this study population (under 5 years of age). c. As previously communicated by memorandum (20 October 2016), the Week 22 serum calcium assessment was removed from the Schedule of Events. d. As previously communicated by memorandum (05 April 2016), updates were made such that blood pressure was to be obtained for subjects aged 3 years or above (at study entry or beginning when the subject turned 3 years of age). The provision for training on blood pressure measurements at the site initiation visit was removed.

12 June 2017	(continued) e. As previously communicated by memorandum (13 December 2016), updates were made to indicate that the scope of the genitourinary exam should have been noninvasive and as per age-appropriate standard of care, at the investigator's discretion based on clinical judgement. f. ECG was changed from an ectopic mineralization assessment to a general safety assessment. ECG was performed to evaluate for changes associated with left ventricular hypertrophy. Ectopic mineralization was not expected to affect ECG parameters and ECG was inadvertently listed in that section in the original protocol. g. Updates were made such that concomitant medications and therapies were reviewed between site visits by telephone call from the study site every 2 weeks and recorded in the subject's CRF. Inclusion of telephone calls provided a mechanism to track use of concomitant medications and therapies at a consistent frequency during the Extension Period. 7. Statistical Analysis and Data Monitoring Committee: The statistical models for efficacy analysis were updated to incorporate Baseline adjustment and repeated measures at multiple time points. A newly added section described the timing of planned analyses for the study and more precisely defined the end of the study. Updates were made to stipulate that the Data Monitoring Committee was to review safety data through the Treatment Period (Week 64); long-term safety during the Extension Period was to be reviewed by the Ultragenyx SSRT on an ongoing basis. 8. Investigators and Study Administrative Structure: As previously communicated by memorandum (30 September 2016), updates were made to include language describing the Coordinating Investigator for the study. The Coordinating Investigator is Erik Imel, MD, Indiana University School of Medicine.
12 June 2017	(continued) 9. Reporting and Follow-up of Adverse Events: Language was revised to reflect the revised study design and safety follow-up procedures. The reporting periods of AEs were defined as those from the time the subjects signs informed consent through "the final protocol-defined safety follow-up telephone call or safety visit". Previously, these were defined as those through "12 weeks (approximately 5 times the elimination half-life) following the last dose of study drug." 10. Nomenclature: Clarification was made in the Schedules of Events to change the explanation of anti-burosumab antibodies from human anti-human antibodies (HAHA) to the more correct and specific term, anti-drug antibodies (ADA).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported