



## Clinical trial results:

### A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Assess the Efficacy and Safety of KRN23 in Adults with X-linked Hypophosphatemia (XLH)

#### Summary

EudraCT number	2014-005529-11
Trial protocol	GB IE FR DK IT
Global end of trial date	06 December 2018

#### Results information

Result version number	v2 (current)
This version publication date	31 January 2021
First version publication date	20 December 2019
Version creation reason	<ul style="list-style-type: none"><li>• Correction of full data set</li><li>Minor corrections to full data set</li></ul>

#### Trial information

##### Trial identification

Sponsor protocol code	UX023-CL303
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02526160
WHO universal trial number (UTN)	-
Other trial identifiers	na: EMA/902676

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)	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	06 December 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	06 December 2018
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To establish the effect of burosumab treatment compared with placebo on increasing serum phosphorus levels in adults with XLH.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 October 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	United States: 69
Country: Number of subjects enrolled	Japan: 11
Country: Number of subjects enrolled	Korea, Republic of: 7
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	France: 30
Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	Italy: 3

Worldwide total number of subjects	134
EEA total number of subjects	47

Notes:

<b>Subjects enrolled per age group</b>	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	133
From 65 to 84 years	1
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 procedures (SV1). Individuals who successfully passed the initial screening requirements returned for the site for a second Screening visit (SV2) to complete the remaining screening assessments and confirm eligibility.

### Period 1

Period 1 title	Double-Blind (Placebo Controlled) Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

The study was conducted as a randomized, double-blind, placebo-controlled study through Week 24. Double-blind conditions were established so that neither the sponsor, subject, or site personnel involved in study conduct knew the identity of a subject's treatment.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Placebo

Arm description:

Subcutaneous (SC) injection of placebo every 4 weeks (Q4W) for 24 weeks (double-blind placebo-controlled Treatment Period)

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects began treatment with an SC injection of placebo administered Q4W.

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

SC injection of 1.0 mg/kg burosumab Q4W for 24 weeks (double-blind placebo-controlled Treatment Period)

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 drug administered was calculated based on Baseline body weight and a 1.0 mg/kg burosumab dose level (rounded to the nearest 10 mg), up to a maximum dose of 90 mg.

Number of subjects in period 1	Placebo	Burosumab
Started	66	68
Completed	66	67
Not completed	0	1
Consent withdrawn by subject	-	1

## Period 2

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

## Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Placebo -> Burosumab

Arm description:

SC injection of placebo Q4W for 24 weeks (double-blind placebo-controlled Treatment Period), SC injection of burosumab 1 mg/kg Q4W for 24 weeks (open-label Treatment Continuation Period)

Arm type	Placebo
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 drug administered was calculated based on Baseline body weight and a 1.0 mg/kg burosumab dose level (rounded to the nearest 10 mg), up to a maximum dose of 90 mg.

<b>Arm title</b>	Burosumab -> Burosumab
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Arm description:

SC injection of 1.0 mg/kg burosumab Q4W for 24 weeks (double-blind placebo-controlled Treatment Period), SC injection of burosumab 1 mg/kg Q4W for 24 weeks (open-label Treatment Continuation Period)

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 drug administered was calculated based on Baseline body weight and a 1.0 mg/kg burosumab dose level (rounded to the nearest 10 mg), up to a maximum dose of 90 mg.

Number of subjects in period 2	Placebo -> Burosumab	Burosumab -> Burosumab
Started	66	67
Completed	63	63
Not completed	3	4
Consent withdrawn by subject	-	1
Other, not specified	3	3

### Period 3

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Placebo -> Burosumab

Arm description:

SC injection of placebo Q4W for 24 weeks (double-blind placebo-controlled Treatment Period), SC injection of burosumab 1 mg/kg Q4W for 24 weeks (open-label Treatment Continuation Period), SC injection of burosumab 1 mg/kg Q4W for 48 weeks (open label Treatment Extension Period I)

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 drug administered was calculated based on Baseline body weight and a 1.0 mg/kg burosumab dose level (rounded to the nearest 10 mg), up to a maximum dose of 90 mg.

<b>Arm title</b>	Burosumab -> Burosumab
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Arm description:

SC injection of 1.0 mg/kg burosumab Q4W for 24 weeks (double-blind Placebo-controlled Treatment Period), SC injection of burosumab 1 mg/kg Q4W for 24 weeks (open-label Treatment Continuation Period), SC injection of burosumab 1 mg/kg Q4W for 48 weeks (open-label Treatment Extension Period I)

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 drug administered was calculated based on Baseline body weight and a 1.0 mg/kg burosumab dose level (rounded to the nearest 10 mg), up to a maximum dose of 90 mg.

Number of subjects in period 3	Placebo -> Burosumab	Burosumab -> Burosumab
Started	63	63
Completed	60	59
Not completed	3	4
Consent withdrawn by subject	-	1
Death	-	1
Not specified	3	-
Other, not specified	-	1
Lost to follow-up	-	1

#### Period 4

Period 4 title	Treatment Extension Period II
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

#### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Placebo -> Burosumab

#### Arm description:

SC injection of placebo Q4W for 24 weeks (double-blind placebo-controlled Treatment Period), SC injection of burosumab 1 mg/kg Q4W for 24 weeks (open-label Treatment Continuation Period), SC injection of burosumab 1 mg/kg Q4W for 48 weeks (open-label Treatment Extension Period I), and SC injection of burosumab 1 mg/kg Q4W up to 53 weeks (open-label Treatment Extension Period II).

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 drug administered was calculated based on Baseline body weight and a 1.0 mg/kg burosumab dose level (rounded to the nearest 10 mg), up to a maximum dose of 90 mg.

<b>Arm title</b>	Burosumab -> Burosumab
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#### Arm description:

SC injection of 1.0 mg/kg burosumab Q4W for 24 weeks (double-blind placebo-controlled Treatment Period), SC injection of burosumab 1 mg/kg Q4W for 24 weeks (open-label Treatment Continuation Period), SC injection of burosumab 1 mg/kg Q4W for 48 weeks (open-label Treatment Extension Period I), and SC injection of burosumab 1 mg/kg Q4W up to 53 weeks (open-label Treatment Extension Period II).

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

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**Dosage and administration details:**

The amount of drug administered was calculated based on Baseline body weight and a 1.0 mg/kg burosumab dose level (rounded to the nearest 10 mg), up to a maximum dose of 90 mg.

<b>Number of subjects in period 4<sup>[1]</sup></b>	Placebo -> Burosumab	Burosumab -> Burosumab
Started	52	49
Completed	51	49
Not completed	1	0
Other, not specified	1	-

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**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: Treatment Extension Period II (US and EU subjects only).



## Baseline characteristics

### Reporting groups

Reporting group title	Placebo
Reporting group description: Subcutaneous (SC) injection of placebo every 4 weeks (Q4W) for 24 weeks (double-blind placebo-controlled Treatment Period)	
Reporting group title	Burosumab
Reporting group description: SC injection of 1.0 mg/kg burosumab Q4W for 24 weeks (double-blind placebo-controlled Treatment Period)	

Reporting group values	Placebo	Burosumab	Total
Number of subjects	66	68	134
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	38.65 ± 12.756	41.29 ± 11.582	-
Gender categorical Units: Subjects			
Female	43	44	87
Male	23	24	47
Primary Race Units: Subjects			
Asian	9	12	21
Black or African American	3	0	3
White	53	55	108
Other, Not Specified	1	1	2
Ethnicity Units: Subjects			
Hispanic or Latino	5	7	12
Not Hispanic or Latino	61	61	122
Brief Pain Inventory (BPI) Worst Pain Score			
The BPI evaluates the condition of all pain over the previous 24 hours. Question 3 of the short-form BPI (BPI-Q3) asks subjects to rate their pain at its worst in the last 24 hours on a scale of 0 (no pain) to 10 (pain as bad as you can imagine). The baseline BPI Worst Pain is defined as the mean of the BPI Worst Pain for 8 days including the 7 days of diary scores prior to baseline visit and the baseline visit score.			
Units: score on a scale arithmetic mean standard deviation	6.54 ± 1.433	6.81 ± 1.308	-
BPI Pain Severity Score			
The BPI evaluates the condition of all pain over the previous 24 hours. Two dimensions are measured: pain severity (worst, least, average, and now) and the impact of pain on functioning (pain interference with general activity, walking, work, mood, enjoyment of life, relations with others, and sleep). The severity of pain in the last 24 hours is rated on a scale of 0 (no pain) to 10 (pain as bad as you can imagine).			
Units: score on a scale arithmetic mean	4.92	5.18	

standard deviation	± 1.547	± 1.531	-
BPI Pain Interference Score			
The BPI evaluates the condition of all pain over the previous 24 hours. Two dimensions are measured: pain severity (worst, least, average, and now) and the impact of pain on functioning (pain interference with general activity, walking, work, mood, enjoyment of life, relations with others, and sleep). Pain interference in the last 24 hours is rated on a scale of 0 (does not interfere) to 10 (completely interferes).			
Units: score on a scale			
arithmetic mean	4.76	5.23	
standard deviation	± 2.174	± 2.237	-
Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Stiffness Score			
The WOMAC is a 24-item participant-reported questionnaire with two domains, Stiffness (2 questions) and Physical Function (17 questions) over the previous 48 hours. The WOMAC is administered in a 5-point Likert-scale format using descriptors of none, mild, moderate, severe, and extreme corresponding to an ordinal scale of 0-4. Higher scores on the WOMAC indicate worse stiffness and functional limitations. Scores are normalized to a 0-100 metric where 0 was the best health state and 100 the worst.			
Units: score on a scale			
arithmetic mean	61.36	64.71	
standard deviation	± 20.770	± 20.253	-
WOMAC Physical Function Score			
The WOMAC is a 24-item participant-reported questionnaire with two domains, Stiffness (2 questions) and Physical Function (17 questions) over the previous 48 hours. The WOMAC is administered in a 5-point Likert-scale format using descriptors of none, mild, moderate, severe, and extreme corresponding to an ordinal scale of 0-4. Higher scores on the WOMAC indicate worse stiffness and functional limitations. Scores are normalized to a 0-100 metric where 0 was the best health state and 100 the worst.			
Units: score on a scale			
arithmetic mean	43.89	50.79	
standard deviation	± 19.938	± 19.660	-
Brief Fatigue Inventory (BFI) Worst Fatigue Score			
The BFI is a self-reported questionnaire consisting of 9 items related to fatigue rated on a 0 to 10 numerical scale with a recall period of 24 hours. Two dimensions are measured: fatigue severity and the interference of fatigue on daily life (activity, mood, walking ability, work, relations with others, and enjoyment of life). Participants are asked to rate their worst fatigue over the past 24 hours from 0 (no fatigue) to 10 (as bad as you can imagine).			
Units: score on a scale			
arithmetic mean	6.74	6.94	
standard deviation	± 1.526	± 1.657	-
BFI Global Fatigue Score			
The BFI is a self-reported questionnaire consisting of 9 items related to fatigue that are rated on a numerical scale with a recall period of 24 hours. Two dimensions are measured: fatigue severity and the interference of fatigue on daily life (activity, mood, walking ability, work, relations with others, and enjoyment of life). BFI Global Fatigue score was calculated by averaging all 9 items on the BFI. Global scores range from 0 to 10, with higher score indicating worse fatigue severity and interference.			
Units: score on a scale			
arithmetic mean	4.86	5.37	
standard deviation	± 1.932	± 2.044	-
Serum Procollagen Type 1 N- Propeptide (P1NP)			
Subjects with a baseline assessment are n=66, 67 for placebo and burosumab, respectively.			
Units: ng/mL			
arithmetic mean	87.6	87.5	
standard deviation	± 53.41	± 53.60	-
Serum Carboxy-Terminal Cross-Linked Telopeptide of Type I Collagen (CTX)			

Subjects with a baseline assessment are n=66, 67 for placebo and burosumab, respectively.			
Units: pg/mL			
arithmetic mean	719.2	718.4	
standard deviation	± 419.24	± 413.71	-
Serum Bone-Specific Alkaline Phosphatase (BALP)			
Subjects with a baseline assessment: n=66, 66 for placebo and burosumab arms, respectively.			
Units: µg/L			
arithmetic mean	24.6	25.1	
standard deviation	± 17.30	± 21.55	-
Serum Phosphorus			
Units: mmol/L			
arithmetic mean	0.617	0.653	
standard deviation	± 0.1001	± 0.1072	-
Serum 1, 25 (OH) <sub>2</sub> D			
Subjects with a baseline assessment: n=64, 66 for placebo and burosumab arms, respectively.			
Units: pg/mL			
arithmetic mean	33.5	32.4	
standard deviation	± 15.61	± 12.96	-
24-Hour Urinary Phosphorus			
Subjects with a baseline assessment: n=65, 68 for placebo and burosumab arms, respectively.			
Units: g/24hr			
arithmetic mean	0.81	0.72	
standard deviation	± 0.262	± 0.241	-
Ratio of Renal Tubular Maximum Reabsorption Rate of Phosphate to Glomerular Filtration Rate(TmP/GFR)			
Subjects with a baseline assessment: n=64, 66 for placebo and burosumab arms, respectively.			
Units: mg/dL			
arithmetic mean	1.598	1.678	
standard deviation	± 0.3693	± 0.4004	-
Tubular Reabsorption of Phosphate (TRP)			
Subjects with a baseline assessment: n=64, 67 for placebo and burosumab arms, respectively.			
Units: fraction of phosphate reabsorbed			
arithmetic mean	0.812	0.807	
standard deviation	± 0.0842	± 0.0832	-

## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description: Subcutaneous (SC) injection of placebo every 4 weeks (Q4W) for 24 weeks (double-blind placebo-controlled Treatment Period)	
Reporting group title	Burosumab
Reporting group description: SC injection of 1.0 mg/kg burosumab Q4W for 24 weeks (double-blind placebo-controlled Treatment Period)	
Reporting group title	Placebo -> Burosumab
Reporting group description: SC injection of placebo Q4W for 24 weeks (double-blind placebo-controlled Treatment Period), SC injection of burosumab 1 mg/kg Q4W for 24 weeks (open-label Treatment Continuation Period)	
Reporting group title	Burosumab -> Burosumab
Reporting group description: SC injection of 1.0 mg/kg burosumab Q4W for 24 weeks (double-blind placebo-controlled Treatment Period), SC injection of burosumab 1 mg/kg Q4W for 24 weeks (open-label Treatment Continuation Period)	
Reporting group title	Placebo -> Burosumab
Reporting group description: SC injection of placebo Q4W for 24 weeks (double-blind placebo-controlled Treatment Period), SC injection of burosumab 1 mg/kg Q4W for 24 weeks (open-label Treatment Continuation Period), SC injection of burosumab 1 mg/kg Q4W for 48 weeks (open label Treatment Extension Period I)	
Reporting group title	Burosumab -> Burosumab
Reporting group description: SC injection of 1.0 mg/kg burosumab Q4W for 24 weeks (double-blind Placebo-controlled Treatment Period), SC injection of burosumab 1 mg/kg Q4W for 24 weeks (open-label Treatment Continuation Period), SC injection of burosumab 1 mg/kg Q4W for 48 weeks (open-label Treatment Extension Period I)	
Reporting group title	Placebo -> Burosumab
Reporting group description: SC injection of placebo Q4W for 24 weeks (double-blind placebo-controlled Treatment Period), SC injection of burosumab 1 mg/kg Q4W for 24 weeks (open-label Treatment Continuation Period), SC injection of burosumab 1 mg/kg Q4W for 48 weeks (open label Treatment Extension Period I), and SC injection of burosumab 1 mg/kg Q4W up to 53 weeks (open-label Treatment Extension Period II).	
Reporting group title	Burosumab -> Burosumab
Reporting group description: SC injection of 1.0 mg/kg burosumab Q4W for 24 weeks (double-blind placebo-controlled Treatment Period), SC injection of burosumab 1 mg/kg Q4W for 24 weeks (open-label Treatment Continuation Period), SC injection of burosumab 1 mg/kg Q4W for 48 weeks (open-label Treatment Extension Period I), and SC injection of burosumab 1 mg/kg Q4W up to 53 weeks (open-label Treatment Extension Period II).	
Subject analysis set title	Primary Analysis Set-Placebo
Subject analysis set type	Full analysis
Subject analysis set description: The Primary Analysis Set included all randomized subjects who received at least 1 dose of study drug during the Placebo-Controlled Treatment Period.	
Subject analysis set title	Primary Analysis Set-Burosumab
Subject analysis set type	Full analysis
Subject analysis set description: The Primary Analysis Set included all randomized subjects who received at least 1 dose of study drug during the Placebo-Controlled Treatment Period.	

## Primary: Percentage of Subjects Who Achieved Mean Serum Phosphorus Above the Lower Limit of Normal (LLN; 2.5 mg/dL [0.81 mmol/L]) Across Midpoints of Dose Intervals Through Week 24

End point title	Percentage of Subjects Who Achieved Mean Serum Phosphorus Above the Lower Limit of Normal (LLN; 2.5 mg/dL [0.81 mmol/L]) Across Midpoints of Dose Intervals Through Week 24
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End point description:

End point type	Primary
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End point timeframe:

Baseline through Week 24

End point values	Primary Analysis Set-Placebo	Primary Analysis Set-Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66	68		
Units: percentage of subjects				
arithmetic mean (confidence interval 95%)	7.6 (3.3 to 16.5)	92.6 (83.9 to 96.8)		

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Primary Analysis Set-Placebo v Primary Analysis Set-Burosumab
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[1]</sup>
Method	Cochran-Mantel-Haenszel

Notes:

[1] - The p-value is from Cochran-Mantel-Haenszel (CMH) testing for association between achieving mean serum phosphorus levels above the LLN and treatment group, adjusting for the actual randomization stratification of BPI Average Pain and region.

## Secondary: Change From Baseline to Week 24 in BPI Worst Pain Score

End point title	Change From Baseline to Week 24 in BPI Worst Pain Score
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End point description:

The BPI evaluates the condition of all pain over the previous 24 hours. Two dimensions are measured: pain severity (worst, least, average, and now) and the impact of pain on functioning (pain interference with general activity, walking, work, mood, enjoyment of life, relations with others, and sleep). Question 3 of the short-form BPI (BPI-Q3) asks subjects to rate their pain at its worst in the last 24 hours on a scale of 0 (no pain) to 10 (pain as bad as you can imagine).

From the generalized estimating equation (GEE) model, which includes the change from Baseline for the endpoint of interest as the dependent variable; region, visit, treatment, actual randomization stratification (not included for analysis of BPI Worst Pain), and visit by treatment as fixed factors; and Baseline value for the endpoint of interest as a covariate, with compound symmetry covariance structure.

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	Placebo	Burosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	68		
Units: score on a scale				
least squares mean (standard error)	-0.32 ( $\pm$ 0.222)	-0.79 ( $\pm$ 0.211)		

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: placebo vs burosumab	
Comparison groups	Placebo v Burosumab
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0919 [2]
Method	GEE
Parameter estimate	Least squares (LS) mean difference
Point estimate	-0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.08
Variability estimate	Standard error of the mean
Dispersion value	0.275

Notes:

[2] - Prespecified significance level for test after Hochberg adjustment: 0.05

## Secondary: Change From Baseline to Week 24 in WOMAC Stiffness Score

End point title	Change From Baseline to Week 24 in WOMAC Stiffness Score
End point description: <p>The WOMAC is a 24-item participant-reported questionnaire with two domains, Stiffness (2 questions) and Physical Function (17 questions) over the previous 48 hours. The WOMAC is administered in a 5-point Likert-scale format using descriptors of none, mild, moderate, severe, and extreme corresponding to an ordinal scale of 0-4. Higher scores on the WOMAC indicate worse stiffness and functional limitations. Scores are normalized to a 0-100 metric where 0 was the best health state and 100 the worst.</p> <p>The GEE Estimates are from the GEE model which includes the change from baseline for WOMAC Stiffness as the dependent variable, region, visit, treatment, actual randomization stratification and visit by treatment as fixed factors, and baseline of WOMAC Stiffness as a covariate, with compound symmetry covariance structure.</p>	
End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	Burosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	68		
Units: score on a scale				
least squares mean (standard error)	0.46 ( $\pm$ 3.139)	-7.85 ( $\pm$ 3.034)		

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: placebo vs burosumab	
Comparison groups	Placebo v Burosumab
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0106 <sup>[3]</sup>
Method	GEE
Parameter estimate	LS mean difference
Point estimate	-8.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.68
upper limit	-1.94
Variability estimate	Standard error of the mean
Dispersion value	3.251

Notes:

[3] - Prespecified significance level for test after Hochberg adjustment: 0.0167

## Secondary: Change From Baseline to Week 24 in WOMAC Physical Function Score

End point title	Change From Baseline to Week 24 in WOMAC Physical Function Score
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End point description:

The WOMAC is a 24-item participant-reported questionnaire with two domains, Stiffness (2 questions) and Physical Function (17 questions) over the previous 48 hours. The WOMAC is administered in a 5-point Likert-scale format using descriptors of none, mild, moderate, severe, and extreme corresponding to an ordinal scale of 0-4. Higher scores on the WOMAC indicate worse stiffness and functional limitations. Scores are normalized to a 0-100 metric where 0 was the best health state and 100 the worst.

The GEE Estimates are from the GEE model which includes the change from baseline for WOMAC Physical Function as the dependent variable, region, visit, treatment, actual randomization stratification and visit by treatment as fixed factors, and baseline of WOMAC Physical Function as a covariate, with compound symmetry covariance structure.

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	Placebo	Burosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	68		
Units: score on a scale				
least squares mean (standard error)	1.79 ( $\pm$ 2.722)	-3.11 ( $\pm$ 2.553)		

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: placebo vs burosumab	
Comparison groups	Placebo v Burosumab
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0478 <sup>[4]</sup>
Method	GEE
Parameter estimate	LS mean difference
Point estimate	-4.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.76
upper limit	-0.05
Variability estimate	Standard error of the mean
Dispersion value	2.479

Notes:

[4] - Prespecified significance level for test after Hochberg adjustment: 0.025

## Secondary: Change From Baseline Over Time in BPI Worst Pain Score

End point title	Change From Baseline Over Time in BPI Worst Pain Score
End point description:	
<p>The BPI evaluates the condition of all pain over the previous 24 hours. Two dimensions are measured: pain severity (worst, least, average, and now) and the impact of pain on functioning (pain interference with general activity, walking, work, mood, enjoyment of life, relations with others, and sleep). Question 3 of the short-form BPI (BPI-Q3) asks subjects to rate their pain at its worst in the last 24 hours on a scale of 0 (no pain) to 10 (pain as bad as you can imagine).</p> <p>The GEE Estimates are from the GEE model which includes the change from baseline for BPI worst pain as the dependent variable, region, visit, treatment and visit by treatment as fixed factors, and baseline of BPI Worst Pain as a covariate, with compound symmetry covariance structure.</p>	
End point type	Secondary
End point timeframe:	
Baseline, Weeks 12, 24, 36, 48, 72, 96	



End point values	Primary Analysis Set- Placebo	Primary Analysis Set- Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66 <sup>[5]</sup>	68 <sup>[6]</sup>		
Units: score on a scale				
least squares mean (standard error)				
Week 12; n=66, 68	-0.37 (± 0.216)	-0.62 (± 0.208)		
Week 24; n=65, 67	-0.31 (± 0.242)	-0.77 (± 0.228)		
Week 36; n=65, 65	-1.25 (± 0.234)	-0.95 (± 0.228)		
Week 48; n=66, 66	-1.49 (± 0.243)	-1.05 (± 0.230)		
Week 72; n=60, 59	-1.28 (± 0.283)	-1.21 (± 0.316)		
Week 96; 59, 59	-0.99 (± 0.265)	-1.48 (± 0.299)		

Notes:

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

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

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline Over Time in BPI Pain Severity Score

End point title	Change From Baseline Over Time in BPI Pain Severity Score
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End point description:

The BPI evaluates the condition of all pain over the previous 24 hours. Two dimensions are measured: pain severity (worst, least, average, and now) and the impact of pain on functioning (pain interference with general activity, walking, work, mood, enjoyment of life, relations with others, and sleep). The severity of pain in the last 24 hours is rated on a scale of 0 (no pain) to 10 (pain as bad as you can imagine).

The GEE Estimates are from the GEE model which includes the change from baseline for each BPI endpoint as the dependent variable, region, visit, treatment, and visit by treatment as fixed factors, and baseline of each BPI endpoint as a covariate, with compound symmetry covariance structure.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 12, 24, 36, 48, 72, 96

End point values	Primary Analysis Set- Placebo	Primary Analysis Set- Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66 <sup>[7]</sup>	68 <sup>[8]</sup>		
Units: score on a scale				
least squares mean (standard error)				

Week 12; n=66, 68	-0.32 (± 0.166)	-0.43 (± 0.163)		
Week 24; n=65, 67	-0.10 (± 0.211)	-0.53 (± 0.172)		
Week 36; n=65, 65	-0.97 (± 0.214)	-0.62 (± 0.184)		
Week 48; n=66, 66	-1.13 (± 0.205)	-0.79 (± 0.162)		
Week 72; n=60, 59	-1.36 (± 0.216)	-1.24 (± 0.231)		
Week 96; n=59, 59	-1.18 (± 0.195)	-1.42 (± 0.229)		

Notes:

[7] - n=subjects with an assessment

[8] - n=subjects with an assessment

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline Over Time in BPI Pain Interference Score

End point title	Change From Baseline Over Time in BPI Pain Interference Score
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End point description:

The BPI evaluates the condition of all pain over the previous 24 hours. Two dimensions are measured: pain severity (worst, least, average, and now) and the impact of pain on functioning (pain interference with general activity, walking, work, mood, enjoyment of life, relations with others, and sleep). Pain interference in the last 24 hours is rated on a scale of 0 (does not interfere) to 10 (completely interferes).

The GEE Estimates are from the GEE model which includes the change from baseline for each BPI endpoint as the dependent variable, region, visit, treatment, and visit by treatment as fixed factors, and baseline of each BPI endpoint as a covariate, with compound symmetry covariance structure.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 12, 24, 36, 48, 72, 96

End point values	Primary Analysis Set-Placebo	Primary Analysis Set-Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66 <sup>[9]</sup>	68 <sup>[10]</sup>		
Units: score on a scale				
least squares mean (standard error)				
Week 12; n=66, 68	-0.29 (± 0.215)	-0.51 (± 0.207)		
Week 24; n=65, 67	-0.28 (± 0.242)	-0.41 (± 0.207)		
Week 36; n=65, 65	-1.30 (± 0.260)	-0.79 (± 0.221)		
Week 48; n=66, 66	-1.28 (± 0.251)	-1.04 (± 0.235)		
Week 72; n=60, 60	-1.22 (± 0.247)	-1.24 (± 0.263)		
Week 96; n=59, 59	-1.08 (± 0.260)	-1.43 (± 0.234)		

Notes:

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

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

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline Over Time in WOMAC Stiffness Score

End point title	Change From Baseline Over Time in WOMAC Stiffness Score
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End point description:

The WOMAC is a 24-item participant-reported questionnaire with two domains, Stiffness (2 questions) and Physical Function (17 questions) over the previous 48 hours. The WOMAC is administered in a 5-point Likert-scale format using descriptors of none, mild, moderate, severe, and extreme corresponding to an ordinal scale of 0-4. Higher scores on the WOMAC indicate worse stiffness and functional limitations. Scores are normalized to a 0-100 metric where 0 was the best health state and 100 the worst.

The GEE Estimates are from the GEE model which includes the change from baseline for WOMAC Stiffness as the dependent variable, region, visit, treatment, actual randomization stratification and visit by treatment as fixed factors, and baseline of WOMAC Stiffness as a covariate, with compound symmetry covariance structure.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 12, 24, 36, 48, 72, 96, 120, 144

End point values	Primary Analysis Set-Placebo	Primary Analysis Set-Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66 <sup>[11]</sup>	68 <sup>[12]</sup>		
Units: score on a scale				
least squares mean (standard error)				
Week 12; n=66, 68	-1.24 (± 2.929)	-7.86 (± 3.622)		
Week 24; n=65, 67	0.20 (± 3.289)	-8.01 (± 2.968)		
Week 36; n=65, 65	-13.50 (± 3.422)	-12.58 (± 3.411)		
Week 48; n=66, 66	-15.83 (± 3.488)	-16.63 (± 3.302)		
Week 72; n=61, 60	-18.02 (± 3.613)	-15.47 (± 3.111)		
Week 96; n=59, 59	-17.67 (± 3.737)	-15.32 (± 3.577)		
Week 120; n=49, 46	-19.23 (± 3.404)	-20.57 (± 3.371)		
Week 144; n=9, 12	-30.64 (± 4.407)	-25.88 (± 4.501)		

Notes:

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

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline Over Time in WOMAC Physical Function Score

End point title	Change From Baseline Over Time in WOMAC Physical Function Score
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End point description:

The WOMAC is a 24-item participant-reported questionnaire with two domains, Stiffness (2 questions) and Physical Function (17 questions) over the previous 48 hours. The WOMAC is administered in a 5-point Likert-scale format using descriptors of none, mild, moderate, severe, and extreme corresponding to an ordinal scale of 0-4. Higher scores on the WOMAC indicate worse stiffness and functional limitations. Scores are normalized to a 0-100 metric where 0 was the best health state and 100 the worst.

The GEE Estimates are from the GEE model which includes the change from baseline for WOMAC Stiffness as the dependent variable, region, visit, treatment, actual randomization stratification and visit by treatment as fixed factors, and baseline of WOMAC Stiffness as a covariate, with compound symmetry covariance structure.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 12, 24, 36, 48, 72, 96, 120, 144

End point values	Primary Analysis Set-Placebo	Primary Analysis Set-Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66 <sup>[13]</sup>	68 <sup>[14]</sup>		
Units: score on a scale				
least squares mean (standard error)				
Week 12; n=66, 68	-1.40 (± 2.418)	-3.96 (± 1.787)		
Week 24; n=65, 66	1.14 (± 2.531)	-3.45 (± 2.193)		
Week 36; n=63, 65	-5.47 (± 2.694)	-7.14 (± 2.133)		
Week 48; n=66, 66	-7.15 (± 2.801)	-8.42 (± 2.057)		
Week 72; n=61, 60	-8.68 (± 2.835)	-8.66 (± 2.523)		
Week 96; n=59, 59	-8.41 (± 2.752)	-9.02 (± 2.270)		
Week 120; n=49, 46	-11.93 (± 2.685)	-11.98 (± 2.291)		
Week 144; n=9, 11	-19.49 (± 3.892)	-17.67 (± 4.061)		

Notes:

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

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

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline Over Time in BFI Worst Fatigue Score

End point title	Change From Baseline Over Time in BFI Worst Fatigue Score
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End point description:

The BFI is a self-reported questionnaire consisting of 9 items related to fatigue rated on a 0 to 10 numerical scale with a recall period of 24 hours. Two dimensions are measured: fatigue severity and the interference of fatigue on daily life (activity, mood, walking ability, work, relations with others, and enjoyment of life). Participants are asked to rate their worst fatigue over the past 24 hours from 0 (no fatigue) to 10 (as bad as you can imagine).

The GEE Estimates are from the GEE model which includes the change from baseline for each BFI endpoint as the dependent variable, region, visit, treatment, actual randomization stratification and visit by treatment as fixed factors, and baseline of each BFI endpoint as a covariate, with compound symmetry covariance structure.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 12, 24, 36, 48, 72, 96

End point values	Primary Analysis Set-Placebo	Primary Analysis Set-Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66 <sup>[15]</sup>	68 <sup>[16]</sup>		
Units: score on a scale				
least squares mean (standard error)				
Week 12; n=66, 68	-0.53 (± 0.266)	-0.44 (± 0.261)		
Week 24; n=65, 67	-0.45 (± 0.298)	-0.65 (± 0.280)		
Week 36; n=65, 65	-1.23 (± 0.305)	-0.90 (± 0.271)		
Week 48; n=66, 66	-1.21 (± 0.317)	-0.99 (± 0.295)		
Week 72; n=60, 60	-0.79 (± 0.352)	-0.58 (± 0.309)		
Week 96; n=59, 58	-0.82 (± 0.362)	-0.75 (± 0.306)		

Notes:

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

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

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline Over Time in BFI Global Fatigue Score

End point title	Change From Baseline Over Time in BFI Global Fatigue Score
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End point description:

The BFI is a self-reported questionnaire consisting of 9 items related to fatigue that are rated on a numerical scale with a recall period of 24 hours. Two dimensions are measured: fatigue severity and the interference of fatigue on daily life (activity, mood, walking ability, work, relations with others, and enjoyment of life). BFI Global Fatigue score was calculated by averaging all 9 items on the BFI. Global scores range from 0 to 10, with higher score indicating worse fatigue severity and interference.

The GEE Estimates are from the GEE model which includes the change from baseline for each BFI endpoint as the dependent variable, region, visit, treatment, actual randomization stratification and visit by treatment as fixed factors, and baseline of each BFI endpoint as a covariate, with compound symmetry covariance structure.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 12, 24, 36, 48, 72, 96

End point values	Primary Analysis Set- Placebo	Primary Analysis Set- Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66 <sup>[17]</sup>	68 <sup>[18]</sup>		
Units: score on a scale				
least squares mean (standard error)				
Week 12; n=66, 68	-0.14 (± 0.262)	-0.18 (± 0.261)		
Week 24; n= 65, 67	-0.08 (± 0.292)	0.05 (± 0.261)		
Week 36; n=65, 65	-0.69 (± 0.315)	-0.54 (± 0.283)		
Week 48; n=66, 66	-0.75 (± 0.303)	-0.45 (± 0.275)		
Week 72; n=60, 60	-0.72 (± 0.304)	-0.78 (± 0.266)		
Week 96; n=59, 58	-0.86 (± 0.291)	-0.80 (± 0.285)		

Notes:

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

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

## 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
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End point description:

End point type	Secondary
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End point timeframe:

Baseline, Weeks 12, 24, 36, 48, 72, 96

End point values	Primary Analysis Set- Placebo	Primary Analysis Set- Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66 <sup>[19]</sup>	67 <sup>[20]</sup>		
Units: ng/mL				
least squares mean (standard error)				
Week 12; n=66, 67	-1.86 (± 5.958)	96.22 (± 14.264)		
Week 24; n=65, 66	2.95 (± 6.423)	63.50 (± 7.239)		
Week 36; n=65, 64	100.00 (± 10.562)	49.71 (± 6.786)		
Week 48; n=66, 63	85.12 (± 11.037)	40.07 (± 7.292)		
Week 72; n=60, 59	48.98 (± 7.286)	18.04 (± 9.186)		
Week 96; n=59, 59	22.98 (± 7.075)	12.48 (± 8.661)		

Notes:

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

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

### 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, Weeks 12, 24, 36, 48, 72, 96

End point values	Primary Analysis Set- Placebo	Primary Analysis Set- Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66 <sup>[21]</sup>	67 <sup>[22]</sup>		
Units: percentage change				
least squares mean (standard error)				
Week 12; n=66, 67	2.30 (± 6.318)	91.78 (± 10.787)		
Week 24; n=65, 66	7.83 (± 7.076)	72.43 (± 8.519)		
Week 36; n=65, 64	116.39 (± 9.726)	63.58 (± 8.562)		
Week 48; n=66, 63	99.10 (± 11.442)	56.51 (± 8.771)		

Week 72; n=60, 59	72.56 ( $\pm$ 10.055)	38.82 ( $\pm$ 10.225)		
Week 96; n=59, 59	41.62 ( $\pm$ 8.163)	31.04 ( $\pm$ 8.126)		

Notes:

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

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

## 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:

The GEE Estimates are from the GEE model which includes the change from baseline for CTx as the dependent variable, region, visit, treatment, actual randomization stratification and visit by treatment as fixed factors, and baseline of CTx as a covariate, with compound symmetry covariance structure.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 12, 24, 36, 48, 72, 96

End point values	Primary Analysis Set-Placebo	Primary Analysis Set-Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66 <sup>[23]</sup>	67 <sup>[24]</sup>		
Units: pg/mL				
least squares mean (standard error)				
Week 12; n=66, 67	26.96 ( $\pm$ 35.689)	322.09 ( $\pm$ 56.924)		
Week 24; n=64, 66	-4.20 ( $\pm$ 34.835)	184.56 ( $\pm$ 39.213)		
Week 36; n=65, 63	350.89 ( $\pm$ 53.131)	193.50 ( $\pm$ 39.461)		
Week 48; n=66, 63	310.67 ( $\pm$ 45.003)	138.61 ( $\pm$ 37.886)		
Week 72; n=60, 59	178.03 ( $\pm$ 42.702)	51.59 ( $\pm$ 42.863)		
Week 96; n=59, 59	79.04 ( $\pm$ 45.622)	10.84 ( $\pm$ 40.761)		

Notes:

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

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

## 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
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End point description:

The GEE Estimates are from the GEE model which includes the percent change from baseline for CTx as



the dependent variable, region, visit, treatment, actual randomization stratification and visit by treatment as fixed factors, and baseline of CTx as a covariate, with compound symmetry covariance structure.

End point type	Secondary
End point timeframe:	
Baseline, Weeks 12, 24, 36, 48, 72, 96	

End point values	Primary Analysis Set-Placebo	Primary Analysis Set-Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66 <sup>[25]</sup>	67 <sup>[26]</sup>		
Units: percentage change				
least squares mean (standard error)				
Week 12; n=66, 67	9.64 (± 5.671)	45.40 (± 7.267)		
Week 24; n=64, 66	4.75 (± 5.280)	32.48 (± 6.414)		
Week 36; n=65, 63	61.31 (± 10.653)	34.07 (± 6.250)		
Week 48; n=66, 63	50.35 (± 6.464)	28.33 (± 5.354)		
Week 72; n=60, 59	34.78 (± 7.007)	17.09 (± 5.957)		
Week 96; n=59, 59	27.38 (± 7.783)	13.47 (± 5.952)		

Notes:

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

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

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline Over Time in Serum BALP

End point title	Change From Baseline Over Time in Serum BALP
End point description:	
The GEE Estimates are from the GEE model which includes the change from baseline for Bone ALP as the dependent variable, region, visit, treatment, actual randomization stratification and visit by treatment as fixed factors, and baseline of Bone ALP as a covariate, with compound symmetry covariance structure.	
End point type	Secondary
End point timeframe:	
Baseline, Weeks 12, 24, 36, 48, 72, 96	

End point values	Primary Analysis Set- Placebo	Primary Analysis Set- Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66 <sup>[27]</sup>	66 <sup>[28]</sup>		
Units: µg/L				
least squares mean (standard error)				
Week 12; n=66, 66	-2.11 (± 1.529)	6.52 (± 2.832)		
Week 24; n=64, 65	1.03 (± 1.801)	5.70 (± 2.038)		
Week 36; n=65, 63	10.42 (± 2.017)	4.46 (± 1.607)		
Week 48; n=66, 61	6.69 (± 1.929)	0.23 (± 1.830)		
Week 72; n=61, 58	-0.92 (± 1.779)	-3.39 (± 1.739)		
Week 96; n=59, 58	-2.49 (± 1.887)	-2.76 (± 1.640)		

Notes:

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

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

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline Over Time in Serum BALP

End point title	Percent Change From Baseline Over Time in Serum BALP
End point description:	
The GEE Estimates are from the GEE model which includes the percent change from baseline for Bone ALP as the dependent variable, region, visit, treatment, actual randomization stratification and visit by treatment as fixed factors, and baseline of Bone ALP as a covariate, with compound symmetry covariance structure.	
End point type	Secondary
End point timeframe:	
Baseline, Weeks 12, 24, 36, 48, 72, 96	

End point values	Primary Analysis Set- Placebo	Primary Analysis Set- Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66 <sup>[29]</sup>	66 <sup>[30]</sup>		
Units: percent change				
least squares mean (standard error)				
Week 12; n=66, 66	7.85 (± 9.867)	30.29 (± 13.476)		
Week 24; n=64, 65	27.56 (± 10.339)	39.13 (± 10.902)		
Week 36; n=65, 63	64.41 (± 11.669)	43.13 (± 11.473)		
Week 48; n=66, 61	50.65 (± 11.317)	23.46 (± 10.041)		
Week 72; n=61, 58	19.79 (± 11.755)	14.40 (± 11.618)		

Week 96; n=59, 58	16.46 ( $\pm$ 11.027)	21.21 ( $\pm$ 9.688)		
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Notes:

[29] - subjects with an assessment at given time point

[30] - subjects with an assessment at given time point

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline Over Time in Serum Phosphorus

End point title	Change From Baseline Over Time in Serum Phosphorus
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End point description:

The GEE Estimates are from the GEE model which includes the change from baseline for serum phosphorus as the dependent variable, region, visit, treatment, actual randomization stratification and visit by treatment as fixed factors, and baseline of serum phosphorus as a covariate, with compound symmetry covariance structure.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 1, 2, 4, 6, 10, 12, 14, 18, 20, 21, 22, 24, 26, 28, 34, 36, 46, 48, 60, 70, 72, 84, 94, 96, 108, 120, 132, 144

End point values	Primary Analysis Set-Placebo	Primary Analysis Set-Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66 <sup>[31]</sup>	68 <sup>[32]</sup>		
Units: mmol/L				
least squares mean (standard error)				
Week 1; n=60, 61	-0.01 ( $\pm$ 0.024)	0.44 ( $\pm$ 0.031)		
Week 2; n=64, 64	-0.03 ( $\pm$ 0.023)	0.43 ( $\pm$ 0.032)		
Week 4; n=65, 67	-0.03 ( $\pm$ 0.022)	0.27 ( $\pm$ 0.034)		
Week 6; n=65, 65	-0.00 ( $\pm$ 0.023)	0.45 ( $\pm$ 0.036)		
Week 10; n=64, 64	0.01 ( $\pm$ 0.022)	0.37 ( $\pm$ 0.033)		
Week 12; n=64, 68	-0.01 ( $\pm$ 0.023)	0.17 ( $\pm$ 0.032)		
Week 14; n=66, 65	0.02 ( $\pm$ 0.022)	0.32 ( $\pm$ 0.032)		
Week 18; n=62, 68	0.02 ( $\pm$ 0.023)	0.32 ( $\pm$ 0.031)		
Week 20; n=65, 65	-0.01 ( $\pm$ 0.023)	0.18 ( $\pm$ 0.028)		
Week 21; n=61, 65	-0.00 ( $\pm$ 0.024)	0.31 ( $\pm$ 0.033)		
Week 22; n= 65, 64	-0.02 ( $\pm$ 0.022)	0.25 ( $\pm$ 0.033)		
Week 24; n=66, 68	-0.00 ( $\pm$ 0.023)	0.13 ( $\pm$ 0.028)		
Week 26; n=62, 66	0.47 ( $\pm$ 0.035)	0.31 ( $\pm$ 0.032)		
Week 28; n=66, 67	0.28 ( $\pm$ 0.028)	0.18 ( $\pm$ 0.028)		
Week 34; n=65, 62	0.36 ( $\pm$ 0.029)	0.28 ( $\pm$ 0.031)		

Week 36; n=66, 64	0.17 (± 0.026)	0.13 (± 0.027)		
Week 46; n=66, 65	0.31 (± 0.026)	0.27 (± 0.030)		
Week 48; n=66, 64	0.13 (± 0.027)	0.11 (± 0.027)		
Week 60; n=62, 61	0.14 (± 0.028)	0.11 (± 0.028)		
Week 70; n=55, 57	0.30 (± 0.029)	0.30 (± 0.030)		
Week 72; n=61, 60	0.13 (± 0.025)	0.11 (± 0.027)		
Week 84; n=60, 59	0.12 (± 0.025)	0.14 (± 0.027)		
Week 94; n=59, 58	0.25 (± 0.029)	0.30 (± 0.029)		
Week 96; n=60, 59	0.07 (± 0.026)	0.13 (± 0.025)		
Week 108; n=49, 48	0.11 (± 0.028)	0.13 (± 0.031)		
Week 120; n=44, 41	0.09 (± 0.027)	0.13 (± 0.033)		
Week 132; n=19, 19	0.12 (± 0.033)	0.15 (± 0.036)		
Week 144; n=2, 0	0.05 (± 0.064)	99999 (± 99999)		

Notes:

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

[32] - n=subjects with an assessment at given time point; 99999=not applicable (n=0 for this time point)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Change From Baseline Over Time in Serum Phosphorus

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

The GEE Estimates are from the GEE model which includes the percent change from baseline for serum phosphorus as the dependent variable, region, visit, treatment, actual randomization stratification and visit by treatment as fixed factors, and baseline of serum phosphorus as a covariate, with compound symmetry covariance structure.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 1, 2, 4, 6, 10, 12, 14, 18, 20, 21, 22, 24, 26, 28, 34, 36, 46, 48, 60, 70, 72, 84, 94, 96, 108, 120, 132, 144

End point values	Primary Analysis Set-Placebo	Primary Analysis Set-Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66 <sup>[33]</sup>	68 <sup>[34]</sup>		
Units: percentage change				
least squares mean (standard error)				
Week 1; n=60,61	-1.11 (± 3.936)	69.24 (± 4.762)		
Week 2; n=64, 64	-5.91 (± 3.969)	69.39 (± 4.881)		
Week 4; n=65, 67	-4.84 (± 3.792)	42.89 (± 5.325)		
Week 6; n=65, 65	-0.41 (± 3.951)	72.96 (± 5.944)		
Week 10; n=64, 64	2.40 (± 3.680)	59.96 (± 5.356)		
Week 12; n=64, 68	-2.14 (± 3.798)	29.50 (± 5.087)		

Week 14; n=66, 65	3.58 ( $\pm$ 3.691)	52.14 ( $\pm$ 5.194)		
Week 18; n=62, 68	3.93 ( $\pm$ 3.857)	53.22 ( $\pm$ 5.106)		
Week 20; n=65, 65	-1.81 ( $\pm$ 3.759)	31.28 ( $\pm$ 4.472)		
Week 21; n=61, 65	0.21 ( $\pm$ 4.011)	50.59 ( $\pm$ 5.123)		
Week 22; n=65, 64	-3.42 ( $\pm$ 3.709)	40.98 ( $\pm$ 5.196)		
Week 24; n=66, 68	-0.61 ( $\pm$ 3.802)	22.01 ( $\pm$ 4.523)		
Week 26; n=62, 66	78.30 ( $\pm$ 5.993)	51.51 ( $\pm$ 5.204)		
Week 28; n=66, 67	46.07 ( $\pm$ 4.766)	31.32 ( $\pm$ 4.415)		
Week 34; n=65, 62	59.18 ( $\pm$ 4.959)	45.83 ( $\pm$ 4.871)		
Week 36; n=66, 64	28.03 ( $\pm$ 4.424)	22.34 ( $\pm$ 4.256)		
Week 46; n=66, 65	51.49 ( $\pm$ 4.380)	45.39 ( $\pm$ 5.018)		
Week 48; n=66, 64	21.58 ( $\pm$ 4.365)	19.12 ( $\pm$ 4.190)		
Week 60; n=62, 61	22.90 ( $\pm$ 4.338)	19.60 ( $\pm$ 4.436)		
Week 70; n=55, 57	50.22 ( $\pm$ 4.916)	47.81 ( $\pm$ 4.768)		
Week 72; n=61, 60	21.59 ( $\pm$ 4.155)	19.45 ( $\pm$ 4.344)		
Week 84; n=60, 59	21.47 ( $\pm$ 4.089)	23.58 ( $\pm$ 4.200)		
Week 94; n=59, 58	43.67 ( $\pm$ 4.834)	49.36 ( $\pm$ 4.501)		
Week 96; n=60, 59	12.97 ( $\pm$ 4.216)	21.65 ( $\pm$ 3.854)		
Week 108; n=49, 48	19.21 ( $\pm$ 4.665)	23.39 ( $\pm$ 4.749)		
Week 120; n=44, 41	15.13 ( $\pm$ 4.365)	21.50 ( $\pm$ 5.268)		
Week 132; n=19, 19	20.43 ( $\pm$ 5.362)	25.34 ( $\pm$ 5.847)		
Week 144; n=2, 0	5.49 ( $\pm$ 12.212)	99999 ( $\pm$ 99999)		

Notes:

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

[34] - n=subjects with an assessment at given time point; 99999=not applicable (n=0 at this time point)

## 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:

The GEE Estimates are from the GEE model which includes the change from baseline for 1, 25 (OH)2 D as the dependent variable, region, visit, treatment, actual randomization stratification and visit by treatment as fixed factors, and baseline of 1, 25 (OH)2 D as a covariate, with compound symmetry covariance structure.

End point type	Secondary
End point timeframe:	
Baseline, Weeks 1, 2, 4, 20, 21, 22, 46, 48, 60, 70, 72, 84, 94, 96, 108, 120, 132, 144	

End point values	Primary Analysis Set- Placebo	Primary Analysis Set- Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64 <sup>[35]</sup>	66 <sup>[36]</sup>		
Units: pg/mL				
least squares mean (standard error)				
Week 1; n=58, 59	2.04 (± 2.251)	87.23 (± 5.500)		
Week 2; n=63, 65	1.40 (± 2.113)	58.20 (± 3.931)		
Week 4; n=63, 66	2.61 (± 2.300)	20.55 (± 2.828)		
Week 20; n=64, 63	2.88 (± 2.163)	8.11 (± 2.294)		
Week 21; n=59, 64	3.09 (± 2.177)	33.95 (± 3.019)		
Week 22; n=64, 65	3.45 (± 2.289)	26.10 (± 2.952)		
Week 46; n=64, 64	25.23 (± 2.576)	23.08 (± 3.243)		
Week 48; n=64, 63	10.50 (± 2.418)	7.24 (± 2.449)		
Week 60; n=59, 60	9.29 (± 2.336)	5.69 (± 2.583)		
Week 70; n=54, 60	24.20 (± 2.529)	18.82 (± 2.486)		
Week 72; n=59, 58	7.12 (± 2.424)	5.52 (± 2.607)		
Week 84; n=58, 57	5.13 (± 2.388)	1.16 (± 2.549)		
Week 94; n=57, 58	18.96 (± 2.655)	15.26 (± 2.502)		
Week 96; n=56, 58	3.43 (± 2.348)	1.95 (± 2.356)		
Week 108; n=48, 48	4.76 (± 2.349)	4.29 (± 2.672)		
Week 120; n=43, 42	4.64 (± 2.496)	5.37 (± 2.935)		
Week 132; n=18, 19	4.08 (± 3.142)	8.05 (± 4.227)		
Week 144; n=2, 0	-0.38 (± 4.677)	99999 (± 99999)		

Notes:

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

[36] - n=subjects with an assessment at given time point; 99999=not applicable (n=0 for this time point)

## Statistical analyses

No statistical analyses for this end point

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

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

The GEE Estimates are from the GEE model which includes the percent change from baseline for 1, 25 (OH)2 D as the dependent variable, region, visit, treatment, actual randomization stratification and visit

by treatment as fixed factors, and baseline of 1, 25 (OH)2 D as a covariate, with compound symmetry covariance structure.

End point type	Secondary
End point timeframe:	
Baseline, Weeks 1, 2, 4, 20, 21, 22, 46, 48, 60, 70, 72, 84, 94, 96, 108, 120, 132, 144	

End point values	Primary Analysis Set- Placebo	Primary Analysis Set- Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64 <sup>[37]</sup>	66 <sup>[38]</sup>		
Units: percentage change				
least squares mean (standard error)				
Week 1; n=58, 59	10.45 (± 13.041)	310.72 (± 23.225)		
Week 2; n=63, 65	10.53 (± 12.760)	207.90 (± 16.728)		
Week 4; n=63, 66	16.07 (± 12.810)	76.22 (± 12.147)		
Week 20; n=64, 63	21.36 (± 12.424)	41.08 (± 11.943)		
Week 21; n=59, 64	21.51 (± 12.825)	131.76 (± 14.862)		
Week 22; n=64, 65	21.07 (± 12.725)	102.81 (± 14.619)		
Week 46; n=64, 64	130.29 (± 22.718)	96.63 (± 16.909)		
Week 48; n=64, 63	70.09 (± 17.114)	34.47 (± 12.903)		
Week 60; n=59, 60	65.46 (± 13.083)	32.32 (± 12.230)		
Week 70; n=54, 60	123.58 (± 17.315)	82.03 (± 12.604)		
Week 72; n=59, 58	58.45 (± 13.957)	31.14 (± 13.070)		
Week 84; n=58, 57	55.67 (± 15.323)	18.83 (± 12.801)		
Week 94; n=57, 58	111.25 (± 21.970)	71.30 (± 12.280)		
Week 96; n=56, 58	50.17 (± 18.857)	22.15 (± 10.487)		
Week 108; n=48, 48	44.78 (± 14.219)	29.16 (± 13.326)		
Week 120; n=43, 42	58.37 (± 19.621)	36.09 (± 13.089)		
Week 132; n=18, 19	67.59 (± 35.770)	42.55 (± 15.925)		
Week 144; n=2, 0	22.65 (± 19.297)	99999 (± 99999)		

Notes:

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

[38] - n=subjects with an assessment at given time point; 99999=not applicable (n=0 for this time point)

## 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
End point description: The GEE Estimates are from the GEE model which includes the change from baseline for 24-Hour urinary phosphorus as the dependent variable, region, visit, treatment, actual randomization stratification and visit by treatment as fixed factors, and baseline of urinary phosphorus as a covariate, with compound symmetry covariance structure.	
End point type	Secondary
End point timeframe: Baseline, Weeks 12, 24, 36, 48, 72, 96	

End point values	Primary Analysis Set- Placebo	Primary Analysis Set- Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65 <sup>[39]</sup>	67 <sup>[40]</sup>		
Units: g/24hr				
least squares mean (standard error)				
Week 12; n=63, 63	0.06 (± 0.052)	0.05 (± 0.046)		
Week 24; n=65, 67	0.07 (± 0.065)	0.05 (± 0.046)		
Week 36; n=64, 64	0.04 (± 0.054)	0.07 (± 0.045)		
Week 48; n=63, 63	0.07 (± 0.060)	0.13 (± 0.067)		
Week 72; n=57, 57	0.08 (± 0.065)	0.05 (± 0.052)		
Week 96; n=58, 59	0.10 (± 0.075)	0.10 (± 0.054)		

Notes:

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

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

## Statistical analyses

No statistical analyses for this end point

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

End point title	Percent Change From Baseline Over Time in 24-Hour Urinary Phosphorus
End point description: The GEE Estimates are from the GEE model which includes the percent change from baseline for 24-Hour urinary phosphorus as the dependent variable, region, visit, treatment, actual randomization stratification and visit by treatment as fixed factors, and baseline of urinary phosphorus as a covariate, with compound symmetry covariance structure.	
End point type	Secondary
End point timeframe: Baseline, Weeks 12, 24, 36, 48, 72, 96	



End point values	Primary Analysis Set- Placebo	Primary Analysis Set- Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65 <sup>[41]</sup>	67 <sup>[42]</sup>		
Units: percentage change				
least squares mean (standard error)				
Week 12; n=63, 63	21.91 (± 11.844)	21.40 (± 11.453)		
Week 24; n=65, 67	28.45 (± 15.518)	20.35 (± 11.567)		
Week 36; n=64, 64	18.19 (± 11.784)	28.31 (± 12.173)		
Week 48; n=63, 63	27.32 (± 14.328)	37.50 (± 14.687)		
Week 72; n=57, 57	29.53 (± 14.485)	25.80 (± 15.476)		
Week 96; n=58, 59	31.17 (± 17.248)	30.64 (± 10.420)		

Notes:

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

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

### 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:	
The GEE Estimates are from the GEE model which includes the change from baseline for TmP/GFR as the dependent variable, region, visit, treatment, actual randomization stratification and visit by treatment as fixed factors, and baseline of TmP/GFR as a covariate, with compound symmetry covariance structure.	
End point type	Secondary
End point timeframe:	
Baseline, Weeks 2, 4, 12, 22, 24, 48, 60, 72, 84, 96	

End point values	Primary Analysis Set- Placebo	Primary Analysis Set- Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	63 <sup>[43]</sup>	66 <sup>[44]</sup>		
Units: mg/dL				
least squares mean (standard error)				
Week 2; n=60, 60	-0.02 (± 0.072)	1.60 (± 0.121)		
Week 4; n=61, 63	-0.03 (± 0.070)	0.91 (± 0.117)		
Week 12; n=61, 64	0.11 (± 0.082)	0.70 (± 0.107)		
Week 22; n=63, 62	0.02 (± 0.069)	1.01 (± 0.123)		
Week 24; n=62, 66	0.07 (± 0.071)	0.51 (± 0.093)		
Week 48; n=62, 61	0.55 (± 0.087)	0.48 (± 0.091)		
Week 60; n=58, 58	0.57 (± 0.097)	0.43 (± 0.086)		

Week 72; n=57, 57	0.55 (± 0.086)	0.43 (± 0.091)		
Week 84; n=57, 56	0.49 (± 0.078)	0.42 (± 0.092)		
Week 96; n= 58, 57	0.29 (± 0.086)	0.46 (± 0.084)		

Notes:

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

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

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Change From Baseline Over Time in TmP/GFR

End point title	Percent Change From Baseline Over Time in TmP/GFR
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End point description:

The GEE Estimates are from the GEE model which includes the percent change from baseline for TmP/GFR as the dependent variable, region, visit, treatment, actual randomization stratification and visit by treatment as fixed factors, and baseline of TmP/GFR as a covariate, with compound symmetry covariance structure.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 2, 4, 12, 22, 24, 48, 60, 72, 84, 96

End point values	Primary Analysis Set- Placebo	Primary Analysis Set- Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	63 <sup>[45]</sup>	66 <sup>[46]</sup>		
Units: percentage change				
least squares mean (standard error)				
Week 2; n=60, 60	-2.15 (± 4.515)	100.10 (± 7.222)		
Week 4; n=-61, 63	-2.73 (± 4.416)	56.53 (± 6.816)		
Week 12; n=61, 64	6.28 (± 4.900)	43.65 (± 6.206)		
Week 22; n=63, 62	1.38 (± 4.252)	62.38 (± 7.144)		
Week 24; n=62, 66	3.63 (± 4.460)	33.02 (± 5.464)		
Week 48; n=62, 61	35.52 (± 5.390)	31.02 (± 5.489)		
Week 60; n=58, 58	37.13 (± 5.855)	27.49 (± 5.002)		
Week 72; n=57, 57	35.89 (± 5.492)	28.98 (± 5.513)		
Week 84; n=57, 56	33.15 (± 4.924)	27.69 (± 5.527)		
Week 96; n=58, 57	19.95 (± 5.417)	29.67 (± 4.759)		

Notes:

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

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

## 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
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End point description:

The GEE Estimates are from the GEE model which includes the change from baseline for TRP as the dependent variable, region, visit, treatment, actual randomization stratification and visit by treatment as fixed factors, and baseline of TRP as a covariate, with compound symmetry covariance structure.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 2, 4, 12, 22, 24, 48, 60, 72, 84, 96

End point values	Primary Analysis Set-Placebo	Primary Analysis Set-Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64 <sup>[47]</sup>	67 <sup>[48]</sup>		
Units: fraction of phosphate reabsorbed				
least squares mean (standard error)				
Week 2; n=62, 63	-0.02 (± 0.013)	0.07 (± 0.008)		
Week 4; n=63, 65	-0.03 (± 0.012)	0.03 (± 0.009)		
Week 12; n=62, 64	-0.00 (± 0.010)	0.04 (± 0.008)		
Week 22; n=63, 64	-0.01 (± 0.009)	0.05 (± 0.011)		
Week 24; n=63; 67	-0.02 (± 0.012)	0.03 (± 0.009)		
Week 48; n=64, 63	0.02 (± 0.012)	0.03 (± 0.009)		
Week 60; n=60, 60	0.03 (± 0.009)	0.02 (± 0.009)		
Week 72; n=60, 59	0.02 (± 0.011)	0.02 (± 0.011)		
Week 84; n=58, 58	0.02 (± 0.010)	0.01 (± 0.012)		
Week 96; n=59, 58	-0.01 (± 0.014)	0.03 (± 0.009)		

Notes:

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

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

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline Over Time in TRP

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

The GEE Estimates are from the GEE model which includes the percent change from baseline for TRP as the dependent variable, region, visit, treatment, actual randomization stratification and visit by treatment as fixed factors, and baseline of TRP as a covariate, with compound symmetry covariance structure.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 2, 4, 12, 22, 24, 48, 60, 72, 84, 96

End point values	Primary Analysis Set- Placebo	Primary Analysis Set- Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64 <sup>[49]</sup>	67 <sup>[50]</sup>		
Units: percentage change				
least squares mean (standard error)				
Week 2; n=62, 63	-2.00 (± 1.530)	9.81 (± 1.111)		
Week 4; n=63, 65	-3.75 (± 1.486)	4.86 (± 1.114)		
Week 12; n=62, 64	0.56 (± 1.261)	5.45 (± 1.079)		
Week 22; n=63, 64	-0.01 (± 1.163)	7.03 (± 1.451)		
Week 24; n=63, 67	-1.56 (± 1.579)	4.21 (± 1.141)		
Week 48; n=64, 63	3.95 (± 1.547)	4.70 (± 1.183)		
Week 60; n=60, 60	3.99 (± 1.096)	3.00 (± 1.123)		
Week 72; n=60, 59	3.90 (± 1.427)	3.24 (± 1.414)		
Week 84; n=58, 58	3.78 (± 1.276)	1.97 (± 1.516)		
Week 96; n=59, 58	-0.09 (± 1.582)	4.44 (± 1.116)		

Notes:

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

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

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects Achieving Mean Serum Phosphorus Levels Above the LLN (2.5 mg/dL [0.81 mmol/L]) at the End of the Dosing Cycle, as Averaged Across Dose Cycles Between Baseline and Week 24

End point title	Percentage of Subjects Achieving Mean Serum Phosphorus Levels Above the LLN (2.5 mg/dL [0.81 mmol/L]) at the End of the 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 through Week 24

End point values	Placebo	Burosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	68		
Units: percentage of subjects				
number (confidence interval 95%)	6.1 (2.4 to 14.6)	67.6 (55.8 to 77.6)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Serum Phosphorus at Each Mid-Point of Dosing Cycle, as Averaged Across Dose Cycles Between Baseline and Week 24

End point title	Change From Baseline in Serum Phosphorus at Each 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 through Week 24

End point values	Placebo	Burosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	68		
Units: mg/dL				
arithmetic mean (standard deviation)	0.16 ( $\pm$ 0.272)	1.21 ( $\pm$ 0.513)		

### Statistical analyses

No statistical analyses for this end point

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

End point title	Percent Change From Baseline in Serum Phosphorus at Each 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 through Week 24

End point values	Placebo	Burosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	68		
Units: percentage change				
arithmetic mean (standard deviation)	9.85 (± 15.292)	61.44 (± 28.961)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Serum Phosphorus at Each End of Dosing Cycle, as Averaged Across Dose Cycles Between Baseline and Week 24

End point title	Change From Baseline in Serum Phosphorus at Each End of Dosing Cycle, as Averaged Across Dose Cycles Between Baseline and Week 24
End point description:	
End point type	Secondary
End point timeframe:	
Baseline through Week 24	

End point values	Placebo	Burosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	68		
Units: mg/dL				
arithmetic mean (standard deviation)	0.13 (± 0.265)	0.69 (± 0.392)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline in Serum Phosphorus at Each End of Dosing Cycle, as Averaged Across Dose Cycles Between Baseline and Week 24

End point title	Percent Change From Baseline in Serum Phosphorus at Each End of Dosing Cycle, as Averaged Across Dose Cycles Between Baseline and Week 24
End point description:	
End point type	Secondary

End point timeframe:  
Baseline through Week 24

End point values	Placebo	Burosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	68		
Units: percentage change				
arithmetic mean (standard deviation)	7.83 ( $\pm$ 14.755)	35.18 ( $\pm$ 20.731)		

### 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 through Week 24

End point values	Placebo	Burosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	68		
Units: mg/dL				
arithmetic mean (standard deviation)	2.08 ( $\pm$ 0.292)	3.08 ( $\pm$ 0.477)		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug through the end of study plus 4 weeks (+ 5 days).

Adverse event reporting additional description:

Mean (SE) duration of exposure to burosumab for all periods combined through EOS II was 771.3 (21.97) days (range: 167 – 957) in the burosumab->burosumab group and 625.7 (19.40) days (range: 165 – 844) in the placebo->burosumab group.

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	Placebo (Double Blind [DB] Period)
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Reporting group description:

SC injection of placebo Q4W for 24 weeks (double-blind placebo-controlled Treatment Period)

Reporting group title	Placebo -> Burosumab (Open Label [OL] Period)
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Reporting group description:

SC injection of placebo Q4W for 24 weeks (double-blind placebo-controlled Treatment Period), SC injection of burosumab 1 mg/kg Q4W for 24 weeks (open-label Treatment Continuation Period), SC injection of burosumab 1 mg/kg Q4W for 48 weeks (open label Treatment Extension Period I), and SC injection of burosumab 1 mg/kg Q4W up to 53 weeks (open-label Treatment Extension Period II [US only]).

Reporting group title	Burosumab -> Burosumab (Combined DB and OL Period)
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Reporting group description:

SC injection of 1.0 mg/kg burosumab Q4W for 24 weeks (double-blind placebo-controlled Treatment Period), SC injection of burosumab 1 mg/kg Q4W for 24 weeks (open-label Treatment Continuation Period), SC injection of burosumab 1 mg/kg Q4W for 48 weeks (open-label Treatment Extension Period I), and SC injection of burosumab 1 mg/kg Q4W up to 53 weeks (open-label Treatment Extension Period II [US only]).

Reporting group title	Total Burosumab (Combined DB and OL Period)
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Reporting group description:

SC injection of 1.0 mg/kg burosumab at any time during the study

Serious adverse events	Placebo (Double Blind [DB] Period)	Placebo -> Burosumab (Open Label [OL] Period)	Burosumab -> Burosumab (Combined DB and OL Period)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 66 (1.52%)	10 / 66 (15.15%)	12 / 68 (17.65%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive Ductal Breast Carcinoma			



subjects affected / exposed	1 / 66 (1.52%)	0 / 66 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parathyroid Tumour Benign			
subjects affected / exposed	0 / 66 (0.00%)	1 / 66 (1.52%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	0 / 66 (0.00%)	0 / 66 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural Nausea			
subjects affected / exposed	0 / 66 (0.00%)	0 / 66 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural Vomiting			
subjects affected / exposed	0 / 66 (0.00%)	0 / 66 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road Traffic Accident			
subjects affected / exposed	0 / 66 (0.00%)	0 / 66 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Subdural Haematoma			
subjects affected / exposed	0 / 66 (0.00%)	1 / 66 (1.52%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 66 (0.00%)	1 / 66 (1.52%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Cerebrospinal Fluid Leakage			
subjects affected / exposed	0 / 66 (0.00%)	0 / 66 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical Radiculopathy			
subjects affected / exposed	0 / 66 (0.00%)	0 / 66 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 66 (0.00%)	1 / 66 (1.52%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelopathy			
subjects affected / exposed	0 / 66 (0.00%)	0 / 66 (0.00%)	2 / 68 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuralgia			
subjects affected / exposed	0 / 66 (0.00%)	1 / 66 (1.52%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 66 (0.00%)	1 / 66 (1.52%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial Seizures			
subjects affected / exposed	0 / 66 (0.00%)	1 / 66 (1.52%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 66 (0.00%)	1 / 66 (1.52%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Colitis			
subjects affected / exposed	0 / 66 (0.00%)	0 / 66 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal Ulcer			
subjects affected / exposed	0 / 66 (0.00%)	0 / 66 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 66 (0.00%)	0 / 66 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Irritable Bowel Syndrome			
subjects affected / exposed	0 / 66 (0.00%)	0 / 66 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periodontal Disease			
subjects affected / exposed	0 / 66 (0.00%)	1 / 66 (1.52%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal Adhesions			
subjects affected / exposed	0 / 66 (0.00%)	1 / 66 (1.52%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 66 (0.00%)	0 / 66 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 66 (0.00%)	1 / 66 (1.52%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Back Pain			
subjects affected / exposed	0 / 66 (0.00%)	0 / 66 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical Spinal Stenosis			
subjects affected / exposed	0 / 66 (0.00%)	1 / 66 (1.52%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint Range Of Motion Decreased			
subjects affected / exposed	0 / 66 (0.00%)	1 / 66 (1.52%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Knee Deformity			
subjects affected / exposed	0 / 66 (0.00%)	0 / 66 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal Pain			
subjects affected / exposed	0 / 66 (0.00%)	0 / 66 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 66 (0.00%)	0 / 66 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudarthrosis			
subjects affected / exposed	0 / 66 (0.00%)	1 / 66 (1.52%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Column Stenosis			
subjects affected / exposed	0 / 66 (0.00%)	0 / 66 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			

subjects affected / exposed	0 / 66 (0.00%)	0 / 66 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Infections and infestations</b>			
Gastroenteritis			
subjects affected / exposed	0 / 66 (0.00%)	0 / 66 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Medical Device Site Infection</b>			
subjects affected / exposed	0 / 66 (0.00%)	0 / 66 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<b>Serious adverse events</b>	Total Burosumab (Combined DB and OL Period)		
<b>Total subjects affected by serious adverse events</b>			
subjects affected / exposed	22 / 134 (16.42%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>			
Invasive Ductal Breast Carcinoma			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Parathyroid Tumour Benign</b>			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Injury, poisoning and procedural complications</b>			
Overdose			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Procedural Nausea</b>			

subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Procedural Vomiting			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Road Traffic Accident			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Subdural Haematoma			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrospinal Fluid Leakage			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cervical Radiculopathy			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myelopathy			

subjects affected / exposed	2 / 134 (1.49%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Neuralgia			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Paraesthesia			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Partial Seizures			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Presyncope			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Duodenal Ulcer			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Irritable Bowel Syndrome			

subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Periodontal Disease			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peritoneal Adhesions			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 134 (1.49%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Back Pain			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cervical Spinal Stenosis			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint Range Of Motion Decreased			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		



Knee Deformity			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal Pain			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pseudarthrosis			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal Column Stenosis			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Spondylolisthesis			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Medical Device Site Infection			
subjects affected / exposed	1 / 134 (0.75%)		
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 %

<b>Non-serious adverse events</b>	Placebo (Double Blind [DB] Period)	Placebo -> Burosumab (Open Label [OL] Period)	Burosumab -> Burosumab (Combined DB and OL Period)
Total subjects affected by non-serious adverse events subjects affected / exposed	57 / 66 (86.36%)	63 / 66 (95.45%)	68 / 68 (100.00%)
Vascular disorders			
Hot Flush			
subjects affected / exposed	0 / 66 (0.00%)	2 / 66 (3.03%)	6 / 68 (8.82%)
occurrences (all)	0	2	8
Hypertension			
subjects affected / exposed	2 / 66 (3.03%)	5 / 66 (7.58%)	8 / 68 (11.76%)
occurrences (all)	2	5	9
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 66 (3.03%)	1 / 66 (1.52%)	5 / 68 (7.35%)
occurrences (all)	4	1	11
Fatigue			
subjects affected / exposed	7 / 66 (10.61%)	14 / 66 (21.21%)	16 / 68 (23.53%)
occurrences (all)	7	19	21
Injection Site Erythema			
subjects affected / exposed	2 / 66 (3.03%)	6 / 66 (9.09%)	6 / 68 (8.82%)
occurrences (all)	2	22	9
Injection Site Pruritus			
subjects affected / exposed	0 / 66 (0.00%)	8 / 66 (12.12%)	3 / 68 (4.41%)
occurrences (all)	0	17	11
Injection Site Reaction			
subjects affected / exposed	2 / 66 (3.03%)	8 / 66 (12.12%)	7 / 68 (10.29%)
occurrences (all)	2	40	35
Pain			
subjects affected / exposed	6 / 66 (9.09%)	9 / 66 (13.64%)	12 / 68 (17.65%)
occurrences (all)	6	10	18
Pyrexia			
subjects affected / exposed	0 / 66 (0.00%)	4 / 66 (6.06%)	5 / 68 (7.35%)
occurrences (all)	0	5	5
Immune system disorders			

Seasonal Allergy subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1	6 / 66 (9.09%) 7	5 / 68 (7.35%) 6
Respiratory, thoracic and mediastinal disorders			
Asthma subjects affected / exposed occurrences (all)	0 / 66 (0.00%) 0	5 / 66 (7.58%) 5	2 / 68 (2.94%) 2
Cough subjects affected / exposed occurrences (all)	3 / 66 (4.55%) 4	11 / 66 (16.67%) 12	10 / 68 (14.71%) 13
Nasal Congestion subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 2	5 / 66 (7.58%) 6	5 / 68 (7.35%) 8
Oropharyngeal Pain subjects affected / exposed occurrences (all)	7 / 66 (10.61%) 8	8 / 66 (12.12%) 10	4 / 68 (5.88%) 7
Rhinorrhoea subjects affected / exposed occurrences (all)	3 / 66 (4.55%) 3	2 / 66 (3.03%) 2	4 / 68 (5.88%) 4
Psychiatric disorders			
Depression subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1	3 / 66 (4.55%) 4	9 / 68 (13.24%) 10
Insomnia subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1	6 / 66 (9.09%) 7	9 / 68 (13.24%) 10
Investigations			
Blood 25-Hydroxycholecalciferol Decreased subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1	3 / 66 (4.55%) 5	6 / 68 (8.82%) 8
Blood Glucose Increased subjects affected / exposed occurrences (all)	0 / 66 (0.00%) 0	1 / 66 (1.52%) 1	5 / 68 (7.35%) 6
Blood Parathyroid Hormone Increased			

subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1	1 / 66 (1.52%) 1	5 / 68 (7.35%) 5
Blood Pressure Increased subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1	1 / 66 (1.52%) 1	6 / 68 (8.82%) 9
Lipase Increased subjects affected / exposed occurrences (all)	0 / 66 (0.00%) 0	0 / 66 (0.00%) 0	4 / 68 (5.88%) 5
Vitamin D Decreased subjects affected / exposed occurrences (all)	0 / 66 (0.00%) 0	9 / 66 (13.64%) 9	8 / 68 (11.76%) 8
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1	5 / 66 (7.58%) 6	4 / 68 (5.88%) 5
Fall subjects affected / exposed occurrences (all)	0 / 66 (0.00%) 0	7 / 66 (10.61%) 9	6 / 68 (8.82%) 7
Ligament Sprain subjects affected / exposed occurrences (all)	6 / 66 (9.09%) 6	2 / 66 (3.03%) 2	4 / 68 (5.88%) 4
Procedural Pain subjects affected / exposed occurrences (all)	0 / 66 (0.00%) 0	6 / 66 (9.09%) 7	9 / 68 (13.24%) 16
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	4 / 66 (6.06%) 4	5 / 66 (7.58%) 5	11 / 68 (16.18%) 20
Headache subjects affected / exposed occurrences (all)	5 / 66 (7.58%) 6	18 / 66 (27.27%) 36	22 / 68 (32.35%) 46
Hypoaesthesia subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1	3 / 66 (4.55%) 3	7 / 68 (10.29%) 8
Migraine			

subjects affected / exposed	1 / 66 (1.52%)	2 / 66 (3.03%)	7 / 68 (10.29%)
occurrences (all)	1	2	8
Restless Legs Syndrome			
subjects affected / exposed	5 / 66 (7.58%)	10 / 66 (15.15%)	11 / 68 (16.18%)
occurrences (all)	5	13	14
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 66 (1.52%)	4 / 66 (6.06%)	3 / 68 (4.41%)
occurrences (all)	2	4	5
Gastrointestinal disorders			
Abdominal Discomfort			
subjects affected / exposed	0 / 66 (0.00%)	3 / 66 (4.55%)	4 / 68 (5.88%)
occurrences (all)	0	3	6
Abdominal Pain			
subjects affected / exposed	2 / 66 (3.03%)	2 / 66 (3.03%)	6 / 68 (8.82%)
occurrences (all)	3	5	15
Abdominal Pain Upper			
subjects affected / exposed	0 / 66 (0.00%)	6 / 66 (9.09%)	3 / 68 (4.41%)
occurrences (all)	0	9	3
Constipation			
subjects affected / exposed	0 / 66 (0.00%)	4 / 66 (6.06%)	10 / 68 (14.71%)
occurrences (all)	0	4	13
Diarrhoea			
subjects affected / exposed	5 / 66 (7.58%)	5 / 66 (7.58%)	13 / 68 (19.12%)
occurrences (all)	8	5	15
Nausea			
subjects affected / exposed	6 / 66 (9.09%)	5 / 66 (7.58%)	11 / 68 (16.18%)
occurrences (all)	7	10	20
Toothache			
subjects affected / exposed	1 / 66 (1.52%)	10 / 66 (15.15%)	12 / 68 (17.65%)
occurrences (all)	1	12	21
Vomiting			
subjects affected / exposed	2 / 66 (3.03%)	4 / 66 (6.06%)	6 / 68 (8.82%)
occurrences (all)	2	8	6
Skin and subcutaneous tissue disorders			

Pruritus			
subjects affected / exposed	0 / 66 (0.00%)	1 / 66 (1.52%)	5 / 68 (7.35%)
occurrences (all)	0	1	5
Rash			
subjects affected / exposed	3 / 66 (4.55%)	1 / 66 (1.52%)	4 / 68 (5.88%)
occurrences (all)	3	1	5
Renal and urinary disorders			
Nephrocalcinosis			
subjects affected / exposed	0 / 66 (0.00%)	4 / 66 (6.06%)	2 / 68 (2.94%)
occurrences (all)	0	4	2
Endocrine disorders			
Hyperparathyroidism Secondary			
subjects affected / exposed	0 / 66 (0.00%)	3 / 66 (4.55%)	4 / 68 (5.88%)
occurrences (all)	0	3	7
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	16 / 66 (24.24%)	23 / 66 (34.85%)	27 / 68 (39.71%)
occurrences (all)	22	37	48
Back Pain			
subjects affected / exposed	6 / 66 (9.09%)	17 / 66 (25.76%)	18 / 68 (26.47%)
occurrences (all)	6	23	23
Bone Pain			
subjects affected / exposed	4 / 66 (6.06%)	6 / 66 (9.09%)	8 / 68 (11.76%)
occurrences (all)	4	6	12
Joint Stiffness			
subjects affected / exposed	0 / 66 (0.00%)	4 / 66 (6.06%)	4 / 68 (5.88%)
occurrences (all)	0	5	4
Joint Swelling			
subjects affected / exposed	0 / 66 (0.00%)	7 / 66 (10.61%)	5 / 68 (7.35%)
occurrences (all)	0	7	6
Muscle Spasms			
subjects affected / exposed	2 / 66 (3.03%)	9 / 66 (13.64%)	11 / 68 (16.18%)
occurrences (all)	2	15	14
Muscular Weakness			
subjects affected / exposed	1 / 66 (1.52%)	2 / 66 (3.03%)	6 / 68 (8.82%)
occurrences (all)	4	2	6

Musculoskeletal Chest Pain subjects affected / exposed occurrences (all)	0 / 66 (0.00%) 0	4 / 66 (6.06%) 5	3 / 68 (4.41%) 3
Musculoskeletal Pain subjects affected / exposed occurrences (all)	4 / 66 (6.06%) 4	10 / 66 (15.15%) 15	12 / 68 (17.65%) 12
Musculoskeletal Stiffness subjects affected / exposed occurrences (all)	3 / 66 (4.55%) 6	4 / 66 (6.06%) 4	4 / 68 (5.88%) 4
Myalgia subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1	5 / 66 (7.58%) 5	8 / 68 (11.76%) 9
Neck Pain subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1	5 / 66 (7.58%) 5	3 / 68 (4.41%) 5
Pain In Extremity subjects affected / exposed occurrences (all)	10 / 66 (15.15%) 12	10 / 66 (15.15%) 17	18 / 68 (26.47%) 18
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1	6 / 66 (9.09%) 6	4 / 68 (5.88%) 5
Gastroenteritis subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 2	4 / 66 (6.06%) 4	2 / 68 (2.94%) 2
Influenza subjects affected / exposed occurrences (all)	3 / 66 (4.55%) 3	6 / 66 (9.09%) 6	9 / 68 (13.24%) 11
Nasopharyngitis subjects affected / exposed occurrences (all)	6 / 66 (9.09%) 8	24 / 66 (36.36%) 34	28 / 68 (41.18%) 53
Oral Herpes subjects affected / exposed occurrences (all)	0 / 66 (0.00%) 0	4 / 66 (6.06%) 5	4 / 68 (5.88%) 7
Pharyngitis			

subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1	0 / 66 (0.00%) 0	4 / 68 (5.88%) 4
Rhinitis			
subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1	4 / 66 (6.06%) 6	1 / 68 (1.47%) 1
Sinusitis			
subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 2	2 / 66 (3.03%) 3	6 / 68 (8.82%) 9
Tooth Abscess			
subjects affected / exposed occurrences (all)	6 / 66 (9.09%) 7	5 / 66 (7.58%) 7	19 / 68 (27.94%) 33
Upper Respiratory Tract Infection			
subjects affected / exposed occurrences (all)	6 / 66 (9.09%) 6	2 / 66 (3.03%) 2	12 / 68 (17.65%) 16
Urinary Tract Infection			
subjects affected / exposed occurrences (all)	4 / 66 (6.06%) 5	6 / 66 (9.09%) 9	5 / 68 (7.35%) 9
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed occurrences (all)	1 / 66 (1.52%) 1	0 / 66 (0.00%) 0	4 / 68 (5.88%) 4
Hyperphosphataemia			
subjects affected / exposed occurrences (all)	0 / 66 (0.00%) 0	4 / 66 (6.06%) 4	1 / 68 (1.47%) 1
Vitamin D Deficiency			
subjects affected / exposed occurrences (all)	3 / 66 (4.55%) 3	7 / 66 (10.61%) 9	15 / 68 (22.06%) 17

<b>Non-serious adverse events</b>	Total Burosumab (Combined DB and OL Period)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	131 / 134 (97.76%)		
Vascular disorders			
Hot Flush			
subjects affected / exposed occurrences (all)	8 / 134 (5.97%) 10		
Hypertension			



subjects affected / exposed occurrences (all)	13 / 134 (9.70%) 14		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 134 (4.48%)		
occurrences (all)	12		
Fatigue			
subjects affected / exposed	30 / 134 (22.39%)		
occurrences (all)	40		
Injection Site Erythema			
subjects affected / exposed	12 / 134 (8.96%)		
occurrences (all)	31		
Injection Site Pruritus			
subjects affected / exposed	11 / 134 (8.21%)		
occurrences (all)	28		
Injection Site Reaction			
subjects affected / exposed	15 / 134 (11.19%)		
occurrences (all)	75		
Pain			
subjects affected / exposed	21 / 134 (15.67%)		
occurrences (all)	28		
Pyrexia			
subjects affected / exposed	9 / 134 (6.72%)		
occurrences (all)	10		
Immune system disorders			
Seasonal Allergy			
subjects affected / exposed	11 / 134 (8.21%)		
occurrences (all)	13		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	7 / 134 (5.22%)		
occurrences (all)	7		
Cough			
subjects affected / exposed	21 / 134 (15.67%)		
occurrences (all)	25		
Nasal Congestion			

subjects affected / exposed	10 / 134 (7.46%)		
occurrences (all)	14		
Oropharyngeal Pain			
subjects affected / exposed	12 / 134 (8.96%)		
occurrences (all)	17		
Rhinorrhoea			
subjects affected / exposed	6 / 134 (4.48%)		
occurrences (all)	6		
Psychiatric disorders			
Depression			
subjects affected / exposed	12 / 134 (8.96%)		
occurrences (all)	14		
Insomnia			
subjects affected / exposed	15 / 134 (11.19%)		
occurrences (all)	17		
Investigations			
Blood 25-Hydroxycholecalciferol Decreased			
subjects affected / exposed	9 / 134 (6.72%)		
occurrences (all)	13		
Blood Glucose Increased			
subjects affected / exposed	6 / 134 (4.48%)		
occurrences (all)	7		
Blood Parathyroid Hormone Increased			
subjects affected / exposed	6 / 134 (4.48%)		
occurrences (all)	6		
Blood Pressure Increased			
subjects affected / exposed	7 / 134 (5.22%)		
occurrences (all)	10		
Lipase Increased			
subjects affected / exposed	4 / 134 (2.99%)		
occurrences (all)	5		
Vitamin D Decreased			
subjects affected / exposed	17 / 134 (12.69%)		
occurrences (all)	17		
Injury, poisoning and procedural complications			

Contusion subjects affected / exposed occurrences (all)	9 / 134 (6.72%) 11		
Fall subjects affected / exposed occurrences (all)	13 / 134 (9.70%) 16		
Ligament Sprain subjects affected / exposed occurrences (all)	6 / 134 (4.48%) 6		
Procedural Pain subjects affected / exposed occurrences (all)	15 / 134 (11.19%) 23		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	16 / 134 (11.94%) 25		
Headache subjects affected / exposed occurrences (all)	40 / 134 (29.85%) 82		
Hypoaesthesia subjects affected / exposed occurrences (all)	10 / 134 (7.46%) 11		
Migraine subjects affected / exposed occurrences (all)	9 / 134 (6.72%) 10		
Restless Legs Syndrome subjects affected / exposed occurrences (all)	21 / 134 (15.67%) 27		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	7 / 134 (5.22%) 9		
Gastrointestinal disorders Abdominal Discomfort subjects affected / exposed occurrences (all)	7 / 134 (5.22%) 9		
Abdominal Pain			

subjects affected / exposed	8 / 134 (5.97%)		
occurrences (all)	20		
Abdominal Pain Upper			
subjects affected / exposed	9 / 134 (6.72%)		
occurrences (all)	12		
Constipation			
subjects affected / exposed	14 / 134 (10.45%)		
occurrences (all)	17		
Diarrhoea			
subjects affected / exposed	18 / 134 (13.43%)		
occurrences (all)	20		
Nausea			
subjects affected / exposed	16 / 134 (11.94%)		
occurrences (all)	30		
Toothache			
subjects affected / exposed	22 / 134 (16.42%)		
occurrences (all)	33		
Vomiting			
subjects affected / exposed	10 / 134 (7.46%)		
occurrences (all)	14		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	6 / 134 (4.48%)		
occurrences (all)	6		
Rash			
subjects affected / exposed	5 / 134 (3.73%)		
occurrences (all)	6		
Renal and urinary disorders			
Nephrocalcinosis			
subjects affected / exposed	6 / 134 (4.48%)		
occurrences (all)	6		
Endocrine disorders			
Hyperparathyroidism Secondary			
subjects affected / exposed	7 / 134 (5.22%)		
occurrences (all)	10		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	50 / 134 (37.31%)		
occurrences (all)	85		
Back Pain			
subjects affected / exposed	35 / 134 (26.12%)		
occurrences (all)	46		
Bone Pain			
subjects affected / exposed	14 / 134 (10.45%)		
occurrences (all)	18		
Joint Stiffness			
subjects affected / exposed	8 / 134 (5.97%)		
occurrences (all)	9		
Joint Swelling			
subjects affected / exposed	12 / 134 (8.96%)		
occurrences (all)	13		
Muscle Spasms			
subjects affected / exposed	20 / 134 (14.93%)		
occurrences (all)	29		
Muscular Weakness			
subjects affected / exposed	8 / 134 (5.97%)		
occurrences (all)	8		
Musculoskeletal Chest Pain			
subjects affected / exposed	7 / 134 (5.22%)		
occurrences (all)	8		
Musculoskeletal Pain			
subjects affected / exposed	22 / 134 (16.42%)		
occurrences (all)	27		
Musculoskeletal Stiffness			
subjects affected / exposed	8 / 134 (5.97%)		
occurrences (all)	8		
Myalgia			
subjects affected / exposed	13 / 134 (9.70%)		
occurrences (all)	14		
Neck Pain			
subjects affected / exposed	8 / 134 (5.97%)		
occurrences (all)	10		

Pain In Extremity subjects affected / exposed occurrences (all)	28 / 134 (20.90%) 35		
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	10 / 134 (7.46%) 11		
Gastroenteritis subjects affected / exposed occurrences (all)	6 / 134 (4.48%) 6		
Influenza subjects affected / exposed occurrences (all)	15 / 134 (11.19%) 17		
Nasopharyngitis subjects affected / exposed occurrences (all)	52 / 134 (38.81%) 87		
Oral Herpes subjects affected / exposed occurrences (all)	8 / 134 (5.97%) 12		
Pharyngitis subjects affected / exposed occurrences (all)	4 / 134 (2.99%) 4		
Rhinitis subjects affected / exposed occurrences (all)	5 / 134 (3.73%) 7		
Sinusitis subjects affected / exposed occurrences (all)	8 / 134 (5.97%) 12		
Tooth Abscess subjects affected / exposed occurrences (all)	24 / 134 (17.91%) 40		
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	14 / 134 (10.45%) 18		
Urinary Tract Infection			

subjects affected / exposed occurrences (all)	11 / 134 (8.21%) 18		
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	4 / 134 (2.99%)		
occurrences (all)	4		
Hyperphosphataemia			
subjects affected / exposed	5 / 134 (3.73%)		
occurrences (all)	5		
Vitamin D Deficiency			
subjects affected / exposed	22 / 134 (16.42%)		
occurrences (all)	26		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 July 2016	<p>(continued)</p> <ul style="list-style-type: none"><li>• Efficacy Measures: Enthesopathy was added as an efficacy measure in the study. Enthesopathy would be measured in all subjects by lateral foot x rays (bilateral) at Baseline (obtained as skeletal survey) and at Weeks 24, 48, and 96, and, if applicable, at the end of Treatment Extension Period II to assess the change from Baseline in enthesopathy at the calcaneus as an exploratory endpoint.<ul style="list-style-type: none"><li>- A statement was added to Section 7.5.3.1 that 2 questions from the short-form BPI about the use of pain medications and relief from pain medications would not be administered. Use of pain medications was captured separately in the diary.</li></ul></li><li>• General Assessments: A provision was added to allow additional testing for mutations consistent with syndromes with overlapping clinical and biochemical characteristics as XLH if the initial PHEX mutation analysis was negative or inconclusive and informed consent was provided by the subject. Testing would 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 would communicate any additional genetic testing results to the subject.</li><li>• Safety Assessments: Several changes were made to the safety assessments.<ul style="list-style-type: none"><li>- Sections 7.4.5 and 7.5.7.6 were updated to indicate echocardiogram (ECHO) would no longer be read locally at the study site. All ECHO assessments would be centrally read by individuals blinded to treatment assignment and subject data.</li><li>- In Section 7.5.7, electrocardiogram (ECG) was listed as a general safety assessment. Previously it was listed within the safety assessments for ectopic mineralization.</li><li>- Blood pressure (Section 7.5.7.2) would be obtained twice (2 measurements within 15 minutes) at indicated clinic visits.</li></ul></li></ul>



21 July 2016	<p>(continued)</p> <ul style="list-style-type: none"> <li>- Section 7.5.7.8 was updated to add assessment of lipase in all subjects and reflexive testing for amylase isoenzymes if serum amylase levels were elevated to <math>\geq 1.5 \times</math> upper limit of normal (ULN).</li> <li>- Descriptions of FGF23 measurements were removed consistent with changes to the Schedule of Events.</li> <li>• Statistical Methods: The following changes were made to Section 7.6. <ul style="list-style-type: none"> <li>- A final analysis was planned at Week 96 to coincide with the end of the Extension Period (Section 7.6.4).</li> <li>- Section 7.6.4.2 was clarified to state the key secondary endpoint would be derived from the average of daily diary scores recorded over 1 week and the study visit score.</li> <li>- Section 7.6.4.3 was updated to clarify that the endpoints for BPI pain severity and pain interference would be evaluated separately. The endpoints for BFI would be based on BF-Q3, 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.</li> </ul> </li> <li>• Ethics: Section 8.1.2 was updated to state that both the Sponsor and Investigator would make every effort to ensure the study described in the protocol was conducted in full conformance with those principles, current Food and Drug Administration (FDA) regulations, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice (ICH GCP) guidelines, and local ethical and regulatory requirements.</li> <li>• 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.</li> <li>• Safety Contact Information: The medical monitor information for the study was updated in Section 8.5.4.7.</li> </ul>
21 July 2016	<ul style="list-style-type: none"> <li>• Overall Study Design: A 48-week Extension Period was added to the study design. The study title was modified with the open-label extension as a descriptor, and the corresponding Schedule of Events for this period was provided.</li> <li>• Study Population: Several changes were made to the inclusion and exclusion criteria as indicated below: <ul style="list-style-type: none"> <li>- Inclusion criterion #5 was modified to correct a duplicative value of 60 mL/min. The estimated glomerular filtration rate (eGFR) was to be <math>\geq 60</math> mL/min; OR eGFR of 45 to <math>&lt; 60</math> mL/min at SV2 with confirmation that the renal insufficiency was not due to nephrocalcinosis.</li> <li>- Inclusion criterion #10 was updated as follows (bolded text indicates newly added text): "Participants of childbearing potential or with partners of childbearing potential who have not undergone a total hysterectomy or bilateral salpingo oophorectomy and are sexually active must consent to use 2 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."</li> <li>- Exclusion criterion #4 was changed to specify timing around screening visit (SV)1.</li> <li>- Exclusion criterion # 8 was modified to remove "oral" and restrict use of any bisphosphonates in the 2 years prior to SV1.</li> <li>- Additional criteria were inserted to exclude individuals who had used denosumab in the 6 months prior to SV1 and teriparatide in the 2 months prior to SV1. These medications were also added to the list of prohibited medications for consistency.</li> <li>- A provision was added to Exclusion criterion #19 to allow individuals to participate who may have had a history of recurrent dental abscesses, which are known to be associated with XLH.</li> </ul> </li> </ul>

21 July 2016	<p>(continued)</p> <ul style="list-style-type: none"> <li>• Schedule of Events: Several changes were made to the Schedule of Events: <ul style="list-style-type: none"> <li>- The timing of assessments for intact fibroblast growth factor 23 (iFGF23), phosphate regulating gene with homology to endopeptidases located on the X chromosome (PHEX) mutation analysis, and pregnancy testing during Screening/Baseline was modified and/or clarified. PHEX mutation analysis was only to be performed once (either at SV2 or the Baseline Visit). A provision was added to allow for a screening period &gt; 31 days.</li> <li>- Additional pharmacokinetic assessments were added at Weeks 34, 36, 46, and 70. The skeletal survey was moved from SV1 to the Baseline Visit in Table 2.1 to align with the description in Section 7.5.6.1. Serum 1,25(OH)2D was also to be assayed at Week 24.</li> <li>- Footnote 12 to the Schedules of Events and Section 7.5.3.3 were updated to clarify that the full 24-item WOMAC would be administered.</li> <li>- The TUG test was added to the Schedules of Events and Section 7.5.5 as an exploratory endpoint. The TUG was to be performed at Weeks 24, 36, 48, and 72.</li> </ul> </li> <li>• Treatments: Two changes were made regarding study drug. 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. Section 7.4.2 was updated to state the composition of the placebo solution is the same as burosumab investigational product except placebo contains no active substance.</li> <li>• Blinding: Language discussing blinding was clarified to state that the study was double blind and placebo controlled through Week 24 and that unblinding of serum phosphorus levels and treatment assignment referred to the placebo-controlled portion of the study. The section also stated subjects and Investigators would remain blinded to original treatment assignment until the Week 48 analysis was completed. Previously it had stated that Investigator and site personnel would remain blinded during the study.</li> </ul>
08 September 2016	<p>(continued)</p> <ul style="list-style-type: none"> <li>• 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.</li> </ul>

08 September 2016	<ul style="list-style-type: none"> <li>• Schedules of Events: Numbering was added to the footnotes for the Schedules of Events. In addition, a duplicative Visit 34 was corrected and the study visits renumbered and an unintended anti-burosumab antibody assessment at Week 70 was removed.</li> <li>• Study Objectives: In Section 6, the pharmacokinetic (PK) Objective was 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."</li> <li>• Genetic Testing: In Section 7.5.8, 1 gene, for Raine Syndrome (FAM20C), was added to the list of genes that may be assessed for mutation in subjects whose initial PHEX mutation analysis was negative or inconclusive and who provided informed consent. The wording "not necessarily limited to" regarding the list of genes was removed.</li> <li>• 6 Minute Walk Test (6MWT): Section 7.5.4 and the Schedules of Events were updated to indicate that the 6MWT would be performed at Week 72 and at Early Termination if the subject discontinued on or before Week 72.</li> <li>• Timed Up and Go (TUG): Section 7.5.5 and the Schedules of Events were updated to indicate that the TUG test would be performed at the Early Termination visit if it occurred between Weeks 24 and 72.</li> <li>• Drug Concentration Measurements: The description of drug concentration measurements was placed under Section 7.5.7. Previously it was misplaced within the heading of Enthesopathy.</li> <li>• Vital Signs: A discrepancy regarding the timing of blood pressure assessments was clarified in Section 7.5.8.2. Seated systolic blood pressure and diastolic blood pressure would be measured twice with the measurements separated by 15 minutes at indicated study visits. Previously this had stated 2 measurements within 15 minutes.</li> <li>• Secondary Endpoints: Language in Section 7.6.4.3 was updated to specify that statistical methods of analysis for additional secondary endpoints including any adjustment for multiplicity would be described in the SAP.</li> </ul>
31 March 2017	<ul style="list-style-type: none"> <li>• Randomization Stratification: Section 7.4.4 (and elsewhere throughout the protocol as relevant) was updated to clarify that randomization is stratified not only by baseline pain intensity, but also by region (North America/European Union, Japan, and South Korea).</li> <li>• Pregnancy Testing and Contraception: In Section 7.5.3.9, the list of examples of effective contraception methods was updated.</li> <li>• Study Design and Duration: In Sections 7.1 and 7.4.3.1 and other relevant sections, a second Treatment Extension Period that included up to approximately 53 additional weeks of burosumab treatment, until end of September 2018, was added for subjects enrolled at sites in the US only. (The duration of this period will vary for individual subjects and will be determined by the time from start of Week 97 through final visit scheduled before 30 September 2018.) In addition, in these sections and Section 8.5.4.1 and other relevant sections, 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. The maximum study duration consequently was changed to up to approximately 157 weeks. For subjects outside of the US, the duration of study treatment remained 96 weeks, followed by Safety Follow-up TCs over an interval of up to 8 weeks if not continuing burosumab treatment under commercial use or another mechanism upon completion of study drug or early withdrawal from this study. The end of study was defined as the last day that protocol-specified assessments (including telephone contact) were conducted for the last subject in the study.</li> </ul>

31 March 2017	<ul style="list-style-type: none"> <li>• Study Objectives: In Section 6, the objectives were modified to elevate 2 "other" secondary objectives to "key" objectives (in addition to the previously specified single key secondary objective involving effect on skeletal pain), as follows: "To establish the effect of KRN23 treatment compared with placebo on skeletal pain, stiffness, and physical functioning."</li> <li>• Key Secondary Efficacy Endpoints: In Section 7.6.4.2, 2 other endpoints were identified as key secondary efficacy endpoints in addition to change from baseline to Week 24 in BPI-Q3 (Worst Pain) score. These included change from baseline to Week 24 in the WOMAC Stiffness score and change from baseline to Week 24 in the WOMAC Physical Function score.</li> <li>• Additional Secondary Efficacy Endpoints: Section 7.6.4.3 was updated to a) clarify that additional secondary endpoints include change from baseline to post-Baseline visits (other than Week 24) in BPI Worst Pain score and WOMAC Physical Function score, b) clarify that change and percent change from baseline to post-baseline visits in serum phosphorus will be assessed, and c) clarify the descriptions of other endpoints.</li> <li>• Exploratory Efficacy Endpoints: In Section 7.6.4.4, the exploratory endpoint of healing of pre-existing pseudofractures and/or Looser zones, as defined by skeletal survey at baseline and subsequent targeted radiography was updated to clarify that it comprised 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, and the number of subjects with baseline active pseudofractures and/or fractures at baseline and the numbers of subjects who had changes from baseline to healed, partially healed, unchanged, and worsened at post-baseline visits. Descriptions of other exploratory endpoints were updated for clarity.</li> </ul>
31 March 2017	<p>(continued)</p> <ul style="list-style-type: none"> <li>• 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 SC injection technique, the subject could self-administer burosumab, or a caregiver could administer burosumab to the subject, in the home setting. Subjects or caregivers were 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 were provided in Section 7.4.6.</li> </ul>
29 September 2017	<ul style="list-style-type: none"> <li>• Study Design: Section 7.1 and related sections were updated to indicate that subjects at study sites in Europe would continue study into Treatment Extension Period II until availability of another mechanism of burosumab treatment and not later than September 2018, to avoid a potential treatment interruption for subjects.</li> <li>• Safety Monitoring: Section 7.6.7 and Section 8.5.4.6 were updated to describe safety monitoring during Treatment Extension Periods I and II of the study. Specifically, the DMC would monitor safety through Week 48. During the Treatment Extension Periods I and II, safety would be monitored on an ongoing basis by the Study Safety Review Team (SSRT), an internal safety review team that was defined and in place since the original protocol.</li> <li>• Study Assessments: Section 7.5.1.2 was updated to indicate that the Brief Pain Inventory and Brief Fatigue Inventory would not be assessed after Week 96. This change was made as results from the Placebo-controlled Treatment Period suggested that pain and fatigue in XLH are multi-systemic syndromes, making it difficult to isolate and measure a direct impact of burosumab. Therefore, these assessments were removed in Treatment Extension Period II.</li> </ul>

26 January 2018	<ul style="list-style-type: none"> <li>• Overall Study Design and Plan: Section 7.1, Section 7.5.3.8, Table 2.2, and Table 2.3 were updated to include a substudy to assess pre- and postprandial serum phosphorus and calcium levels following 2 different meals on the same day, when burosumab serum concentration was at steady state. The effect of burosumab on postprandial physiological excursions of serum phosphorus has not been studied. The substudy was added to evaluate the postprandial increases in serum phosphorus during burosumab treatment.</li> <li>• Treatments: Section 7.4.1, Section 7.4.6, and Table 2.1 – Table 2.3 were updated to remove the provision for administration of burosumab by subjects or their caregivers in the US. Given that the end of the study was approaching, the implementation of self administration of burosumab, including the requisite training on SC injection techniques, were not feasible.</li> <li>• The Schedule of Events table for Treatment Extension Period II (Table 2.3) was updated to clarify that the WOMAC, 6MWT and TUG test would be assessed for those subjects who discontinued from the study early to ensure that the above assessments were fully captured for all subjects enrolled in Treatment Extension Period II, including those who discontinued from the study early.</li> <li>• In Section 7.5.3.8.2 and Table 2.1 – Table 2.3, the parenthetical explanation of anti burosumab antibodies was changed from human anti-human antibodies (HAHA) to anti-drug antibodies (ADAs). This change was a clarification. While the study protocol previously used the term “HAHA” for this assessment, it was replaced with the more correct and specific term, ADA.</li> </ul>
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Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported

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## Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31165191>

<http://www.ncbi.nlm.nih.gov/pubmed/29947083>