



Clinical trial results:

An Open-Label, Single-Arm, Phase 3 Study to Evaluate the Effects of KRN23 on Osteomalacia in Adults with X-linked Hypophosphatemia (XLH)

Summary

EudraCT number	2015-001775-41
Trial protocol	DK FR
Global end of trial date	13 December 2018

Results information

Result version number	v1 (current)
This version publication date	29 December 2019
First version publication date	29 December 2019

Trial information

Trial identification

Sponsor protocol code	UX023-CL304
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02537431
WHO universal trial number (UTN)	-
Other trial identifiers	EMA/902676: Unique Product Identifier

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 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)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 December 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	13 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to establish the effect of KRN23 treatment on improvement in XLH-associated osteomalacia as determined by osteoid volume (osteoid volume/bone volume, OV/BV).

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	23 December 2015
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	France: 1
Country: Number of subjects enrolled	United States: 9
Country: Number of subjects enrolled	Japan: 4
Worldwide total number of subjects	14
EEA total number of subjects	1

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	14
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Potential subjects came in to the site to sign informed consent and complete the initial Screening. Subjects were contacted by telephone within 1 week of the Screening visit to communicate available test results related to eligibility.

Period 1

Period 1 title	Open-Label Period (Week 0 to Week 48)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Open-Label Burosumab Q4W
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Arm description:

1.0 mg/kg burosumab monthly (Q4W), calculated based on baseline weight and up to a maximum dose of 90 mg.

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

Dosage and administration details:

The amount of drug administered was calculated based on Baseline weight, up to a maximum dose of 90 mg.

Number of subjects in period 1	Open-Label Burosumab Q4W
Started	14
Completed	13
Not completed	1
Consent withdrawn by subject	1

Period 2

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

Arms

Arm title	Open-Label Burosumab Q4W
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Arm description:

1.0 mg/kg burosumab monthly (Q4W), calculated based on baseline weight and up to a maximum dose of 90 mg.

Arm type	Experimental
Investigational medicinal product name	burosumab
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Other name	UX023, Crysvita
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Dosage and administration details:

The amount of drug administered was calculated based on Baseline weight, up to a maximum dose of 90 mg.

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

Dosage and administration details:

The amount of drug administered was calculated based on Baseline weight, up to a maximum dose of 90 mg.

Number of subjects in period 2	Open-Label Burosumab Q4W
Started	13
Completed	13

Period 3

Period 3 title	Treatment Extension Period II
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Open-Label Burosumab Q4W
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Arm description:

1.0 mg/kg burosumab monthly (Q4W), calculated based on baseline weight and up to a maximum dose of 90 mg.

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

Dosage and administration details:

The amount of drug administered was calculated based on Baseline weight, up to a maximum dose of 90 mg.

Number of subjects in period 3 ^[1]	Open-Label Burosumab Q4W
Started	8
Completed	8

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 5 subjects completing Treatment Extension Period I did not enter Treatment Extension Period II

Baseline characteristics

Reporting groups

Reporting group title	Open-Label Burosumab Q4W
Reporting group description: 1.0 mg/kg burosumab monthly (Q4W), calculated based on baseline weight and up to a maximum dose of 90 mg.	

Reporting group values	Open-Label Burosumab Q4W	Total	
Number of subjects	14	14	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	40.13 ± 8.725	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	6	6	
Ethnicity Units: Subjects			
Hispanic or Latino	1	1	
Not Hispanic or Latino	13	13	
Unknown or Not Reported	0	0	
Race Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	4	4	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	1	
White	9	9	
More than one race	0	0	
Unknown or Not Reported	0	0	
Osteoid Volume/Bone Volume (OV/ BV)			
Percent of a given volume of bone tissue that consists of unmineralized bone (osteoid).			
Primary Analysis Set: enrolled subjects with baseline and follow-up (Week 48/end of treatment) bone biopsy data; subjects with nonmissing results (n=10).			
Units: percentage of osteoid volume arithmetic mean standard deviation	26.12 ± 12.357	-	
Serum Phosphorus Units: mg/dL arithmetic mean standard deviation	2.24 ± 0.396	-	
Osteoid Thickness (O.Th)			
Mean thickness, given in micrometers, for osteoid seams.			

Primary Analysis Set: enrolled subjects with baseline and follow-up (Week 48/end of treatment) bone biopsy data (n=11).			
Units: μm			
arithmetic mean	17.21		
standard deviation	± 4.105	-	
Osteoid Surface/Bone Surface (OS/ BS)			
Percent of bone surface covered in osteoid.			
Primary Analysis Set: enrolled subjects with baseline and follow-up (Week 48/end of treatment) bone biopsy data (n=11).			
Units: percentage of osteoid surface			
arithmetic mean	91.73		
standard deviation	± 3.438	-	
Mineralization Lag Time (MLt)			
Average time interval between osteoid formation and its subsequent mineralization; calculated by dividing the osteoid thickness by the adjusted apposition rate (O.Th/Aj.AR). Aj.AR; amount of new bone created (bone formation rate over the entire osteoid surface). The imputed result was used for some of the baseline data for MLt.			
Primary Analysis Set: enrolled subjects with baseline and follow-up (Week 48/end of treatment) bone biopsy data (n=11).			
Units: days			
arithmetic mean	1539.81		
standard deviation	± 1587.086	-	
Mineral Apposition Rate (MAR)			
Linear rate of new bone deposition; mean distance between the double labels, divided by the time interval between them.			
Primary Analysis Set: enrolled subjects with baseline and follow-up (Week 48/end of treatment) bone biopsy data (n=11).			
Units: $\mu\text{m}/\text{day}$			
arithmetic mean	0.58		
standard deviation	± 0.448	-	
Mineralizing Surface/Bone Surface (MS/BS)			
Percent of bone surface that displays a tetracycline label reflecting active mineralization; calculated as the double-labeled surface plus one half of the single-labeled surface and is expressed as a function of total bone surface $[(\text{dLS} + \text{sLS}/2)/\text{BS}]$. It is a measure of the proportion of bone surface upon which new mineralized bone was being deposited during the period of tetracycline labeling.			
Primary Analysis Set: enrolled subjects with baseline and follow-up (Week 48/end of treatment) bone biopsy data (n=11).			
Units: percentage of mineralizing surface			
arithmetic mean	5.99		
standard deviation	± 4.763	-	
Bone Formation Rate/Bone Surface (BFR/BS)			
Amount of new bone formed in unit time per unit of bone surface; calculated by multiplying MS/BS by the MAR (see previous measure descriptions for MS/BS and MAR definitions).			
Primary Analysis Set: enrolled subjects with baseline and follow-up (Week 48/end of treatment) bone biopsy data; subjects with nonmissing results (n=6).			
Units: $\mu\text{m}^3/\mu\text{m}^2/\text{year}$			
arithmetic mean	26.68		
standard deviation	± 19.480	-	
Bone Formation Rate/Osteoblast Surface (BFR/OS)			
Bone formation rate to osteoid surface ratio, related to the adjusted apposition rate (Aj.AR; amount of			

new bone created [bone formation rate over the entire osteoid surface]).			
Primary Analysis Set: enrolled subjects with baseline and follow-up (Week 48/end of treatment) bone biopsy data; subjects with nonmissing results (n=4).			
Units: $\mu\text{m}^3/\mu\text{m}^2/\text{year}$ arithmetic mean standard deviation	2309.00 ± 2941.970	-	
Bone Formation Rate/Bone Volume (BFR/BV)			
BFR/BV is equivalent to bone turnover rate.			
Primary Analysis Set: enrolled subjects with baseline and follow-up (Week 48/end of treatment) bone biopsy data; subjects with nonmissing results (n=6).			
Units: percent/year arithmetic mean standard deviation	38.33 ± 37.173	-	
1,25(OH) 2D			
Full Analysis Set: enrolled and dosed subjects with a baseline measurement (n=12).			
Units: pg/mL arithmetic mean standard deviation	37.25 ± 11.686	-	
24-Hour Urinary Phosphorus			
Full Analysis Set: enrolled and dosed subjects with a baseline measurement (n=12).			
Units: g/24hr arithmetic mean standard deviation	0.82 ± 0.237	-	
Ratio of Renal Tubular Maximum Reabsorption Rate of Phosphate to Glomerular Filtration Rate(TmP/GFR) Units: mg/dL arithmetic mean standard deviation	1.87 ± 0.307	-	
Tubular Reabsorption of Phosphate (TRP) Units: fraction of phosphorus reabsorbed arithmetic mean standard deviation	0.84 ± 0.048	-	
Procollagen Type 1 N-Propeptide (P1NP) Units: ng/mL arithmetic mean standard deviation	77.00 ± 33.273	-	
Carboxy-Terminal Cross-Linked Telopeptide of Type I Collagen (CTX-I) Units: pg/mL arithmetic mean standard deviation	646.93 ± 401.641	-	
Bone-Specific Alkaline Phosphatase (BALP) Units: $\mu\text{g/L}$ arithmetic mean standard deviation	20.43 ± 9.288	-	
Mineralizing Surface/ OsteoidSurface (MS/OS)			
Primary Analysis Set: enrolled subjects with baseline and follow-up (Week 48/end of treatment) bone biopsy data; subjects with nonmissing results (n=11).			

Units: percentage of mineralizing surface			
arithmetic mean	6.47		
standard deviation	± 5.120	-	

End points

End points reporting groups

Reporting group title	Open-Label Burosumab Q4W
Reporting group description: 1.0 mg/kg burosumab monthly (Q4W), calculated based on baseline weight and up to a maximum dose of 90 mg.	
Reporting group title	Open-Label Burosumab Q4W
Reporting group description: 1.0 mg/kg burosumab monthly (Q4W), calculated based on baseline weight and up to a maximum dose of 90 mg.	
Reporting group title	Open-Label Burosumab Q4W
Reporting group description: 1.0 mg/kg burosumab monthly (Q4W), calculated based on baseline weight and up to a maximum dose of 90 mg.	
Subject analysis set title	Primary Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: Enrolled subjects with baseline and follow-up (Week 48/end of treatment) bone biopsy data.	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: All enrolled subjects who receive at least one dose of study drug.	

Primary: Percent Change From Baseline in OV/BV at Week 48

End point title	Percent Change From Baseline in OV/BV at Week 48 ^[1]
End point description: OV/BV: percent of a given volume of bone tissue that consists of unmineralized bone (osteoid).	
End point type	Primary
End point timeframe: Baseline, 48 weeks	

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 provided in the pdf attachment (data could not be entered due to system limitations).

End point values	Primary Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	10 ^[2]			
Units: percentage change of unmineralized bone				
arithmetic mean (standard deviation)	-54.18 (± 20.211)			

Notes:

[2] - subjects with non-missing results

Attachments (see zip file)	Statistical Analysis Percent Change From Baseline in OV_BV at
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Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Mean Serum Phosphorus Levels Above the Lower Limit of Normal (LLN) at the Mid-Point of the Dose Interval, as Averaged Across Dose Cycles Between Baseline and Week 24

End point title	Percentage of Participants Achieving Mean Serum Phosphorus Levels Above the Lower Limit of Normal (LLN) at the Mid-Point of the Dose Interval, as Averaged Across Dose Cycles Between Baseline and Week 24
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End point description:

The LLN was defined as 2.5 mg/dL (0.81 mmol/L). The 95% confidence interval (CI) was calculated using Wilson score method.

End point type	Secondary
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End point timeframe:

Baseline, up to 24 weeks

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: percentage of subjects				
number (confidence interval 95%)	92.9 (68.5 to 98.7)			

Attachments (see zip file)	Percentage of Participants Achieving Mean Serum Phosphorus
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Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in O.Th at Week 48

End point title	Percent Change From Baseline in O.Th at Week 48
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End point description:

O.Th: mean thickness, given in micrometers, for osteoid seams.

End point type	Secondary
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End point timeframe:

Baseline, 48 weeks

End point values	Primary Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	11			
Units: percentage change in thickness				
arithmetic mean (standard deviation)	-32.21 ($\pm$ 11.966)			

Attachments (see zip file)	Statistical Analysis Percent Change From Baseline in O.Th at
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Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in OS/BS at Week 48

End point title	Percent Change From Baseline in OS/BS at Week 48
End point description: OS/Bs: percent of bone surface covered in osteoid.	
End point type	Secondary
End point timeframe: Baseline, 48 weeks	

End point values	Primary Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	11 ^[3]			
Units: percent change of bone surface covered				
arithmetic mean (standard deviation)	-26.00 (± 15.012)			

Notes:

[3] - subjects with non-missing results

Attachments (see zip file)	Statistical Analysis Percent Change From Baseline in OS_BS at
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Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in MLt at Week 48

End point title	Percent Change From Baseline in MLt at Week 48
End point description: MLt: average time interval between osteoid formation and its subsequent mineralization; calculated by dividing the osteoid thickness by the adjusted apposition rate (O.Th/Aj.AR). Aj.AR; amount of new bone created (bone formation rate over the entire osteoid surface). Based on imputed MLt values.	
End point type	Secondary
End point timeframe: Baseline, 48 weeks	

End point values	Primary Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	10 ^[4]			
Units: percent change in average time interval				
arithmetic mean (standard deviation)	-52.24 (± 58.487)			

Notes:

[4] - subjects who had non-missing results

Attachments (see zip file)	Statistical Analysis Percent Change From Baseline in MLt at
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Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in MAR at Week 48

End point title	Change From Baseline in MAR at Week 48
End point description: MAR: linear rate of new bone deposition; mean distance between the double labels, divided by the time interval between them.	
End point type	Secondary
End point timeframe: Baseline, 48 weeks	

End point values	Primary Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	11			
Units: µm/day				
arithmetic mean (standard deviation)	0.04 (± 0.506)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in MS/BS at Week 48

End point title	Change From Baseline in MS/BS at Week 48
End point description: MS/BS: percent of bone surface that displays a tetracycline label reflecting active mineralization; calculated as the double-labeled surface plus one half of the single-labeled surface and is expressed as a function of total bone surface ($[\text{dLS} + \text{sLS}/2]/\text{BS}$). It is a measure of the proportion of bone surface upon which new mineralized bone was being deposited during the period of tetracycline labeling.	

End point type	Secondary
End point timeframe:	
Baseline, 48 weeks	

End point values	Primary Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	10 ^[5]			
Units: percent of mineralizing surface				
arithmetic mean (standard deviation)	1.32 (± 4.365)			

Notes:

[5] - subjects who had non-missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in BFR/BS at Week 48

End point title	Change From Baseline in BFR/BS at Week 48
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End point description:

BFR/BS: amount of new bone formed in unit time per unit of bone surface; calculated by multiplying MS/BS by the MAR.

MS/BS: percent of bone surface that displays a tetracycline label reflecting active mineralization; calculated as the double-labeled surface plus one half of the single-labeled surface and is expressed as a function of total bone surface ($[dLS + sLS/2]/BS$). It is a measure of the proportion of bone surface upon which new mineralized bone was being deposited during the period of tetracycline labeling. MAR: linear rate of new bone deposition; mean distance between the double labels, divided by the time interval between them.

End point type	Secondary
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End point timeframe:

Baseline, 48 weeks

End point values	Primary Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	6 ^[6]			
Units: $\mu m^3/\mu m^2/year$				
arithmetic mean (standard deviation)	-4.90 (± 27.356)			

Notes:

[6] - subjects with non-missing results.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in BFR/OS at Week 48

End point title	Change From Baseline in BFR/OS at Week 48
End point description: BFR/OS: bone formation rate to osteoid surface ratio, related to the Aj.AR (amount of new bone created [bone formation rate over the entire osteoid surface]).	
End point type	Secondary
End point timeframe: Baseline, 48 weeks	

End point values	Primary Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	4 ^[7]			
Units: $\mu\text{m}^3/\mu\text{m}^2/\text{year}$				
arithmetic mean (standard deviation)	-1557.25 ($\pm$ 3139.075)			

Notes:

[7] - subjects with non-missing results

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in BFR/BV at Week 48

End point title	Change From Baseline in BFR/BV at Week 48
End point description: BFR/BV: equivalent to bone turnover rate.	
End point type	Secondary
End point timeframe: Baseline, 48 weeks	

End point values	Primary Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	6 ^[8]			
Units: percentage of bone turnover/year				
arithmetic mean (standard deviation)	-13.50 ($\pm$ 32.904)			

Notes:

[8] - subjects with non-missing results

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Mean Serum Phosphorus Levels Above the LLN at the End of the Dosing Cycle Between Baseline and Week 24

End point title	Percentage of Participants Achieving Mean Serum Phosphorus
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End point description:

The LLN was defined as 2.5 mg/dL (0.81 mmol/L). The 95% CI was calculated using Wilson score method.

End point type	Secondary
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End point timeframe:

Baseline, up to 24 weeks

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: percentage of subjects				
number (confidence interval 95%)	78.6 (52.4 to 92.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change of Serum Phosphorus Levels at the Mid-Point of Dosing Cycle, as Averaged Across Dose Cycles Between Baseline and Week 24

End point title	Mean Change of Serum Phosphorus Levels at the Mid-Point of Dosing Cycle, as Averaged Across Dose Cycles Between Baseline and Week 24
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End point description:

End point type	Secondary
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End point timeframe:

Baseline, up to 24 weeks

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: mg/dL				
arithmetic mean (standard deviation)	1.07 (± 0.300)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change of Serum Phosphorus Levels at the Mid-Point of Dosing Cycle, as Averaged Across Dose Cycles Between Baseline and Week 24

End point title	Percent Change of Serum Phosphorus Levels at the Mid-Point of Dosing Cycle, as Averaged Across Dose Cycles Between Baseline and Week 24
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End point description:

End point type	Secondary
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End point timeframe:

Baseline, up to 24 weeks

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: percent change of serum phosphorus level				
arithmetic mean (standard deviation)	50.39 (± 19.942)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change of Serum Phosphorus Levels at the End of Dosing Cycle, as Averaged Across Dose Cycles Between Baseline and Week 24

End point title	Mean Change of Serum Phosphorus Levels at the End of Dosing Cycle, as Averaged Across Dose Cycles Between Baseline and Week 24
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End point description:

End point type	Secondary
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End point timeframe:

Baseline, up to 24 weeks

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: mg/dL				
arithmetic mean (standard deviation)	0.46 (± 0.303)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change of Serum Phosphorus Levels at the End of Dosing Cycle, as Averaged Across Dose Cycles Between Baseline and Week 24

End point title	Percentage Change of Serum Phosphorus Levels at the End of Dosing Cycle, as Averaged Across Dose Cycles Between Baseline and Week 24
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End point description:

End point type	Secondary
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End point timeframe:

Baseline, up to 24 weeks

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: percent change of serum phosphorus level				
arithmetic mean (standard deviation)	23.32 ($\pm$ 19.836)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time-Adjusted Area Under the Curve (AUC) of Serum Phosphorus Between Baseline and Week 24

End point title	Time-Adjusted Area Under the Curve (AUC) of Serum Phosphorus Between Baseline and Week 24
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End point description:

End point type	Secondary
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End point timeframe:

Baseline, up to 24 weeks

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: mg/dL				
arithmetic mean (standard deviation)	3.023 ($\pm$ 0.2716)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Change From Baseline Over Time in Serum 1,25(OH)2D
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End point description:

End point type	Secondary
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End point timeframe:

Baseline, Week 1, Week 2, Week 4, Week 20, Week 21, Week 22, Week 24, Week 48, Week 60, Week 70, Week 72, Week 84, Week 94, Week 96, Week 108, Week 120, Week 132

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	12 ^[9]			
Units: pg/mL				
least squares mean (standard error)				
Week 1; n=12	107.75 (± 15.964)			
Week 2; n=12	48.41 (± 7.397)			
Week 4; n=12	13.58 (± 3.435)			
Week 20; n=12	-1.34 (± 3.617)			
Week 21; n=12	31.75 (± 5.233)			
Week 22; n=11	11.50 (± 4.060)			
Week 24; n=8	-3.04 (± 4.891)			
Week 48; n=11	-1.72 (± 4.190)			
Week 60; n=11	-5.73 (± 3.395)			
Week 70; n=11	3.36 (± 3.987)			
Week 72; n=11	-5.55 (± 2.895)			
Week 84; n=11	-5.55 (± 2.962)			
Week 94; n=11	9.63 (± 4.239)			
Week 96; n=11	-6.09 (± 2.403)			
Week 108; n=7	0.02 (± 4.714)			
Week 120; n=2	1.45 (± 4.197)			

Week 132; n=1	-1.69 ($\pm$ 1.993)			
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Notes:

[9] - subjects with non-missing results at given time point

Attachments (see zip file)	Statistical Analysis Change From Baseline Over Time in Serum
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Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in 24-Hour Urinary Phosphorus

End point title	Change From Baseline Over Time in 24-Hour Urinary Phosphorus
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End point description:

End point type	Secondary
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End point timeframe:

Baseline, Week 12, Week 24, Week 36, Week 48, Week 72, Week 96, End of Study II (up to Week 141)

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	12 ^[10]			
Units: g/24 hours				
least squares mean (standard error)				
Week 12; n=11	0.10 ($\pm$ 0.128)			
Week 24; n=12	-0.04 ($\pm$ 0.075)			
Week 36; n=12	-0.01 ($\pm$ 0.059)			
Week 48; n=11	-0.04 ($\pm$ 0.076)			
Week 72; n=11	0.00 ($\pm$ 0.096)			
Week 96; n=9	-0.13 ($\pm$ 0.082)			
EOSII; n=5	-0.07 ($\pm$ 0.171)			

Notes:

[10] - n=subjects with non-missing results at given time point

Attachments (see zip file)	Statistical Analysis Change From Baseline Over Time in 24-
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Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in TmP/GFR

End point title	Change From Baseline Over Time in TmP/GFR
End point description:	
TmP/GFR: ratio of renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate.	
End point type	Secondary
End point timeframe:	
Baseline, Week 2, Week 4, Week 12, Week 22, Week 24, Week 48, Week 60, Week 72, Week 84, Week 96, EOSII (up to Week 141)	

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	13 ^[11]			
Units: mg/dL				
least squares mean (standard error)				
Week 2; n=13	1.76 (± 0.136)			
Week 4; n=13	0.78 (± 0.097)			
Week 12; n=13	0.58 (± 0.122)			
Week 22; n=13	0.87 (± 0.064)			
Week 24; n=13	0.44 (± 0.101)			
Week 48; n=13	0.20 (± 0.097)			
Week 60; n=13	0.30 (± 0.171)			
Week 72; n=12	0.28 (± 0.127)			
Week 84; n=13	0.39 (± 0.136)			
Week 96; n=13	0.29 (± 0.097)			
EOSII; n=8	0.21 (± 0.068)			

Notes:

[11] - n=subjects with non-missing results at given time point

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

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in TRP

End point title	Change From Baseline Over Time in TRP
End point description:	
TRP: tubular reabsorption of phosphate.	
End point type	Secondary
End point timeframe:	
Baseline, Week 2, Week 4, Week 12, Week 22, Week 24, Week 48, Week 60, Week 72, Week 84, Week 96, EOSII (up to Week 141)	

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	14 ^[12]			
Units: fraction of phosphorus reabsorbed				
least squares mean (standard error)				
Week 2; n=14	0.07 (± 0.005)			
Week 4; n=14	0.03 (± 0.013)			
Week 12; n=13	0.01 (± 0.013)			
Week 22; n=12	0.04 (± 0.007)			
Week 24; n=14	0.01 (± 0.015)			
Week 48; n=13	-0.00 (± 0.021)			
Week 60; n=13	0.03 (± 0.016)			
Week 72; n=13	-0.02 (± 0.035)			
Week 84; n=13	0.02 (± 0.019)			
Week 96; n=13	0.02 (± 0.014)			
EOSII; n=8	0.01 (± 0.011)			

Notes:

[12] - n=subjects with an assessment at given time point

Attachments (see zip file)	Statistical Analysis Change From Baseline Over Time in TRP.
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Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in P1NP

End point title	Change From Baseline Over Time in P1NP
End point description:	P1NP: procollagen type 1 N-propeptide.
End point type	Secondary
End point timeframe:	Baseline, Week 12, Week 24, Week 48, Week 72, Week 96, EOSII (up to Week 141)

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	14 ^[13]			
Units: ng/mL				
least squares mean (standard error)				
Week 12; n=13	99.18 (± 11.403)			
Week 24; n=14	104.33 (± 11.153)			
Week 48; n=13	52.49 (± 11.554)			
Week 72; n=13	37.29 (± 12.294)			

Week 96; n=13	29.29 ($\pm$ 13.321)			
EOSII; n=8	2.14 ($\pm$ 10.105)			

Notes:

[13] - n=subjects with non-missing results at given time point

Attachments (see zip file)	Statistical Analysis Change From Baseline Over Time in P1NP.
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Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline Over Time in P1NP

End point title	Percent Change From Baseline Over Time in P1NP
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End point description:

End point type	Secondary
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End point timeframe:

Baseline, Week 12, Week 24, Week 48, Week 72, Week 96, EOSII (up to Week 141)

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	14 ^[14]			
Units: percent change in P1NP				
least squares mean (standard error)				
Week 12; n=13	133.08 ($\pm$ 13.680)			
Week 24; n=14	137.80 ($\pm$ 15.741)			
Week 48; n=14	76.86 ($\pm$ 14.114)			
Week 72; n=13	50.46 ($\pm$ 13.659)			
Week 96; n=13	41.36 ($\pm$ 11.566)			
EOSII; n=8	26.20 ($\pm$ 9.919)			

Notes:

[14] - n=subjects with non-missing results at given time point

Attachments (see zip file)	Statistical Analysis Percent Change From Baseline Over Time in
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Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in CTx

End point title	Change From Baseline Over Time in CTx
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End point description:	
CTx: carboxy-terminal cross-linked telopeptide of type I collagen.	
End point type	Secondary
End point timeframe:	
Baseline, Week 12, Week 24, Week 48, Week 72, Week 96, EOSII (up to Week 141)	

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	14 ^[15]			
Units: pg/mL				
least squares mean (standard error)				
Week 12; n=14	464.84 (± 61.696)			
Week 24; n=14	404.13 (± 55.948)			
Week 48; n=13	175.13 (± 44.022)			
Week 72; n=13	143.11 (± 92.503)			
Week 96; n=13	76.80 (± 57.357)			
EOSII; n=8	-41.32 (± 83.144)			

Notes:

[15] - n=subjects with non-missing results at given time point

Attachments (see zip file)	Statistical Analysis Change From Baseline Over Time in CTx.
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Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline Over Time in CTx

End point title	Percent Change From Baseline Over Time in CTx
End point description:	
CTx: carboxy-terminal cross-linked telopeptide of type I collagen.	
End point type	Secondary
End point timeframe:	
Baseline, Week 12, Week 24, Week 48, Week 72, Week 96, EOSII (up to Week 141)	

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	14 ^[16]			
Units: percent change in CTx				
least squares mean (standard error)				

Week 12; n=14	89.68 (± 13.316)			
Week 24; n=14	70.17 (± 10.341)			
Week 48; n=13	35.86 (± 7.396)			
Week 72; n=13	34.00 (± 14.016)			
Week 96; n=13	25.86 (± 8.461)			
EOSII; n=8	17.88 (± 9.284)			

Notes:

[16] - n=subjects with non-missing results at given time point

Attachments (see zip file)	Statistical Analysis Percent Change From Baseline Over Time in
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Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in BALP

End point title	Change From Baseline Over Time in BALP
End point description: BALP: bone-specific alkaline phosphatase.	
End point type	Secondary
End point timeframe: Baseline, Week 12, Week 24, Week 48, Week 72, Week 96, EOSII (up to Week 141)	

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	13 ^[17]			
Units: µg/L				
least squares mean (standard error)				
Week 12; n=13	10.93 (± 3.547)			
Week 24; n=13	5.82 (± 2.980)			
Week 48; n=13	4.50 (± 3.990)			
Week 72; n=12	3.13 (± 2.435)			
Week 96; n=16	1.14 (± 2.028)			
EOSII; n=8	-5.80 (± 3.396)			

Notes:

[17] - n=subjects with non-missing results at given time point

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline Over Time in BALP

End point title	Percent Change From Baseline Over Time in BALP
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End point description:

BALP: bone-specific alkaline phosphatase.

End point type	Secondary
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End point timeframe:

Baseline, Week 12, Week 24, Week 48, Week 72, Week 96, EOSII (up to Week 141)

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	13 ^[18]			
Units: percent change in BALP				
least squares mean (standard error)				
Week 12; n=13	52.54 (± 15.999)			
Week 24; n=24	31.37 (± 11.808)			
Week 48; n=13	24.35 (± 17.630)			
Week 72; n=12	15.13 (± 13.431)			
Week 96; n=13	6.92 (± 10.387)			
EOSII; n=8	-27.30 (± 12.767)			

Notes:

[18] - n=subjects with non-missing results at given time point

Attachments (see zip file)

Statistical Analysis Percent Change From Baseline Over Time in

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Week 0 to EOSII (up to Week 141). Mean (SE) duration of exposure to study drug was 716 (35.1) days

Adverse event reporting additional description:

Treatment-emergent adverse events are presented.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Burosumab
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Reporting group description:

1.0 mg/kg burosumab monthly (Q4W), calculated based on baseline weight and up to a maximum dose of 90 mg.

Serious adverse events	Burosumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 14 (28.57%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Splenic Rupture			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Migraine			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Paraesthesia			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Obstruction Gastric			
subjects affected / exposed	1 / 14 (7.14%)		
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		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 14 (100.00%)		
Vascular disorders			
Hot Flush			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
General disorders and administration site conditions			
Application Site Rash			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Asthenia			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		
Chest Discomfort			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Chest Pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Drug Withdrawal Syndrome			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	4		
Influenza Like Illness			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	4		
Injection Site Bruising			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Injection Site Pain			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Injection Site Pruritus			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Injection Site Reaction			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	16		
Injection Site Urticaria			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	3		
Local Swelling			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Nodule			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Oedema Peripheral			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Pain			

subjects affected / exposed occurrences (all)	5 / 14 (35.71%) 5		
Peripheral Swelling subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Pyrexia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 3		
Immune system disorders Drug Hypersensitivity subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2		
Seasonal Allergy subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Ovarian Cyst subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Uterine Haemorrhage subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 6		
Nasal Congestion subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 5		
Oropharyngeal Pain subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 6		
Productive Cough			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Respiratory Tract Congestion			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Sinus Congestion			
subjects affected / exposed	4 / 14 (28.57%)		
occurrences (all)	4		
Sinus Perforation			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 14 (28.57%)		
occurrences (all)	5		
Confusional State			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Depressive Symptom			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	5		
Irritability			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Nightmare			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Investigations			
Blood 25-Hydroxycholecalciferol			
Decreased			

subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Blood Calcium Decreased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Blood Cholesterol Increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Blood Glucose Increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Blood Pressure Increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Blood Parathyroid Hormone Increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Blood Testosterone Decreased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Blood Uric Acid Increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Ejection Fraction Decreased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Eosinophil Count Increased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Ultrasound Kidney Abnormal			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Vitamin D Decreased			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		

Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Contusion			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	6		
Incision Site Pruritus			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Injection Related Reaction			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Ligament Sprain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Post Procedural Swelling			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Procedural Pain			
subjects affected / exposed	7 / 14 (50.00%)		
occurrences (all)	10		
Stress Fracture			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Sunburn			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Tooth Fracture			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		
Tooth Injury			

subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Pericarditis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	3		
Dysaesthesia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	4		
Hypoaesthesia			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	5		
Migraine			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	3		
Motor Dysfunction			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Nerve Compression			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Neuralgia			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	4		
Restless Legs Syndrome			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Sciatica			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Somnolence			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Syncope			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal Discomfort			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		
Abdominal Distension			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Abdominal Pain			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	6		
Abdominal Pain Upper			

subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	4		
Constipation			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	7		
Diarrhoea			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		
Dyspepsia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Gastrooesophageal Reflux Disease			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Gingival Pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Gingival Swelling			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		
Irritable Bowel Syndrome			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Mouth Ulceration			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Oral Pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Periodontal Disease			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Toothache			

subjects affected / exposed	4 / 14 (28.57%)		
occurrences (all)	5		
Vomiting			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Vomiting Projectile			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hepatobiliary disorders			
Hepatic Steatosis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Eczema			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Pruritus Generalised			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	3		
Rash			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Skin Irritation			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Xanthoma			

subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 3		
Renal and urinary disorders			
Glycosuria			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Urinary Retention			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 14 (35.71%)		
occurrences (all)	17		
Arthritis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Back Pain			
subjects affected / exposed	6 / 14 (42.86%)		
occurrences (all)	7		
Bone Pain			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	5		
Fibromyalgia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Joint Instability			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Joint Swelling			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		
Limb Discomfort			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Muscle Atrophy			

subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Muscle Spasms			
subjects affected / exposed	4 / 14 (28.57%)		
occurrences (all)	8		
Muscular Weakness			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Musculoskeletal Chest Pain			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Musculoskeletal Pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Musculoskeletal Stiffness			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Neck Pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Osteoarthritis			
subjects affected / exposed	4 / 14 (28.57%)		
occurrences (all)	4		
Pain In Extremity			
subjects affected / exposed	4 / 14 (28.57%)		
occurrences (all)	6		
Pain In Jaw			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Spinal Pain			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Tendonitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Infections and infestations			

Bronchitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Conjunctivitis Bacterial			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Gingival Abscess			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Gingivitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hordeolum			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	4 / 14 (28.57%)		
occurrences (all)	4		
Laryngitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Lice Infestation			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Lung Infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	4 / 14 (28.57%)		
occurrences (all)	8		
Periodontitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Pharyngitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		

Pharyngitis Streptococcal subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2		
Postoperative Wound Infection subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Respiratory Tract Infection Viral subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Root Canal Infection subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Tooth Abscess subjects affected / exposed occurrences (all)	7 / 14 (50.00%) 10		
Sinusitis subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 4		
Tooth Infection subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 3		
Urinary Tract Infection subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2		
Vulvovaginal Mycotic Infection subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2		
Metabolism and nutrition disorders Hyperuricaemia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Hypocalcaemia			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Vitamin D Deficiency			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 March 2016	• Sample Size: The sample size was increased from approximately 10 subjects to approximately 14 subjects. A provision was also added that at least 3 subjects from each sex were to be enrolled. • Study Population: Several changes were made to the inclusion and exclusion criteria (Section 7.3.1) as indicated below: - Inclusion criterion #1 was modified to change the age of eligibility to 18 to 65, inclusive. Previously the age was 25 to 65. - Inclusion criterion #5 was modified to correct a duplicative value of 60 mL/min. The eGFR was to be ≥ 60 mL/min (using the CKD- EPI equation); OR eGFR of 45 to < 60 mL/min at Screening with confirmation that the renal insufficiency was not due to nephrocalcinosis. - Inclusion criterion #6 was updated to add informed consent language for minors enrolled in the study. - Inclusion criterion #9 was updated as follows (bolded text indicates newly added text): "Participants of childbearing potential or with partners of child-bearing potential who have not undergone a total hysterectomy or bilateral salpingo oophorectomy and are sexually active must consent to use two effective methods of contraception as determined by the site investigator (ie, oral hormonal contraceptives, patch hormonal contraceptives, vaginal ring, intrauterine device, physical double-barrier methods, surgical hysterectomy, vasectomy, tubal ligation, or true abstinence) from the period following the signing of the informed consent through 12 weeks after last dose of study drug." - Exclusion criterion #4 was modified to remove "oral" and restrict use of any bisphosphonates in the 2 years prior to Screening. - Additional criteria were inserted to exclude individuals who have used denosumab in the 6 months prior to Screening and teriparatide in the 2 months prior to Screening. These medications were also added to the list of prohibited medications for consistency.
29 March 2016	(continued) - Exclusion criterion #9 (previously #7) was modified to state that patients with serum iPTH ≥ 2.5 times the upper limit of normal (ULN) will be excluded. Previously this value was serum iPTH ≥ 1.5 times ULN. - An addition was made to exclusion criterion #19 to state that patients with a history or allergic reaction or adverse reaction tetracycline or demeclocycline will be excluded. - A provision was added to Exclusion criterion #21 to allow individuals to participate who may had a history of recurrent dental abscesses, which are known to be associated with XLH. • Schedule of Events: The schedule of events was updated to add that serum 1,25(OH)2D would be assayed at Week 24. In addition, post-baseline serum FGF23 assessments were only at Weeks 24 and 48, instead of previously scheduled for Weeks 4, 22, 24, 36, and 48. • Investigational Product: Section 7.4.1 was modified to provide additional flexibility in SC dosing sites; subjects could receive study drug via SC injection to the abdomen, upper arms or thighs. • Study Procedures and Assessments: Section 7.5 and Section 7.5.1.1 were clarified to indicate that tetracycline or demeclocycline could be used for labeling for bone biopsy. In addition, the timing of the tetracycline labeling was clarified: The bone biopsy was performed 5 days after the last dosing day for tetracycline or demeclocycline. The first dose was given on days -20 (20 days prior to Baseline Visit), -19, and -18, and the second dose given on days -8, -7, and -6.

29 March 2016	(continued) • General Assessments: Section 7.5.3 was modified to add that additional genetic testing for mutations in genes consistent with syndromes with clinical and biochemical phenotypic overlap with XLH could be performed if the initial PHEX mutation analysis result was negative or inconclusive and informed consent was provided by the subject. This testing included, but was not necessarily 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). • Safety Assessments: Several changes were made to the safety assessments. • a. Blood pressure (Section 7.5.3.2) was obtained twice (2 measurements separated by 15 minutes) at indicted clinic visits. • b. Section 7.5.3.6 was updated to indicate echocardiograms (ECHO) would no longer be read locally at the study site. All ECHO assessments were centrally read. • c. Section 7.5.3.8 (Table 7.5.3.8.1) was updated to add assessment of lipase in all subjects. • Ethics: Section 8.1.2 was updated to state that both the sponsor and investigator would make every effort to assure the study described in this protocol was conducted in full conformance with those principles, current FDA regulations, ICH Good Clinical Practices (GCP) guidelines, and local ethical and regulatory requirements. • 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. • Safety Contact Information: The medical monitor information for this study was updated in Section 8.5.4.7.
07 October 2016	• Overall Study Design: A 48-week Treatment Extension Period was added to the study design. The corresponding Schedule of Events for this period is provided in Table 2.3. • Primary Analysis: Section 7.6.4.1 was narrowed to focus on osteoid volume (osteoid volume/bone volume, OV/BV) as the primary efficacy endpoint. The other histomorphometric parameters were specified as secondary endpoints under Section 7.6.4.2. • Contraception Methods: The list of examples of highly effective contraception methods was updated in Section 7.5.3.9. • Schedule of Events: The frequency of pregnancy testing in females with child bearing potential was increased to every 4 weeks. • End of Study: Section 7.4.3.1 was updated to clarify that the End of Study is the last subject's Safety Follow-up Phone Call (12 weeks ($\pm$ 5 days) after the Final Dose). • Exploratory Endpoints: In Section 7.6.4.4, language describing the exploratory endpoint of pseudofracture healing was modified to read: Healing of pre-existing pseudofractures and/or Looser zones, as defined by skeletal survey at baseline and subsequent targeted radiography. Previously this endpoint had indicated "time to healing" of pre-existing pseudofractures and/or Looser zones. An additional change was made in Section 7.6.4.4 to clarify that the endpoints for Brief Fatigue Inventory (BFI) will be based on BFI question 3-Worst Fatigue, and a BFI Global Fatigue score calculated by averaging all 9 items on the BFI, rather than separate BFI Severity and BFI Interference scores. • Study Objectives: In Section 6, the Pharmacokinetics Objective has been clarified as: Assess the PK of burosumab throughout the dosing cycle following the first doses and at steady state. It had previously stated, "...following single and multiple doses."
07 October 2016	• Genetic Testing: In Section 7.5.3, one gene, for Raine Syndrome (FAM20C), has been added to the list of genes that may be assessed for mutation in subjects whose initial PHEX mutation analysis is negative or inconclusive and who provide informed consent. The wording "not necessarily limited to" regarding the list of genes has been removed.

29 August 2017	• Study Design and Duration: In Sections 7.1 and 7.4.3.1, a second Treatment Extension Period II that included an approximately 45 additional weeks of burosumab treatment, until end of September 2018, was added for subjects enrolled at sites in the US only. The maximum study duration was changed approximately 149 weeks. • Safety Monitoring: In Section 8.5.4.1, Safety Follow-up telephone calls (TCs) over an interval of up to 8 weeks following the End of Study or Early Termination Visit were added for subjects not immediately continuing burosumab treatment under commercial use or another mechanism upon completion of study drug treatment or early withdrawal from this study. Section 7.6.7 and Section 8.5.4.6 were updated to describe safety monitoring during the Treatment Extension Periods I and II of the study. The DMC monitored safety through Week 48. During the Treatment Extension Periods I and II, safety was monitored on an ongoing basis by the Study Safety Review Team (SSRT), an internal safety review team defined and in place since the original protocol. • Exploratory Efficacy Endpoint: In Section 7.6.4.4, the exploratory endpoint of healing of pre-existing pseudofractures and/or Looser zones was updated to clarify that it comprises the following components: - the number of active pseudofractures and/or fractures as defined by skeletal survey at baseline and the numbers and percentages of the baseline active pseudofractures/fractures that were healed, partially healed, unchanged, and worsened at post-baseline visits - the number of subjects with baseline active pseudofractures and/or fractures at baseline and the numbers of those subjects who had changes from baseline to healed, partially healed, unchanged, and worsened at post-baseline visits. This was done to reflect the exploratory efficacy endpoints planned for analysis in this study.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported