EU Clinical Trials Register

Clinical trial results:

A Randomized, open Label, Dose Finding, Phase 2 Study to Assess the Pharmacodynamics and Safety of the anti-FGF23 antibody, KRN23, in Pediatric Patients with X-linked Hypophosphatemia (XLH)

Summary

EudraCT number	2014-000406-35
Trial protocol	GB NL FR
Global end of trial date	30 October 2018

Results information

Result version number	v1 (current)
This version publication date	15 May 2019
First version publication date	15 May 2019

Trial information

Trial identification

Sponsor protocol code	UX023-CL201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02163577
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-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	30 October 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of the study are to:
- Identify a dose and dosing regimen of burosumab (KRN23), based on safety and PD effect, in pediatric XLH patients
- Establish the safety profile of burosumab for the treatment of children with XLH including ectopic mineralization risk, cardiovascular effects, and immunogenicity profile
- Characterize the PK/PD of the burosumab doses tested in the monthly (Q4) and biweekly (Q2) dose regimens in pediatric XLH patients
- Determine the PD effects of burosumab treatment on markers of bone health in pediatric XLH patients
- Obtain a preliminary assessment of the clinical effects of burosumab on bone health and deformity, muscle strength, and motor function
- Obtain a preliminary assessment of the effects of burosumab on patient-reported outcomes, including pain, disability, and quality of life in pediatric XLH patients
- Evaluate the long-term safety and efficacy of burosumab

Protection of trial subjects:

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

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	02 July 2014
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	Netherlands: 4
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	United States: 36
Worldwide total number of subjects	52
EEA total number of subjects	16

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	50
Adolescents (12-17 years)	2
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:

Potential subjects provided informed consent at an Screening Visit 1 at the study site. Screening Visit 2 was conducted 14 to 35 days following Screening Visit 1, and the remaining screening assessments to confirm eligibility were performed. Screening Visit 2 and Baseline visits were conducted no more than 7 days apart.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Burosumab Q2W

Arm description:

Burosumab subcutaneous (SC) injections every 2 weeks (Q2W). Dose was determined by the subject's weight and prescribed dose by their study doctor.

Arm type	Experimental
Investigational medicinal product name	burosumab
Investigational medicinal product code	
Other name	KRN23, Crysvita®, ux023
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The amount of KRN23 administered was calculated based on the subject's weight.

Arm title	Burosumab Q4W Then Q2W

Arm description:

Burosumab SC injections every 4 weeks (Q4W). Dose was determined by the subject's weight and prescribed dose by their study doctor. Subjects in Q4W were to switch to Q2W beginning with Week 64 dosing.

Arm type	Experimental
Investigational medicinal product name	burosumab
Investigational medicinal product code	
Other name	KRN23, Crysvita®, ux023
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The amount of KRN23 administered was calculated based on the subject's weight.

Number of subjects in period 1	Burosumab Q2W	Burosumab Q4W Then Q2W
Started	26	26
Completed	26	26

Baseline characteristics

Reporting groups

Reporting group title	Burosumab Q2W
Reporting group description:	
Burosumab subcutaneous (SC) injections every 2 weeks (Q2W). Dose was determined by the subject's weight and prescribed dose by their study doctor.	
Reporting group title	Burosumab Q4W Then Q2W
Reporting group description:	
Burosumab SC injections every 4 weeks (Q4W). Dose was determined by the subject's weight and prescribed dose by their study doctor. Subjects in Q4W were to switch to Q2W beginning with Week 64 dosing.	

Reporting group values	Burosumab Q2W	Burosumab Q4W Then Q2W	Total
Number of subjects	26	26	52
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	8.7	8.3	
standard deviation	± 1.72	± 2.04	-
Gender categorical			
Units: Subjects			
Female	14	14	28
Male	12	12	24
Race			
Units: Subjects			
Black or African American	2	0	2
White	23	23	46
Other, Not Specified	1	3	4
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	2	2
Not Hispanic or Latino	26	24	50
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: score on a scale			
arithmetic mean	1.92	1.67	
standard deviation	± 1.172	± 0.999	-
Serum Phosphorus			
Units: mg/dL			
arithmetic mean	2.38	2.28	
standard deviation	± 0.405	± 0.299	-
Serum 1, 25- Dihydroxyvitamin D			

Units: pg/mL			
arithmetic mean	41.28	41.37	
standard deviation	± 21.967	± 15.293	-

Ratio of Renal Tubular Maximum Reabsorption Rate of Phosphate to Glomerular Filtration Rate(TmP/GFR)			

Data for urinary phosphorus and tubular reabsorption of phosphate (TRP) were used in the calculation of TmP/GFR.

Analysis Population Description: subjects with a Baseline measurement (n=25, 25)

Units: mg/dL			
arithmetic mean	2.176	1.978	
standard deviation	± 0.4925	± 0.3474	-

RSS Knee Scores			

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: score on a scale			
arithmetic mean	1.21	1.19	
standard deviation	± 0.681	± 0.601	-

RSS Wrist Scores			

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: score on a scale			
arithmetic mean	0.71	0.48	
standard deviation	± 0.619	± 0.519	-

Growth Velocity			

Baseline growth velocity was calculated based on the standing height measured within 2 years prior to Baseline.

Analysis Population Description: Data presented for subjects with evaluable growth velocity data at Baseline. Growth velocity could not be calculated for 3 subjects for whom pretreatment height data were not available within 2 years prior to Baseline (n=25, 24).

Units: cm/year			
arithmetic mean	5.45	5.24	
standard deviation	± 1.171	± 1.402	-

Standing Height Z Score			

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	-1.72	-2.05	
standard deviation	± 1.026	± 0.957	-

Growth (Standing Height)			
Units: cm			
arithmetic mean	123.28	119.42	
standard deviation	± 10.326	± 12.623	-

Growth (Sitting Height)			
Units: cm			

arithmetic mean	70.10	67.04	
standard deviation	± 5.632	± 5.691	-

Growth (Arm Length)

Units: cm

arithmetic mean	54.80	52.59	
standard deviation	± 4.930	± 6.129	-

Growth (Leg Length)

Units: cm

arithmetic mean	66.06	63.71	
standard deviation	± 7.027	± 8.322	-

6-Minute Walk Test (6MWT) Distance (Predicted Percent of Normal)

The total distance walked (meters) in a 6-minute period was measured. The percent of predicted values were calculated using published normative data based on age, gender, and height (Geiger et al. 2007).

Units: percentage of predicted distance

arithmetic mean	79.32	81.42	
standard deviation	± 13.257	± 15.101	-

POSNA-PODCI Normative Scores: Upper Extremity Scale

The Pediatric Orthopedic Society of North America Pediatric Outcomes Data Collection Instrument (POSNA-PODCI) yields 4 functional assessment scores: Upper Extremity Function, Transfers and Basic Mobility, Sports/Physical Function, and Comfort/Pain. Also a Global Function score, an average of the 4 functional assessments, and a Happiness score are calculated. Normative scores are calculated so that higher scores indicate better functioning. All scores are referenced to the general, healthy population with a normative mean score of 50 and a standard deviation of 10. (n=26, 25)

Units: score on a scale

arithmetic mean	52.1	48.5	
standard deviation	± 6.77	± 13.04	-

POSNA-PODCI: Transfer and Basic Mobility Scale

The POSNA-PODCI yields 4 functional assessment scores: Upper Extremity Function, Transfers and Basic Mobility, Sports/Physical Function, and Comfort/Pain. Also a Global Function score, an average of the 4 functional assessments, and a Happiness score are calculated. Normative scores are calculated so that higher scores indicate better functioning. All scores are referenced to the general, healthy population with a normative mean score of 50 and a standard deviation of 10. (n=26, 25)

Units: score on a scale

arithmetic mean	45.7	46.0	
standard deviation	± 10.88	± 10.53	-

POSNA-PODCI: Sports/Physical Functioning Scale

The POSNA-PODCI yields 4 functional assessment scores: Upper Extremity Function, Transfers and Basic Mobility, Sports/Physical Function, and Comfort/Pain. Also a Global Function score, an average of the 4 functional assessments, and a Happiness score are calculated. Normative scores are calculated so that higher scores indicate better functioning. All scores are referenced to the general, healthy population with a normative mean score of 50 and a standard deviation of 10. (n=26, 25)

Units: score on a scale

arithmetic mean	34.6	32.2	
standard deviation	± 15.70	± 19.29	-

POSNA-PODCI: Pain/Comfort Scale

The POSNA-PODCI yields 4 functional assessment scores: Upper Extremity Function, Transfers and Basic Mobility, Sports/Physical Function, and Comfort/Pain. Also a Global Function score, an average of the 4 functional assessments, and a Happiness score are calculated. Normative scores are calculated so that higher scores indicate better functioning. All scores are referenced to the general, healthy population with a normative mean score of 50 and a standard deviation of 10. (n=26, 25)

Units: score on a scale

arithmetic mean	35.2	34.8	
standard deviation	± 15.26	± 16.76	-

POSNA-PODCI: Happiness Scale

The POSNA-PODCI yields 4 functional assessment scores: Upper Extremity Function, Transfers and Basic Mobility, Sports/Physical Function, and Comfort/Pain. Also a Global Function score, an average of the 4 functional assessments, and a Happiness score are calculated. Normative scores are calculated so that higher scores indicate better functioning. All scores are referenced to the general, healthy population with a normative mean score of 50 and a standard deviation of 10. (n=26, 25)			
Units: score on a scale			
arithmetic mean	43.6	43.4	
standard deviation	± 13.75	± 13.69	-
POSNA-PODCI: Global Functioning Scale			
The POSNA-PODCI yields 4 functional assessment scores: Upper Extremity Function, Transfers and Basic Mobility, Sports/Physical Function, and Comfort/Pain. Also a Global Function score, an average of the 4 functional assessments, and a Happiness score are calculated. Normative scores are calculated so that higher scores indicate better functioning. All scores are referenced to the general, healthy population with a normative mean score of 50 and a standard deviation of 10. (n=26, 25)			
Units: score on a scale			
arithmetic mean	37.5	35.6	
standard deviation	± 13.96	± 17.24	-
Fractional Excretion of Phosphorus (FEP)			
FEP is defined as 100% × (urine phosphorus × serum creatinine)/(urine creatinine × serum phosphorus), where the 2-hour urine sample was used for urine phosphorus and urine creatinine. Analysis Population Description: subjects with a Baseline assessment (n=25,26).			
Units: percentage of phosphorus excreted			
arithmetic mean	13.91	15.42	
standard deviation	± 6.775	± 7.373	-
Procollagen Type 1 N Propeptide (P1NP)			
Analysis Population Description: subjects with a Baseline assessment (n=24, 26)			
Units: ng/mL			
arithmetic mean	843.11	742.35	
standard deviation	± 214.367	± 209.727	-
Carboxy-Terminal Crosslinked Telopeptide of Type I Collagen (CTx) Units: ng/mL			
arithmetic mean	2.23	2.10	
standard deviation	± 0.642	± 0.679	-
Alkaline Phosphatase (ALP) Units: U/L			
arithmetic mean	461.92	456.08	
standard deviation	± 110.209	± 101.157	-
Bone Specific Alkaline Phosphatase (BALP)			
Analysis Population Description: subjects with a baseline assessment (n=20, 20).			
Units: mcg/L			
arithmetic mean	163.54	165.62	
standard deviation	± 58.610	± 45.534	-
Burosumab Concentration			
For the lower limit of quantitation (< 50), the value 25 was used.			
Units: ng/mL			
arithmetic mean	25.00	25.00	
standard deviation	± 0.000	± 0.000	-

End points

End points reporting groups

Reporting group title	Burosumab Q2W

Reporting group description:

Burosumab subcutaneous (SC) injections every 2 weeks (Q2W). Dose was determined by the subject's weight and prescribed dose by their study doctor.

Reporting group title	Burosumab Q4W Then Q2W

Reporting group description:

Burosumab SC injections every 4 weeks (Q4W). Dose was determined by the subject's weight and prescribed dose by their study doctor. Subjects in Q4W were to switch to Q2W beginning with Week 64 dosing.

Subject analysis set title	Intent to Treat Analysis Set: Burosumab Q2W
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Burosumab SC injections Q2W. Dose was determined by the subject's weight and prescribed dose by their study doctor.

Intent to Treat Analysis Set: All subjects who received at least 1 dose of study therapy and had at least 1 post-dose measurement at given time point.

Subject analysis set title	Intent to Treat Analysis Set: Burosumab Q4W Then Q2W
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Burosumab SC injections Q4W. Dose was determined by the subject's weight and prescribed dose by their study doctor. Subjects in Q4W were to switch to Q2W beginning with Week 64 dosing.

Intent to Treat Analysis Set: All subjects who received at least 1 dose of study therapy and had at least 1 post-dose measurement at given time point.

Subject analysis set title	PK/PD Analysis Set: Burosumab Q2W
Subject analysis set type	Full analysis

Subject analysis set description:

Burosumab SC injections Q2W. Dose was determined by the subject's weight and prescribed dose by their study doctor.

Pharmacokinetic/Pharamcodynamic (PK/PD) Analysis Set: all subjects who received at least 1 dose of therapy and had evaluable serum data at given time point.

Subject analysis set title	PK/PD Analysis Set: Burosumab Q4W Then Q2W
Subject analysis set type	Full analysis

Subject analysis set description:

Burosumab SC injections Q4W. Dose was determined by the subject's weight and prescribed dose by their study doctor. Subjects in Q4W were to switch to Q2W beginning with Week 64 dosing.

Pharmacokinetic/Pharamcodynamic (PK/PD) Analysis Set: all subjects who received at least 1 dose of therapy and had evaluable serum data at given time point.

Subject analysis set title	Safety Analysis Set: Burosumab Q2W
Subject analysis set type	Safety analysis

Subject analysis set description:

Burosumab SC injections Q2W. Dose was determined by the subject's weight and prescribed dose by their study doctor.

Safety Analysis Set: All subjects who received at least 1 dose of study therapy.

Subject analysis set title	Safety Analysis Set: Burosumab Q4W Then Q2W
Subject analysis set type	Safety analysis

Subject analysis set description:

Burosumab SC injections Q4W. Dose was determined by the subject's weight and prescribed dose by their study doctor. Subjects in Q4W were to switch to Q2W beginning with Week 64 dosing.

Safety Analysis Set: All subjects who received at least 1 dose of study therapy and had an assessment at given time point.

Primary: Change From Baseline in RSS Total Score Over Time

End point title	Change From Baseline in RSS Total Score Over Time[1]

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.

End point type	Primary

End point timeframe:

Baseline, Week 40, 64, 160

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 attached as a separate document (see zip file below) since they couldn't be entered due to formatting restrictions in EudraCT.

End point values	Intent to Treat Analysis Set: Burosumab Q2W	Intent to Treat Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[2]	26[3]		
Units: score on a scale				
least squares mean (standard error)				
Change to Week 40; n=26, 26	-1.06 (± 0.100)	-0.73 (± 0.100)		
Change to Week 64; n=26, 26	-1.00 (± 0.110)	-0.84 (± 0.098)		
Change to Week 160; n=19, 22	-0.98 (± 0.129)	-0.83 (± 0.122)		

Notes:

[2] - n=subjects who had at least 1 post-dose measurement at given time point.

[3] - n=subjects who had at least 1 post-dose measurement at given time point.

Attachments (see zip file)	RSS Total Score Statistical Analysis.docx

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Serum Phosphorus Over Time

End point title	Change From Baseline in Serum Phosphorus Over Time[4]

End point description:

End point type	Primary

End point timeframe:

Baseline, Week 40, 64, 160

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: Statistical analyses are attached as a separate document (see zip file below) since they couldn't be entered due to formatting restrictions in EudraCT.

End point values	PK/PD Analysis Set: Burosumab Q2W	PK/PD Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[5]	26[6]		
Units: mg/dL				
arithmetic mean (standard deviation)				
Change at Week 40; n=26, 26	0.92 (± 0.480)	0.57 (± 0.265)		
Change at Week 64; n=24, 23	0.99 (± 0.502)	0.69 (± 0.370)		
Change at Week 160; n=26, 26	0.97 (± 0.338)	1.08 (± 0.377)		

Notes:

[5] - n=subjects who had evaluable serum data at given time point.

[6] - n=subjects who had evaluable serum data at given time point.

Attachments (see zip file)	Serum Phosphorus Statistical Analysis.docx

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Serum 1,25(OH)2D Over Time

End point title	Change From Baseline in Serum 1,25(OH)2D Over Time[7]

End point description:

End point type	Primary

End point timeframe:

Baseline, Week 40, 64, 160

Notes:

[7] - 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 attached as a separate document (see zip file below) since they couldn't be entered due to formatting restrictions in EudraCT.

End point values	PK/PD Analysis Set: Burosumab Q2W	PK/PD Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[8]	26[9]		
Units: pg/mL				
arithmetic mean (standard deviation)				
Change at Week 40; n=26, 26	28.27 (± 29.312)	17.62 (± 18.802)		
Change at Week 64; n=26, 24	23.58 (± 24.502)	11.50 (± 16.522)		
Change at Week 160; n=26, 26	17.03 (± 24.889)	19.64 (± 22.857)		

Notes:

[8] - n=subjects who had evaluable serum data at given time point.

[9] - n=subjects who had evaluable serum data at given time point.

Attachments (see zip file)	Serum 1,25(OH)2D Statistical Analysis.docx

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in TmP/GFR Over Time

End point title	Change From Baseline in TmP/GFR Over Time[10]

End point description:

Data for urinary phosphorus and TRP were used in calculation TmP/GFR.

End point type	Primary

End point timeframe:

Baseline, Week 40, 64, 160

Notes:

[10] - 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 attached as a separate document (see zip file below) since they couldn't be entered due to formatting restrictions in EudraCT.

End point values	PK/PD Analysis Set: Burosumab Q2W	PK/PD Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[11]	26[12]		
Units: mg/dL				
arithmetic mean (standard deviation)				
Change at Week 40; n=24, 23	1.14 (± 0.686)	0.80 (± 0.506)		
Change at Week 64; n=20, 19	1.11 (± 0.626)	0.90 (± 0.632)		
Change at Week 160; n=23, 24	1.24 (± 0.548)	1.45 (± 0.653)		

Notes:

[11] - n=subjects who had evaluable serum data at given time point.

[12] - n=subjects had evaluable serum data at given time point.

Attachments (see zip file)	TmP_GFR Statistical Analysis.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in RSS Knee Scores Over Time

End point title	Change From Baseline in RSS Knee Scores Over Time

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.

End point type	Secondary

End point timeframe:
Baseline, Week 40, 64, 160

End point values	Intent to Treat Analysis Set: Burosumab Q2W	Intent to Treat Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[13]	26[14]		
Units: score on a scale				
least squares mean (standard error)				
Change at Week 40; n=26, 26	-0.62 (± 0.08)	-0.55 (± 0.08)		
Change at Week 64; n=26, 26	-0.70 (± 0.087)	-0.61 (± 0.072)		
Change at Week 160; n=19, 22	-0.70 (± 0.105)	-0.62 (± 0.093)		

Notes:

[13] - n=subjects who had at least 1 post-dose measurement at given time point.

[14] - n=subjects who had at least 1 post-dose measurement at given time point.

Attachments (see zip file)	RSS Knee Score Statistical Analysis.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in RSS Wrist Scores Over Time

End point title	Change From Baseline in RSS Wrist Scores Over Time

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.

End point type	Secondary

End point timeframe:
Baseline, Week 40, 64, 160

End point values	Intent to Treat Analysis Set: Burosumab Q2W	Intent to Treat Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[15]	26[16]		
Units: score on a scale				
least squares mean (standard error)				
Change at Week 40; n=26, 26	-0.44 (± 0.05)	-0.18 (± 0.05)		
Change at Week 64; n=26, 26	-0.30 (± 0.057)	-0.24 (± 0.051)		
Change at Week 160; n=19, 21	-0.27 (± 0.065)	-0.20 (± 0.047)		

Notes:

[15] - n=subjects who had at least 1 post-dose measurement at given time point.

[16] - n=subjects who had at least 1 post-dose measurement at given time point.

Attachments (see zip file)	RSS Wrist Score Statistical Analysis.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Radiographic Global Impression of Change (RGI-C) Global Scores Over Time

End point title	Radiographic Global Impression of Change (RGI-C) Global Scores Over Time

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).

End point type	Secondary

End point timeframe:

Baseline, Week 40, 64, 160

End point values	Intent to Treat Analysis Set: Burosumab Q2W	Intent to Treat Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	26		
Units: score on a scale				
least squares mean (standard error)				
Change at Week 40	1.67 (± 0.12)	1.46 (± 0.12)		
Change at Week 64	1.56 (± 0.112)	1.58 (± 0.112)		
Change at Week 160	1.92 (± 0.111)	1.86 (± 0.119)		

Attachments (see zip file)	RGIC Global Score Statistical Analysis.docx

Statistical analyses

No statistical analyses for this end point

Secondary: RGI-C Knee Scores Over Time

End point title	RGI-C Knee Scores Over Time

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).

End point type	Secondary

End point timeframe:

Baseline, Week 40, 64, 160

End point values	Intent to Treat Analysis Set: Burosumab Q2W	Intent to Treat Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	26		
Units: scores on a scale				
least squares mean (standard error)				
Change at Week 40	1.60 (± 0.13)	1.34 (± 0.13)		
Change at Week 64	1.57 (± 0.104)	1.53 (± 0.099)		
Change at Week 160	2.01 (± 0.106)	1.85 (± 0.118)		

Attachments (see zip file)	RGIC Knee Score Statistical Analysis.docx

Statistical analyses

No statistical analyses for this end point

Secondary: RGI-C Wrist Scores Over Time

End point title	RGI-C Wrist Scores Over Time

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).

End point type	Secondary

End point timeframe:

Baseline, Week 40, 64, 160

End point values	Intent to Treat Analysis Set: Burosumab Q2W	Intent to Treat Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[17]	26		
Units: scores on a scale				
least squares mean (standard error)				
Change at Week 40; n=26, 26	1.64 (± 0.14)	1.45 (± 0.14)		
Change at Week 64; n=26, 26	1.65 (± 0.153)	1.55 (± 0.124)		
Change at Week 160; n=26, 25	1.78 (± 0.133)	1.83 (± 0.132)		

Notes:

[17] - n=subjects who had at least 1 post-dose measurement at given time point.

Attachments (see zip file)	RGIC Wrist Score Statistical Analysis.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Growth Velocity Over Time

End point title	Change From Baseline in Growth Velocity Over Time

End point description:

End point type	Secondary

End point timeframe:

Baseline, Week 40, 64, 160

End point values	Intent to Treat Analysis Set: Burosumab Q2W	Intent to Treat Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	24		
Units: cm/year				

arithmetic mean (standard deviation)				
Week 0 to Week 40: Change from Baseline	0.96 (± 1.677)	0.39 (± 2.559)		
Week 0 to Week 64: Change from Baseline	0.73 (± 1.399)	0.37 (± 2.164)		
Week 64 to Week 112: Change from Baseline	0.29 (± 2.284)	0.09 (± 2.523)		
Week 112 to Week 160: Change from Baseline	0.67 (± 2.318)	0.54 (± 3.158)		

Attachments (see zip file)	Growth Velocity Statistical Analysis.docx

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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.

End point type	Secondary

End point timeframe:

Baseline, Week 40, 64, 160

End point values	Intent to Treat Analysis Set: Burosumab Q2W	Intent to Treat Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[18]	26[19]		
Units: Z Score				
least squares mean (standard error)				
Change to Week 40; n=24, 23	0.17 (± 0.042)	0.10 (± 0.051)		
Change to Week 64; n=26, 26	0.19 (± 0.051)	0.12 (± 0.061)		
Change to Week 160; n=26, 26	0.35 (± 0.084)	0.19 (± 0.089)		

Notes:

[18] - n=subjects who had at least 1 post-dose measurement at given time point.

[19] - n=subjects who had at least 1 post-dose measurement at given time point.

Attachments (see zip file)	Standing Height Z Score Statistical Analysis.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Growth (Standing Height) Over Time

End point title	Change From Baseline in Growth (Standing Height) Over Time
End point description:	
End point type	Secondary
End point timeframe:	
Baseline, Week 40, 64, 160	

End point values	Intent to Treat Analysis Set: Burosumab Q2W	Intent to Treat Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[20]	26[21]		
Units: cm				
arithmetic mean (standard deviation)				
Change at Week 40; n=24, 23	5.03 (± 1.232)	4.49 (± 1.455)		
Change at Week 64; n=26, 26	7.48 (± 1.934)	6.98 (± 1.594)		
Change at Week 160; n=26, 26	18.38 (± 2.958)	17.22 (± 2.653)		

Notes:

[20] - n=subjects who had at least 1 post-dose measurement at given time point.

[21] - n=subjects who had at least 1 post-dose measurement at given time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Growth (Sitting Height) Over Time

End point title	Change From Baseline in Growth (Sitting Height) Over Time
End point description:	
End point type	Secondary
End point timeframe:	
Baseline, Week 40, 64, 160	

End point values	Intent to Treat Analysis Set: Burosumab Q2W	Intent to Treat Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[22]	26[23]		
Units: cm				
arithmetic mean (standard deviation)				
Change at Week 40; n=23, 23	2.66 (± 5.496)	2.39 (± 1.486)		
Change at Week 64; n=26, 26	3.08 (± 2.405)	3.45 (± 1.390)		

Change at Week 160; n=26, 26	8.29 (± 2.928)	8.62 (± 2.163)

Notes:

[22] - n=subjects who had at least 1 post-dose measurement at given time point.

[23] - n=subjects who had at least 1 post-dose measurement at given time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Growth (Arm Length) Over Time

End point title	Change From Baseline in Growth (Arm Length) Over Time
End point description:	

End point type	Secondary
End point timeframe:	
Baseline, Week 40, 64, 160	

End point values	Intent to Treat Analysis Set: Burosumab Q2W	Intent to Treat Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[24]	26[25]		
Units: cm				
arithmetic mean (standard deviation)				
Change at Week 40; n=24, 23	2.36 (± 1.058)	2.08 (± 0.905)		
Change at Week 64; n=26, 26	3.99 (± 1.556)	4.77 (± 7.382)		
Change at Week 160; n=26, 26	8.50 (± 1.537)	8.32 (± 1.798)		

Notes:

[24] - n=subjects who had at least 1 post-dose measurement at given time point.

[25] - n=subjects who had at least 1 post-dose measurement at given time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Growth (Leg Length) Over Time

End point title	Change From Baseline in Growth (Leg Length) Over Time
End point description:	

End point type	Secondary
End point timeframe:	
Baseline, Week 40, 64, 160	

End point values	Intent to Treat Analysis Set: Burosumab Q2W	Intent to Treat Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[26]	26[27]		
Units: cm				
arithmetic mean (standard deviation)				
Change to Week 40; n=24, 23	2.90 (± 1.365)	2.82 (± 1.270)		
Change at Week 64; n=26, 26	5.03 (± 1.879)	5.16 (± 1.283)		
Change at Week 160; n=26, 26	11.78 (± 3.040)	11.67 (± 2.338)		

Notes:

[26] - n=subjects who had at least 1 post-dose measurement at given time point.

[27] - n=subjects who had at least 1 post-dose measurement at given time point.

Statistical analyses

No statistical analyses for this end point

Secondary: 6MWT Distance (Predicted Percent of Normal) Change from Baseline Over Time

End point title	6MWT Distance (Predicted Percent of Normal) Change from Baseline Over Time
End point description:	

The total distance walked (meters) in a 6-minute period was measured. The percent of predicted values were calculated using published normative data based on age, gender, and height (Geiger et al. 2007).

End point type	Secondary
End point timeframe:	

Baseline, Week 40, 64, 160

End point values	Intent to Treat Analysis Set: Burosumab Q2W	Intent to Treat Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	26		
Units: percentage of predicted distance				
least squares mean (standard error)				
Change at Week 40	3.25 (± 1.841)	0.24 (± 2.153)		
Change at Week 64	5.29 (± 1.568)	3.70 (± 1.731)		
Change at Week 160	1.96 (± 1.483)	2.15 (± 1.932)		

Attachments (see zip file)	6MWT Statistical Analysis.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in POSNA-PODCI (Normative Score) Upper Extremity Scale Scores Over Time

End point title	Change From Baseline in POSNA-PODCI (Normative Score) Upper Extremity Scale Scores Over Time

End point description:

The POSNA-PODCI yields 4 functional assessment scores: Upper Extremity Function,Transfers and Basic Mobility, Sports and Physical Function, and Comfort/Pain. In addition, a Global Function score, which is an average of the 4 functional assessments, and a Happiness score are calculated. Raw, mean, standardized, and normative scores are calculated for each scale. Normative scores are calculated so that higher scores indicate better functioning. All scores are referenced to the general, healthy population with a normative mean score of 50 and a standard deviation of 10.

End point type	Secondary

End point timeframe:

Baseline, Week 40, 64, 160

End point values	Intent to Treat Analysis Set: Burosumab Q2W	Intent to Treat Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[28]	25[29]		
Units: score on a scale				
least squares mean (standard error)				
Change at Week 40; n=25, 24	2.97 (± 0.710)	2.97 (± 1.212)		
Change at Week 64; n=26, 25	1.89 (± 0.914)	3.20 (± 0.829)		
Change at Week 160; n=26, 25	-0.02 (± 0.740)	1.82 (± 1.449)		

Notes:

[28] - n=subjects who had at least 1 post-dose measurement at given time point.

[29] - n=subjects who had at least 1 post-dose measurement at given time point.

Attachments (see zip file)	POSNA-PODCI Upper Extremity Scale Scores Statistical

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in POSNA-PODCI (Normative Score) Transfer and Basic Mobility Scale Scores Over Time

End point title	Change From Baseline in POSNA-PODCI (Normative Score) Transfer and Basic Mobility Scale Scores Over Time

End point description:

The POSNA-PODCI yields 4 functional assessment scores: Upper Extremity Function,Transfers and Basic Mobility, Sports and Physical Function, and Comfort/Pain. In addition, a Global Function score, which is an average of the 4 functional assessments, and a Happiness score are calculated. Raw, mean, standardized, and normative scores are calculated for each scale. Normative scores are calculated so that higher scores indicate better functioning. All scores are referenced to the general, healthy population with a normative mean score of 50 and a standard deviation of 10.

End point type	Secondary

End point timeframe:

Baseline, Week 40, 64, 160

End point values	Intent to Treat Analysis Set: Burosumab Q2W	Intent to Treat Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[30]	25[31]		
Units: score on a scale				
least squares mean (standard error)				
Change at Week 40; n=25, 24	4.04 (± 0.827)	3.69 (± 1.648)		
Change at Week 64; n=26, 25	-0.34 (± 3.123)	4.32 (± 1.364)		
Change at Week 160; n=26, 25	1.88 (± 3.285)	5.44 (± 1.113)		

Notes:

[30] - n=subjects who had at least 1 post-dose measurement at given time point.

[31] - n=subjects who had at least 1 post-dose measurement at given time point.

Attachments (see zip file)	POSNA-PODCI Transfer and Basic Mobility Scale Scores

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in POSNA-PODCI (Normative Score) Sports/Physical Functioning Scale Scores Over Time

End point title	Change From Baseline in POSNA-PODCI (Normative Score) Sports/Physical Functioning Scale Scores Over Time

End point description:

The POSNA-PODCI yields 4 functional assessment scores: Upper Extremity Function,Transfers and Basic Mobility, Sports and Physical Function, and Comfort/Pain. In addition, a Global Function score, which is an average of the 4 functional assessments, and a Happiness score are calculated. Raw, mean, standardized, and normative scores are calculated for each scale. Normative scores are calculated so that higher scores indicate better functioning. All scores are referenced to the general, healthy population with a normative mean score of 50 and a standard deviation of 10.

End point type	Secondary

End point timeframe:

Baseline, Week 40, 64, 160

End point values	Intent to Treat Analysis Set: Burosumab Q2W	Intent to Treat Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[32]	25[33]		
Units: score on a scale				
least squares mean (standard error)				

Change at Week 40; n=25, 24	9.78 (± 1.679)	9.15 (± 2.249)		
Change at Week 64; n=26, 25	7.74 (± 2.636)	9.84 (± 2.534)		
Change at Week 160; n=26, 25	12.04 (± 2.102)	14.33 (± 1.834)		

Notes:

[32] - n=subjects who had at least 1 post-dose measurement at given time point.

[33] - n=subjects who had at least 1 post-dose measurement at given time point.

Attachments (see zip file)	POSNA-PODCI Sports_Physical Functioning Scale Scores

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in POSNA-PODCI (Normative Score) Pain/Comfort Scale Scores Over Time

End point title	Change From Baseline in POSNA-PODCI (Normative Score) Pain/Comfort Scale Scores Over Time

End point description:

The POSNA-PODCI yields 4 functional assessment scores: Upper Extremity Function,Transfers and Basic Mobility, Sports and Physical Function, and Comfort/Pain. In addition, a Global Function score, which is an average of the 4 functional assessments, and a Happiness score are calculated. Raw, mean, standardized, and normative scores are calculated for each scale. Normative scores are calculated so that higher scores indicate better functioning. All scores are referenced to the general, healthy population with a normative mean score of 50 and a standard deviation of 10.

End point type	Secondary

End point timeframe:

Baseline, Week 40, 64, 160

End point values	Intent to Treat Analysis Set: Burosumab Q2W	Intent to Treat Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[34]	25[35]		
Units: score on a scale				
least squares mean (standard error)				
Change at Week 40; n=25, 24	7.67 (± 2.399)	7.39 (± 2.477)		
Change at Week 64; n=26, 25	5.60 (± 2.904)	7.74 (± 2.077)		
Change at Week 160; n=26, 25	13.06 (± 2.187)	12.38 (± 2.265)		

Notes:

[34] - n=subjects who had at least 1 post-dose measurement at given time point.

[35] - n=subjects who had at least 1 post-dose measurement at given time point.

Attachments (see zip file)	POSNA-PODCI Pain_Comfort Scale Scores Statistical Analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in POSNA-PODCI (Normative Score) Happiness Scale Scores Over Time

End point title	Change From Baseline in POSNA-PODCI (Normative Score) Happiness Scale Scores Over Time

End point description:

The POSNA-PODCI yields 4 functional assessment scores: Upper Extremity Function,Transfers and Basic Mobility, Sports and Physical Function, and Comfort/Pain. In addition, a Global Function score, which is an average of the 4 functional assessments, and a Happiness score are calculated. Raw, mean, standardized, and normative scores are calculated for each scale. Normative scores are calculated so that higher scores indicate better functioning. All scores are referenced to the general, healthy population with a normative mean score of 50 and a standard deviation of 10.

End point type	Secondary

End point timeframe:

Baseline, Week 40, 64, 160

End point values	Intent to Treat Analysis Set: Burosumab Q2W	Intent to Treat Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[36]	25[37]		
Units: score on a scale				
least squares mean (standard error)				
Change at Week 40; n=25, 24	2.84 (± 2.328)	3.01 (± 1.902)		
Change at Week 64; n=26, 25	2.18 (± 1.914)	3.34 (± 1.914)		
Change at Week 160; n=26, 25	6.46 (± 2.486)	9.19 (± 1.075)		

Notes:

[36] - n=subjects who had at least 1 post-dose measurement at given time point.

[37] - n=subjects who had at least 1 post-dose measurement at given time point.

Attachments (see zip file)	POSNA-PODCI Happiness Scale Scores Statistical Analysis.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in POSNA-PODCI (Normative Score) Global Functioning Scale Scores Over Time

End point title	Change From Baseline in POSNA-PODCI (Normative Score) Global Functioning Scale Scores Over Time

End point description:

The POSNA-PODCI yields 4 functional assessment scores: Upper Extremity Function,Transfers and Basic Mobility, Sports and Physical Function, and Comfort/Pain. In addition, a Global Function score, which is an average of the 4 functional assessments, and a Happiness score are calculated. Raw, mean, standardized, and normative scores are calculated for each scale. Normative scores are calculated so that higher scores indicate better functioning. All scores are referenced to the general, healthy population with a normative mean score of 50 and a standard deviation of 10.

End point type	Secondary

End point timeframe:

Baseline, Week 40, 64, 160

End point values	Intent to Treat Analysis Set: Burosumab Q2W	Intent to Treat Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	26		
Units: score on a scale				
least squares mean (standard error)				
Change at Week 40; n=25, 24	9.06 (± 1.560)	8.12 (± 2.351)		
Change at Week 64; n=26, 25	6.02 (± 2.706)	8.72 (± 2.019)		
Change at Week 160; n=25, 25	11.37 (± 1.804)	11.94 (± 2.024)		

Attachments (see zip file)	POSNA-PODCI Global Functioning Scale Scores Statistical

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in FEP Over Time

End point title	Change From Baseline in FEP Over Time
End point description:	

FEP is defined as 100% × (urine phosphorus × serum creatinine)/(urine creatinine × serum phosphorus), where the 2-hour urine sample was used for urine phosphorus and urine creatinine.

End point type	Secondary
End point timeframe:	

Baseline, Week 40, 64, 160

End point values	Safety Analysis Set: Burosumab Q2W	Safety Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25[38]	26[39]		
Units: percentage of phosphorus excreted				
arithmetic mean (standard deviation)				
Change at Week 40; n=25, 26	-3.97 (± 7.161)	-4.85 (± 7.170)		
Change at Week 64; n=20, 22	-2.63 (± 4.446)	-3.96 (± 7.522)		
Change at Week 160; n=23, 26	-5.43 (± 6.985)	-6.47 (± 8.072)		

Notes:

[38] - n=subjects who had an assessment at given time point.

[39] - n=subjects who had an assessment at given time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in P1NP Over Time

End point title	Change From Baseline in P1NP Over Time
End point description:	
End point type	Secondary
End point timeframe:	
Baseline, Week 40, 64	

End point values	PK/PD Analysis Set: Burosumab Q2W	PK/PD Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24[40]	26[41]		
Units: ng/mL				
arithmetic mean (standard deviation)				
Change at Week 40; n=24, 26	275.98 (± 329.587)	224.91 (± 161.053)		
Change at Week 64; n=22, 23	137.35 (± 354.315)	133.56 (± 192.306)		

Notes:

[40] - n=subjects who had evaluable serum data at given time point.

[41] - n=subjects who had evaluable serum data at given time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CTx Over Time

End point title	Change From Baseline in CTx Over Time
End point description:	
End point type	Secondary
End point timeframe:	
Baseline, Week 40, 64	

End point values	PK/PD Analysis Set: Burosumab Q2W	PK/PD Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[42]	26[43]		
Units: ng/mL				
arithmetic mean (standard deviation)				
Change at Week 40; n=26, 26	1.01 (± 0.802)	0.64 (± 0.578)		
Change at Week 64; n=25, 25	1.08 (± 0.870)	0.81 (± 0.706)		

Notes:

[42] - n=subjects who had evaluable serum data at given time point.

[43] - n=subjects who had evaluable serum data at given time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in ALP Over Time

End point title	Change From Baseline in ALP Over Time
End point description:	

End point type	Secondary
End point timeframe:	

Baseline, Week 40, 64, 160

End point values	PK/PD Analysis Set: Burosumab Q2W	PK/PD Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[44]	26[45]		
Units: U/L				
arithmetic mean (standard deviation)				
Change at Week 40; n=26, 26	-79.4 (± 97.40)	-47.8 (± 70.86)		
Change at Week 64: n=24, 23	-113.9 (± 81.28)	-80.9 (± 67.11)		
Change at Week 160; n=26, 26	-153.1 (± 132.45)	-140.0 (± 115.82)		

Notes:

[44] - n=subjects who had evaluable serum data at given time point.

[45] - n=subjects who had evaluable serum data at given time point.

Attachments (see zip file)	ALP Statistical Analysis.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in BALP Over Time

End point title	Change From Baseline in BALP Over Time
End point description:	
End point type	Secondary
End point timeframe:	
Baseline, Week 40, 64, 160	

End point values	PK/PD Analysis Set: Burosumab Q2W	PK/PD Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20[46]	20[47]		
Units: mcg/L				
arithmetic mean (standard deviation)				
Change at Week 40; n=20, 20	-35.55 (± 46.738)	-27.80 (± 31.409)		
Change at Week 64; n=19, 20	-50.40 (± 36.478)	-47.13 (± 28.822)		
Change at Week 160; n=20, 20	-67.25 (± 59.309)	-56.73 (± 52.284)		

Notes:

[46] - n=subjects who had evaluable serum data at given time point.

[47] - n=subjects who had evaluable serum data at given time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Pre-Dose Concentrations of Burosumab

End point title	Serum Pre-Dose Concentrations of Burosumab
End point description:	
End point type	Secondary
End point timeframe:	
Week 40, 64, 160	

End point values	PK/PD Analysis Set: Burosumab Q2W	PK/PD Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	26		
Units: ng/mL				
arithmetic mean (standard deviation)				

Week 40; n=26, 26	13188.81 (± 7188.588)	6443.08 (± 3266.215)		
Week 64; n= 26, 24	15846.65 (± 9385.393)	8525.63 (± 3968.821)		
Week 160; n=26, 26	13975.27 (± 8168.877)	13163.96 (± 6593.120)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs) and Discontinuations Due to Adverse Events (AEs)

End point title	Number of Subjects With Treatment Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs) and Discontinuations Due to Adverse Events (AEs)

End point description:

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An SAE is defined as an AE or suspected adverse reaction that at any dose results in any of the following outcomes: death; 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. Severity was graded as 1 (mild), 2 (moderate), 3 (severe), 4 (life-threatening), 5 (death). TEAEs are defined as AEs with onset on or after the time of initiation of study drug administration.

End point type	Secondary

End point timeframe:

Up to 216 weeks

End point values	Safety Analysis Set: Burosumab Q2W	Safety Analysis Set: Burosumab Q4W Then Q2W		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	26		
Units: subjects				
All TEAEs	26	26		
Serious TEAE	0	1		
Related TEAE	17	21		
Serious Related TEAE	0	1		
Grade 3 or 4 TEAE	1	1		
TEAE Leading to Study Discontinuation	0	0		
TEAE Leading to Treatment Discontinuation	0	0		
TEAE Leading to Death	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 216 weeks

Adverse event reporting additional description:

TEAEs, defined as AEs with onset on or after the time of initiation of study drug administration, are presented.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Burosumab Q2W

Reporting group description:

Burosumab SC injections Q2W. Dose was determined by the subject's weight and prescribed dose by their study doctor.

Reporting group title	Burosumab Q4W Then Q2W

Reporting group description:

Burosumab SC injections Q4W. Dose was determined by the subject's weight and prescribed dose by their study doctor. Subjects in Q4W were to switch to Q2W beginning with Week 64 dosing.

Serious adverse events	Burosumab Q2W	Burosumab Q4W Then Q2W	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Myalgia			

subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Burosumab Q2W	Burosumab Q4W Then Q2W	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 26 (100.00%)	26 / 26 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin Papilloma			
subjects affected / exposed	3 / 26 (11.54%)	0 / 26 (0.00%)	
occurrences (all)	3	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 26 (19.23%)	3 / 26 (11.54%)	
occurrences (all)	7	5	
Influenza Like Illness			
subjects affected / exposed	2 / 26 (7.69%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
Injection Site Bruising			
subjects affected / exposed	5 / 26 (19.23%)	4 / 26 (15.38%)	
occurrences (all)	6	5	
Injection Site Erythema			
subjects affected / exposed	14 / 26 (53.85%)	9 / 26 (34.62%)	
occurrences (all)	78	92	
Injection Site Pain			
subjects affected / exposed	3 / 26 (11.54%)	3 / 26 (11.54%)	
occurrences (all)	6	3	
Injection Site Pruritus			
subjects affected / exposed	2 / 26 (7.69%)	4 / 26 (15.38%)	
occurrences (all)	2	8	
Injection Site Rash			
subjects affected / exposed	2 / 26 (7.69%)	2 / 26 (7.69%)	
occurrences (all)	4	4	

Injection Site Reaction		
subjects affected / exposed	13 / 26 (50.00%)	13 / 26 (50.00%)
occurrences (all)	48	38
Injection Site Swelling		
subjects affected / exposed	5 / 26 (19.23%)	1 / 26 (3.85%)
occurrences (all)	7	2
Malaise		
subjects affected / exposed	3 / 26 (11.54%)	3 / 26 (11.54%)
occurrences (all)	7	3
Medical Device Pain		
subjects affected / exposed	3 / 26 (11.54%)	2 / 26 (7.69%)
occurrences (all)	5	2
Non-Cardiac Chest Pain		
subjects affected / exposed	0 / 26 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	4
Pain		
subjects affected / exposed	6 / 26 (23.08%)	4 / 26 (15.38%)
occurrences (all)	6	5
Peripheral Swelling		
subjects affected / exposed	1 / 26 (3.85%)	2 / 26 (7.69%)
occurrences (all)	1	2
Pyrexia		
subjects affected / exposed	12 / 26 (46.15%)	13 / 26 (50.00%)
occurrences (all)	37	36
Immune system disorders		
Seasonal Allergy		
subjects affected / exposed	6 / 26 (23.08%)	11 / 26 (42.31%)
occurrences (all)	12	18
Reproductive system and breast disorders		
Dysmenorrhoea		
subjects affected / exposed	3 / 26 (11.54%)	1 / 26 (3.85%)
occurrences (all)	7	2
Menorrhagia		
subjects affected / exposed	2 / 26 (7.69%)	0 / 26 (0.00%)
occurrences (all)	6	0
Respiratory, thoracic and mediastinal disorders		

Asthma		
subjects affected / exposed	2 / 26 (7.69%)	0 / 26 (0.00%)
occurrences (all)	6	0
Cough		
subjects affected / exposed	21 / 26 (80.77%)	15 / 26 (57.69%)
occurrences (all)	60	34
Dyspnoea		
subjects affected / exposed	2 / 26 (7.69%)	0 / 26 (0.00%)
occurrences (all)	3	0
Epistaxis		
subjects affected / exposed	6 / 26 (23.08%)	2 / 26 (7.69%)
occurrences (all)	9	3
Nasal Congestion		
subjects affected / exposed	10 / 26 (38.46%)	10 / 26 (38.46%)
occurrences (all)	20	24
Nasal Obstruction		
subjects affected / exposed	3 / 26 (11.54%)	1 / 26 (3.85%)
occurrences (all)	3	1
Oropharyngeal Pain		
subjects affected / exposed	14 / 26 (53.85%)	12 / 26 (46.15%)
occurrences (all)	36	24
Respiratory Tract Congestion		
subjects affected / exposed	2 / 26 (7.69%)	0 / 26 (0.00%)
occurrences (all)	2	0
Rhinorrhoea		
subjects affected / exposed	12 / 26 (46.15%)	10 / 26 (38.46%)
occurrences (all)	24	28
Sinus Congestion		
subjects affected / exposed	2 / 26 (7.69%)	0 / 26 (0.00%)
occurrences (all)	3	0
Sneezing		
subjects affected / exposed	6 / 26 (23.08%)	6 / 26 (23.08%)
occurrences (all)	8	16
Throat Irritation		
subjects affected / exposed	1 / 26 (3.85%)	2 / 26 (7.69%)
occurrences (all)	1	4

Upper Respiratory Tract Congestion		
subjects affected / exposed	1 / 26 (3.85%)	2 / 26 (7.69%)
occurrences (all)	1	2
Wheezing		
subjects affected / exposed	3 / 26 (11.54%)	2 / 26 (7.69%)
occurrences (all)	4	3
Psychiatric disorders		
Anxiety		
subjects affected / exposed	3 / 26 (11.54%)	0 / 26 (0.00%)
occurrences (all)	4	0
Initial Insomnia		
subjects affected / exposed	0 / 26 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	2
Insomnia		
subjects affected / exposed	4 / 26 (15.38%)	1 / 26 (3.85%)
occurrences (all)	4	3
Investigations		
Blood 1,25-Dihydroxycholecalciferol Increased		
subjects affected / exposed	0 / 26 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	2
Blood 25-Hydroxycholecalciferol Decreased		
subjects affected / exposed	2 / 26 (7.69%)	1 / 26 (3.85%)
occurrences (all)	3	1
Blood Parathyroid Hormone Increased		
subjects affected / exposed	1 / 26 (3.85%)	2 / 26 (7.69%)
occurrences (all)	1	2
Vitamin D Decreased		
subjects affected / exposed	6 / 26 (23.08%)	5 / 26 (19.23%)
occurrences (all)	7	6
Injury, poisoning and procedural complications		
Arthropod Bite		
subjects affected / exposed	1 / 26 (3.85%)	3 / 26 (11.54%)
occurrences (all)	3	4
Contusion		

subjects affected / exposed	6 / 26 (23.08%)	5 / 26 (19.23%)
occurrences (all)	8	7
Fall		
subjects affected / exposed	3 / 26 (11.54%)	3 / 26 (11.54%)
occurrences (all)	3	4
Joint Injury		
subjects affected / exposed	2 / 26 (7.69%)	2 / 26 (7.69%)
occurrences (all)	3	2
Laceration		
subjects affected / exposed	2 / 26 (7.69%)	0 / 26 (0.00%)
occurrences (all)	2	0
Ligament Sprain		
subjects affected / exposed	3 / 26 (11.54%)	2 / 26 (7.69%)
occurrences (all)	3	2
Procedural Pain		
subjects affected / exposed	0 / 26 (0.00%)	6 / 26 (23.08%)
occurrences (all)	0	8
Skin Abrasion		
subjects affected / exposed	3 / 26 (11.54%)	4 / 26 (15.38%)
occurrences (all)	3	4
Thermal Burn		
subjects affected / exposed	3 / 26 (11.54%)	0 / 26 (0.00%)
occurrences (all)	3	0
Nervous system disorders		
Dizziness		
subjects affected / exposed	2 / 26 (7.69%)	7 / 26 (26.92%)
occurrences (all)	3	7
Headache		
subjects affected / exposed	20 / 26 (76.92%)	19 / 26 (73.08%)
occurrences (all)	139	91
Lethargy		
subjects affected / exposed	1 / 26 (3.85%)	2 / 26 (7.69%)
occurrences (all)	2	2
Migraine		
subjects affected / exposed	5 / 26 (19.23%)	1 / 26 (3.85%)
occurrences (all)	19	1

Post-Traumatic Headache		
subjects affected / exposed	0 / 26 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	2
Ear and labyrinth disorders		
Ear Pain		
subjects affected / exposed	10 / 26 (38.46%)	8 / 26 (30.77%)
occurrences (all)	12	13
Eye disorders		
Dry Eye		
subjects affected / exposed	0 / 26 (0.00%)	3 / 26 (11.54%)
occurrences (all)	0	3
Eye Pain		
subjects affected / exposed	2 / 26 (7.69%)	2 / 26 (7.69%)
occurrences (all)	3	2
Eye Pruritus		
subjects affected / exposed	3 / 26 (11.54%)	2 / 26 (7.69%)
occurrences (all)	3	3
Lacrimation Increased		
subjects affected / exposed	1 / 26 (3.85%)	3 / 26 (11.54%)
occurrences (all)	1	3
Gastrointestinal disorders		
Abdominal Discomfort		
subjects affected / exposed	4 / 26 (15.38%)	2 / 26 (7.69%)
occurrences (all)	4	5
Abdominal Pain		
subjects affected / exposed	2 / 26 (7.69%)	7 / 26 (26.92%)
occurrences (all)	3	15
Abdominal Pain Upper		
subjects affected / exposed	10 / 26 (38.46%)	8 / 26 (30.77%)
occurrences (all)	29	22
Constipation		
subjects affected / exposed	2 / 26 (7.69%)	4 / 26 (15.38%)
occurrences (all)	2	5
Dental Caries		
subjects affected / exposed	0 / 26 (0.00%)	3 / 26 (11.54%)
occurrences (all)	0	4
Diarrhoea		

subjects affected / exposed	7 / 26 (26.92%)	11 / 26 (42.31%)
occurrences (all)	28	23

Gingival Pain

subjects affected / exposed	0 / 26 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	2

Lip Swelling

subjects affected / exposed	0 / 26 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	2

Mouth Ulceration

subjects affected / exposed	3 / 26 (11.54%)	1 / 26 (3.85%)
occurrences (all)	4	2

Nausea

subjects affected / exposed	9 / 26 (34.62%)	8 / 26 (30.77%)
occurrences (all)	22	15

Oral Pain

subjects affected / exposed	2 / 26 (7.69%)	3 / 26 (11.54%)
occurrences (all)	2	5

Toothache

subjects affected / exposed	6 / 26 (23.08%)	11 / 26 (42.31%)
occurrences (all)	6	23

Vomiting

subjects affected / exposed	13 / 26 (50.00%)	16 / 26 (61.54%)
occurrences (all)	41	28

Skin and subcutaneous tissue disorders

Dermatitis Contact

subjects affected / exposed	0 / 26 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	2

Dry Skin

subjects affected / exposed	1 / 26 (3.85%)	4 / 26 (15.38%)
occurrences (all)	1	5

Eczema

subjects affected / exposed	1 / 26 (3.85%)	3 / 26 (11.54%)
occurrences (all)	1	4

Erythema

subjects affected / exposed	1 / 26 (3.85%)	3 / 26 (11.54%)
occurrences (all)	2	4

Pruritus		
subjects affected / exposed	4 / 26 (15.38%)	5 / 26 (19.23%)
occurrences (all)	4	6
Rash		
subjects affected / exposed	7 / 26 (26.92%)	8 / 26 (30.77%)
occurrences (all)	8	12
Swelling Face		
subjects affected / exposed	1 / 26 (3.85%)	2 / 26 (7.69%)
occurrences (all)	1	4
Renal and urinary disorders		
Glycosuria		
subjects affected / exposed	2 / 26 (7.69%)	0 / 26 (0.00%)
occurrences (all)	2	0
Musculoskeletal and connective tissue disorders		
Arthralgia		
subjects affected / exposed	11 / 26 (42.31%)	17 / 26 (65.38%)
occurrences (all)	41	40
Back Pain		
subjects affected / exposed	4 / 26 (15.38%)	4 / 26 (15.38%)
occurrences (all)	15	5
Bone Pain		
subjects affected / exposed	2 / 26 (7.69%)	3 / 26 (11.54%)
occurrences (all)	2	3
Groin Pain		
subjects affected / exposed	0 / 26 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	3
Musculoskeletal Pain		
subjects affected / exposed	3 / 26 (11.54%)	4 / 26 (15.38%)
occurrences (all)	3	5
Myalgia		
subjects affected / exposed	4 / 26 (15.38%)	7 / 26 (26.92%)
occurrences (all)	7	10
Neck Pain		
subjects affected / exposed	4 / 26 (15.38%)	2 / 26 (7.69%)
occurrences (all)	4	3
Pain In Extremity		

subjects affected / exposed	10 / 26 (38.46%)	17 / 26 (65.38%)
occurrences (all)	30	35

Scoliosis
subjects affected / exposed	3 / 26 (11.54%)	1 / 26 (3.85%)
occurrences (all)	4	1

Infections and infestations

Conjunctivitis
subjects affected / exposed	3 / 26 (11.54%)	0 / 26 (0.00%)
occurrences (all)	3	0

Ear Infection
subjects affected / exposed	4 / 26 (15.38%)	3 / 26 (11.54%)
occurrences (all)	5	6

Enterobiasis
subjects affected / exposed	0 / 26 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	2

Gastroenteritis
subjects affected / exposed	2 / 26 (7.69%)	0 / 26 (0.00%)
occurrences (all)	4	0

Gastroenteritis Viral
subjects affected / exposed	2 / 26 (7.69%)	4 / 26 (15.38%)
occurrences (all)	3	6

Gingival Abscess
subjects affected / exposed	1 / 26 (3.85%)	2 / 26 (7.69%)
occurrences (all)	1	2

Infectious Mononucleosis
subjects affected / exposed	0 / 26 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	2

Influenza
subjects affected / exposed	6 / 26 (23.08%)	4 / 26 (15.38%)
occurrences (all)	9	4

Lice Infestation
subjects affected / exposed	2 / 26 (7.69%)	1 / 26 (3.85%)
occurrences (all)	3	1

Nasopharyngitis
subjects affected / exposed	13 / 26 (50.00%)	15 / 26 (57.69%)
occurrences (all)	35	43

Pharyngitis Streptococcal			
subjects affected / exposed	4 / 26 (15.38%)	6 / 26 (23.08%)	
occurrences (all)	4	7	
Rhinitis			
subjects affected / exposed	2 / 26 (7.69%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Sinusitis			
subjects affected / exposed	3 / 26 (11.54%)	3 / 26 (11.54%)	
occurrences (all)	3	4	
Tooth Abscess			
subjects affected / exposed	3 / 26 (11.54%)	6 / 26 (23.08%)	
occurrences (all)	6	10	
Upper Respiratory Tract Infection			
subjects affected / exposed	12 / 26 (46.15%)	13 / 26 (50.00%)	
occurrences (all)	17	16	
Viral Infection			
subjects affected / exposed	3 / 26 (11.54%)	2 / 26 (7.69%)	
occurrences (all)	3	2	
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	5 / 26 (19.23%)	3 / 26 (11.54%)	
occurrences (all)	8	4	
Metabolism and nutrition disorders			
Vitamin D Deficiency			
subjects affected / exposed	4 / 26 (15.38%)	6 / 26 (23.08%)	
occurrences (all)	5	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 May 2014	Key changes impacting the conduct of the study were: • Pregnancy testing (for female subjects of childbearing potential who had experienced menarche), contraception requirements, and follow up for pregnancies were incorporated into the protocol. Although the study enrolled pre-pubertal subjects of Tanner Stage 2 or less, contraception requirements and regular pregnancy testing for subjects entering puberty during trial participation was included as an added safety precaution, given that burosumab has been found to be associated with premature births, embryo/fetal deaths, and abortions in cynomolgus monkeys. • Subjects were to be discontinued from study drug if they experienced new or clinically significant worsening in mineralization that was considered clinically meaningful by the investigator and/or sponsor and was related was to study drug. Ectopic mineralization is a characteristic feature of patients with XLH and is also related to the current conventional therapy treatment with oral phosphate and active forms of vitamin D. It is unknown whether burosumab may increase the risk of ectopic mineralization including nephrocalcinosis. • The standing height inclusion criterion was broadened from < 25th percentile to < 50th percentile to include pediatric XLH subjects with significant bone disease who met all other eligibility criteria and who would previously have been excluded from participation in the study based on their stature alone.
02 July 2014	Key changes impacting the conduct of the study were: • The number of study sites was increased from 8 to 9. • Tanner staging criteria was to be assessed for all subjects, for consistency of data collection and to ensure that any subjects with early pubertal status due to underlying conditions were identified. • Subjects receiving growth hormone therapy within 3 months (previously: 12 months) of screening were excluded from the study.
02 March 2015	Key changes impacting the conduct of the study were: • The number of study sites was increased from 9 to 12. • Dose Cohort 3 was expanded to include up to 30 subjects for a total study population of up to 50 subjects. "Pre-expansion subjects" (n = 36) were fully enrolled under the earlier versions of the protocol; Dose Cohort 3 "expansion subjects" (n = approximately 15) were to be enrolled under the Amendment 3. • Added assessment of changes in rickets severity by the RSS method to complement assessments by RGI C. Methods for blinding of radiographic assessments also were added. • RSS at the knee of at least 1.5, as determined by a central reader, was required for inclusion in the expansion group. Requiring subjects in the expansion group to have an RSS of at least 1.5 at the knee increases the probability of seeing a meaningful reduction in rickets severity with burosumab. • Because the enrollment criteria were adjusted to require a specific level of rickets severity, gender-related differences in the severity of skeletal disease were minimized and the requirement for gender balance was removed for the expansion group.

22 April 2015	Key changes impacting the conduct of the study were: • The upper limit of the target serum phosphorus range was updated to 5.0 mg/dL (1.61 mmol/L) from 4.5 mg/dL (1.45 mmol/L). The normal reference serum phosphorus range for children aged 5 to 12 years is approximately 3.2 to 6.1 mg/dL (1.03 to 1.97 mmol/L). Increasing the upper limit of the target fasting serum phosphorus range for this study maintained the target within the low- to mid- normal range and would avoid unnecessary fluctuations in dose levels. • Dose titration adjustments, whether upward or downward, could be made in increments of 0.3 mg/kg for the Q2W regimen (vs 0.1 mg/kg previously) and in increments of 0.4 mg/kg for the Q4W regimen (vs 0.2 mg/kg previously). The dose increments in the initial version of the protocol were selected to slowly increase the dose to prevent any unexpected or exaggerated increases in serum phosphorus. Available data showed small proportional increases in serum phosphorus with the previous titration scheme, and many dose cycles were required to reach a dose that produced serum phosphorus levels in the target range. Therefore, in the absence of any safety signal and to allow subjects to achieve their serum phosphorus target range earlier, the dose titration scheme was modified. • Unscheduled blood draws for peak serum phosphorus measurements could be obtained at study visits if titration continues into the Treatment Period to enable appropriate dose management.
22 April 2015	(continued) • The maximum dose of burosumab in regimen Q2W was increased to 2.0 mg/kg. In addition, the maximum allowable dose was capped at 90 mg (for both the Q2W and Q4W groups). The target therapeutic goal remained the same, ie, peak serum phosphorus levels between 3.5 and 5.0 mg/dL (1.13 and 1.62 mmol/L). This change was based on the finding that some subjects needed doses higher than 1.0 mg/dL (0.32 mmol/L) to achieve the serum phosphorus target, regardless of whether the dose was given at the Q2W or Q4W dose regimen. Approximately half of the subjects in the Q4W regimen were already receiving doses above 1.0 mg/dL (0.32 mmol/L) to achieve the proposed target serum phosphorus range, and no safety concerns were raised. The increases in serum phosphorus were proportional to the dose administered, independently of the whether the subject is receiving burosumab monthly or biweekly. No cumulative dose effect in the Q2W regimen group was observed. The maximum dose was set at 90 mg because there is limited experience in adults with burosumab doses above 90 mg. • Changes were made in the timing of serum phosphorus, calcium, and 1,25(OH)2D measurements at Weeks 48 through 62 to better characterize the longer-term PD effects of burosumab by assessing both peak and trough measurements toward the end of the study. • The dosing window was changed so that subjects will be dosed at Q2W or Q4W week intervals (±3 days) and no fewer than 8 days apart (previously: no fewer than 12 days apart). Adjusting the dosing window provided additional convenience to subjects and study sites without impacting safety.

28 August 2015	• A 96-week Treatment Extension Period was incorporated into the study design to evaluate the long-term safety and efficacy of burosumab. It is expected that the maintenance of phosphate control will allow for continued healing of rickets and bowing and maximize growth outcomes. Changes in growth and correction of lower extremity bowing may take longer to observe than the healing of rickets, and these outcomes continued to be followed in the Treatment Extension Period. • During the Treatment Extension Period, all subjects receive Q2W administration of burosumab. The transition of subjects to Q2W dosing reflects interim Week 40 findings related to serum phosphorus levels, rickets, and dose. Subjects in the Q2W dosing regimen showed a more stable and consistent increase in serum phosphorus levels with less fluctuation over time than in subjects who received burosumab Q4W for whom serum phosphorus levels increased at the middle of the dose cycle (week 2) but tended to return to baseline at the end of the dose interval (week 4). - Subjects who had been receiving Q2W dosing continued receiving the same dose at the same dose interval. - Subjects who had been receiving the Q4W regimen switched to the Q2W regimen beginning with the Week 64 dose. The dose was 60% of the most recent monthly dose (rounded to the nearest 10 mg), the total dose was approximately 20% higher per month compared with the subject's Q4W dose. • Vital signs measurements were required to be performed before any additional assessments were completed and after the subject had rested for 5 minutes. A second BP measurement was required to be obtained at the end of the study visit after all procedures have been performed.
07 July 2016	(continued) Statistical Analyses • In Section 7.6.4.3, the statistical methodology for the Week 40 analysis was updated to include the GEE model rather than the Mixed Model for Repeated Measures. Record Retention • Section 8.4.3 was updated to state that all study records must be retained for at least 25 years after the end of the clinical trial or in accordance with national law. Definition of Adverse Events • In Section 8.5.1, language was added to clarify that hospitalizations planned prior to study enrollment (eg, for elective surgeries) are not considered SAEs but hospitalizations that occur for pre existing conditions that are scheduled after study enrollment are considered SAEs.

07 July 2016	Key changes impacting the conduct of the study were: Drug Administration • In Section 7.1 and Section 7.2, language and procedures regarding dose adjustment were updated and clarified. The information was also reorganized for easier reference to dosing for a specific period of the study (eg, Titration Period or Treatment Extension Period). Specifically, the protocol states that after the initial dose titration is complete, during the Treatment Period and Treatment Extension Period dose adjustments may be made in any subject if specific serum phosphorus criteria are met. When post-titration dose adjustment is needed, doses should be adjusted in 10 mg total dose increments (eg, a 20 mg rounded total dose would be increased to a 30 mg total dose). • Section 7.4.1 was updated to state that "At the discretion of the investigator and after proper training by study personnel in SC injection technique, a subject's parent or non-healthcare provider caregiver may administer burosumab to the subject under the supervision of a Home Health (HH) nurse where local regulations permit and where logistically feasible. Parents or caregivers will be instructed to follow the directions provided in the Instructions for Use. The dosing schedule will remain the same." Inclusion Criteria • In Section 7.3.1, inclusion criterion #10 was updated to state that sexually active male and female subjects must be willing to use 2 highly effective methods of contraception during the study. Previously it stated, "an acceptable method."
07 July 2016	(continued) Removal of Subjects • In Section 7.3.3, language was added to indicate that orthopedic surgery will be permitted during the Treatment Extension Period if recommended by the investigator or consulting physician and that subjects who develop hyperparathyroidism may remain on study but use of medication to suppress PTH (eg, Sensipar®, cinacalcet, calcimimetics) is not permitted at any time. Subjects should be removed from study if treatment for hyperparathyroidism becomes medically necessary. Study Procedures and Assessments • The Schedule of Events was updated to add serum phosphorus and serum 1,25(OH)2D measurements at Weeks 124 and 148. • Section 7.5.3.2 was modified to add a 6MWT assessment at Week 160 and to indicate the POSNA-PODCI instrument will be administered at Weeks 88 and 160 but not at Weeks 112 and 136. • Measurement of pre-dose serum burosumab concentration at Week 24 using retrospective samples was added to Section 7.5.4 and the Schedule of Events. • The Schedule of Events was updated to indicate post-treatment Tanner staging will be performed beginning at Week 64 and every 6 months thereafter during the extension phase of the study. • Bilateral AP knee X-rays were added at Week 160 to the Schedule of Events and in Section 7.5.3.1. In addition, it is noted that beginning at Week 64 and during the extension, radiographs will be evaluated for epiphyseal closure, and that RGI C assessment of radiographs will occur at Weeks 88 and 160.

07 July 2016	(continued) **Genetic Testing** • Section 7.5.5 was modified to add that genetic testing for mutations in genes consistent with syndromes that have clinical and biochemical phenotypic overlap with XLH will be performed if the initial PHEX mutation analysis result is negative or inconclusive and informed consent is provided. This testing will include, but not necessarily be limited to, genes for Autosomal Dominant Hypophosphatemic Rickets (FGF23), Autosomal Recessive Hypophosphatemic Rickets (DMP1, ENPP1), X Linked Recessive Hypophosphatemic Rickets (CLCN5), and Hereditary Hypophosphatemic Rickets with Hypercalciuria (SLC34A3). The investigator will be provided the genetic testing results and will determine when and whether the information should be shared with the subject. **Central Reads of Echocardiograms** • Section 7.5.5.6 was updated to state that ECHOs will be read centrally rather than locally. The central core lab will provide a study specific protocol to be followed by the sites to ensure adequate image acquisition for the assessment of mineralization. **Safety Measures** • In Section 7.5.5, ECG is listed as a general safety assessment. Previously it was listed within the safety assessments for ectopic mineralization. • Section 7.5.5.8 was updated to add assessment of lipase in all subjects and specify additional laboratory analyses will be performed reflexively if serum amylase levels are elevated to ≥ 1.5 times the upper limit of the reference range (ULRR). • Language in Section 7.5.5.8 regarding FGF23 assays was updated to indicate testing will be performed by a contract laboratory and not the sponsor's development partner, Kyowa Hakko Kirin Pharma, Inc **Ethics** • Section 8.1.2 was updated to state that both the sponsor and investigator will make every effort to assure the study described in this protocol is conducted in full conformance with those principles, current FDA regulations, ICH GCP guidelines, and local ethical and regulatory requirements.
08 May 2017	**Treatment Duration** • The study treatment period was extended for subjects at study sites in the US for up to an additional 56 weeks until September 2018; therefore, the total treatment duration varied by region. The study consisted of an individual dose Titration Period (16 weeks), a Treatment Period (48 weeks), and a Treatment Extension Period I (up to 96 weeks), for a total treatment duration of up to 160 weeks for subjects at study sites outside the US. In the US, the study also included a Treatment Extension Period II (up to 56 weeks) until September 2018 for a maximum total treatment duration of up to 216 weeks. The total duration of treatment varied for the individual US subjects based on their initial time of enrollment but was not to exceed 216 weeks. For subjects at study sites in Europe, Week 160 was the final efficacy visit for the study. Additional safety follow-up phone calls and visits occurred for certain subjects. **End of Study Definition, Timing, and Procedures** • In Section 7.1 and related sections, the description of the study periods was updated to indicate that the study duration would vary by region. The study consisted of an individual dose Titration Period (16 weeks), a Treatment Period (48 weeks), and a Treatment Extension Period I (up to 96 weeks), for a total treatment duration of up to 160 weeks for subjects at study sites outside the US. For subjects at study sites outside the US, the Week 160 visit was their end of study (EOS) efficacy visit (referred to as EOSI). In the US, the study also included a Treatment Extension Period II (up to 56 weeks) until September 2018, at which time subjects had their EOS efficacy visit (referred to as EOS II), for a maximum total treatment duration of up to 216 weeks.

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A safety follow-up telephone call was to occur at 5 weeks (+ 5 days) after the EOS (I or II) efficacy visit, and a final safety visit was to occur at 10 weeks (± 1 week) after the EOS (I or II) efficacy visit for subjects who were not continuing on burosumab treatment through commercial use or another mechanism. The end of study was defined as the date of the last protocol-specified procedures (including telephone contact) for the last subject in the study.

Study Drug Administration
• Sections 7.4.1 and 7.4.6 were updated to indicate that for subjects in the US, after proper training by study personnel in subcutaneous injection technique, the subject's parent or caregiver may administer KRN23 to the subject, in the home setting without the supervision of a home health nurse during Treatment Extension Period II. Parents or caregivers were to be instructed to follow the directions provided in the Instructions for Use. The dosing schedule remained the same. Additional instructions regarding the timing of the training and implementation of the subject/caregiver administration are provided in Section 7.4.6. In addition, in Section 7.4.1, the language was updated to indicate that 1.5 mL is the maximum volume that should be administered at a single injection site, and that rotation of injections may include rotation to a different quadrant of the abdomen.

Dose Limiting Toxicity
• In Section 7.5.5.13 the definition of dose limiting toxicity (DLT) for serum phosphorus was corrected to be a confirmed serum phosphorus level of ≥ 6.5 mg/dL rather than ≥ 6.1 mg/dL. |
| 08 May 2017 | (continued)
Statistical Analyses
• In Section 7.6.4.5, Treatment Extension Period Analysis, language was updated to account for the addition of Treatment Extension Period II. Efficacy analysis was to be performed at the completion of Treatment Extension Period I for the overall population and a final analysis was to be performed at the end of the study, which is defined as the date of the last protocol-specified procedures (including telephone contact) for the last subject in the study.

Pregnancy Testing and Contraception
• Section 7.5.5.10 and the Schedule of Events were updated to indicate that during Treatment Extension Period II, pregnancy testing will be conducted at study site visits every 12 weeks for subjects of childbearing potential. In addition, the acceptable methods of contraception were updated.

Anti-Burosumab Antibodies
• In Section 5.3, Section 7.5.5.9, and the Schedule of Events, the term HAHA (human anti-human antibody) in reference to anti- burosumab antibody testing, was replaced with the term ADA (anti-drug antibody). |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported