

**Clinical trial results:****A Randomized, Open-Label, Phase 3 Study to Assess the Efficacy and Safety of KRN23 Versus Oral Phosphate and Active Vitamin D Treatment in Pediatric Patients with X-linked Hypophosphatemia (XLH)****Summary**

EudraCT number	2016-000600-29
Trial protocol	DK IE DE ES SE GB IT
Global end of trial date	15 July 2019

**Results information**

Result version number	v1 (current)
This version publication date	31 January 2020
First version publication date	31 January 2020

**Trial information****Trial identification**

Sponsor protocol code	UX023-CL301
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02915705
WHO universal trial number (UTN)	-
Other trial identifiers	Unique product identifier (UPI): EMA/902676

Notes:

**Sponsors**

Sponsor organisation name	Ultragenyx Pharmaceutical Inc.
Sponsor organisation address	60 Leveroni Court, Novato, California , United States, 94949
Public contact	Medical Information, Ultragenyx Pharmaceutical Inc., 1 8887568567, medinfo@ultragenyx.com
Scientific contact	Medical Information, Ultragenyx Pharmaceutical Inc., 1 8887568567, medinfo@ultragenyx.com

Notes:

**Paediatric regulatory details**

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001659-PIP01-15
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 July 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 July 2019
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the effect of KRN23 (burosumab) therapy in improving rickets in children with XLH compared with active control (oral phosphate/active vitamin D).

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

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United States: 31
Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Japan: 5
Country: Number of subjects enrolled	Korea, Republic of: 2
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 4

Worldwide total number of subjects	61
EEA total number of subjects	5

Notes:

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### Subjects enrolled per age group

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In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	6
Children (2-11 years)	53
Adolescents (12-17 years)	2
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Eligible subjects discontinued oral phosphate and active vitamin D therapy for 7 days prior to randomization. Subjects were then randomized 1:1 to receive either open label burosumab administered by subcutaneous (SC) injection every 2 weeks (Q2W) or phosphate and active vitamin D therapy administered orally daily for a total of 64 weeks

### Period 1

Period 1 title	Treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Active Control
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Arm description:

Multiple daily doses of oral phosphate and one or more daily doses of active vitamin D therapy, titrated and individualized by the investigator based on published recommendations during the Treatment Period (up to Week 64).

Arm type	Active comparator
Investigational medicinal product name	Oral Phosphate Supplement
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Oral solution, Oral powder
Routes of administration	Oral use

Dosage and administration details:

Detailed information about the brand, starting dosages, and any changes in oral phosphate and active vitamin D therapy were determined by the treating Investigator within the expert guidelines and recorded at every site visit.

Investigational medicinal product name	Active Vitamin D
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution, Tablet
Routes of administration	Oral use

Dosage and administration details:

Detailed information about the brand, starting dosages, and any changes in oral phosphate and active vitamin D therapy were determined by the treating Investigator within the expert guidelines and recorded at every site visit.

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

Burosumab 0.8 mg/kg starting dose, administered every 2 weeks by subcutaneous injection during the Treatment Period (up to Week 64).

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

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**Dosage and administration details:**

Burosumab dosing should occur no sooner than 8 days after the last dose administered.

<b>Number of subjects in period 1</b>	Active Control	Burosumab
Started	32	29
Completed Week 40	32	29
Completed Week 64	32	29
Completed	32	29

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**Period 2**

Period 2 title	Long Term Extension 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>	Active Control

**Arm description:**

During the Treatment Extension Period (Week 64 to Week 140), subjects crossed over to receive a starting dose of SC burosumab 0.8 mg/kg Q2W. Subjects in Japan and Korea did not enter the Treatment Extension 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:**

Burosumab dosing should occur no sooner than 8 days after the last dose of oral phosphate and active vitamin D.

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

During the Treatment Extension Period (Week 64 to Week 140), subjects continued to receive a starting dose of SC burosumab 0.8 mg/kg Q2W. Subjects in Japan and Korea did not enter the Treatment Extension Period.

Arm type	Experimental
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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:

Burosumab dosing should occur no sooner than 8 days after the last dose administered.

<b>Number of subjects in period 2<sup>[1]</sup></b>	Active Control	Burosumab
Started	26	25
Completed	26	25

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: 7 subjects in Japan and Korea and 3 subjects who started treatment with commercially available burosumab did not enter the Treatment Extension Period.

## Baseline characteristics

### Reporting groups

Reporting group title	Active Control
Reporting group description: Multiple daily doses of oral phosphate and one or more daily doses of active vitamin D therapy, titrated and individualized by the investigator based on published recommendations during the Treatment Period (up to Week 64).	
Reporting group title	Burosumab
Reporting group description: Burosumab 0.8 mg/kg starting dose, administered every 2 weeks by subcutaneous injection during the Treatment Period (up to Week 64).	

Reporting group values	Active Control	Burosumab	Total
Number of subjects	32	29	61
Age categorical			
Units: Subjects			

Age continuous			
age at first dose			
Units: years			
arithmetic mean	6.50	6.01	
standard deviation	± 3.250	± 3.408	-
Gender categorical			
Units: Subjects			
Female	18	16	34
Male	14	13	27
Ethnicity			
Units: Subjects			
Hispanic or Latino	3	3	6
Not Hispanic or Latino	29	26	55
Unknown or Not Reported	0	0	0
Race			
Units: Subjects			
Asian	6	2	8
White	25	25	50
Other/not specified	1	2	3
Rickets Severity Score (RSS) Total Score			
The RSS system is a 10-point radiographic scoring method. Scores are assigned for the unilateral wrist and knee X-rays deemed by the rater to be the more severe of the bilateral images. The maximum total score on the RSS is 10 points and the minimum score is 0, with a total possible score of 4 points for the wrists and 6 points for the knees (the total score is the sum of the wrist and knee score). Higher scores indicate greater rickets severity.			
Units: score on a scale			
arithmetic mean	3.19	3.17	
standard deviation	± 1.141	± 0.975	-
Height-For-Age Z Score			
Recumbent length/Standing height z scores are measures of height adjusted for a child's age and sex. The Z-score indicates the number of standard deviations away from a reference population (from the Centers for Disease Control [CDC] growth charts) in the same age range and with the same sex. A Z-score of 0 is equal to the mean with negative numbers indicating values lower than the mean and			

positive values higher. Higher Z-scores indicate a better outcome.			
One subject in the burosumab group did not have a baseline measurement (n=28 for this group).			
Units: Z score			
arithmetic mean	-2.05	-2.32	
standard deviation	± 0.868	± 1.167	-
Growth Velocity Z Score From Pre-Treatment			
The Z score indicates the number of standard deviations away from a reference population (from Tanner's standard) in the same age range and with the same sex. The baseline growth velocity was calculated for subjects who had data available from within 1.5 years prior to baseline. Children with a mid-point age under 2.25 years were excluded (younger ages are not available in Tanner's standard). A Z score of 0 is equal to the mean with negative numbers indicating values lower than the mean and positive values higher. Higher Z scores indicate a better outcome. n=22, 22 (active control, burosumab)			
Units: Z score			
arithmetic mean	-2.14	-1.37	
standard deviation	± 5.571	± 1.334	-
Serum Phosphorus			
Units: mg/dL			
arithmetic mean	2.30	2.42	
standard deviation	± 0.257	± 0.244	-
Serum 1,25(OH)D			
n=30, 28 (active control, burosumab)			
Units: pg/mL			
arithmetic mean	40.18	46.00	
standard deviation	± 14.886	± 20.060	-
Ratio of Renal Tubular Maximum Reabsorption Rate of Phosphate to Glomerular Filtration Rate(TmP/GFR)			
Data for urinary phosphorus and tubular reabsorption of phosphate (TRP) were used in the calculation of TmP/GFR.			
n=30, 24 (active control, burosumab)			
Units: mg/dL			
arithmetic mean	2.008	2.193	
standard deviation	± 0.3300	± 0.3733	-
Serum Alkaline Phosphatase (ALP) Concentration			
Units: U/L			
arithmetic mean	523.44	510.76	
standard deviation	± 154.419	± 124.903	-
Patient-Reported Outcomes Measurement Information System (PROMIS) Pediatric Pain Interference Domain			
The PROMIS was developed by the National Institutes of Health and uses domain specific measures to assess patient well-being (Broderick et al. 2013), (NIH 2015). It uses a T-score metric in which 50 is the mean of a relevant reference population and 10 is the standard deviation (SD) of that population. For the Pain Interference Domain, decreases indicate less pain.			
n=20, 15 (active control, burosumab)			
Units: T-score			
arithmetic mean	49.9	53.1	
standard deviation	± 12.05	± 10.95	-
PROMIS Physical Function Mobility Domain			
The PROMIS was developed by the National Institutes of Health and uses domain specific measures to assess patient well-being (Broderick et al. 2013), (NIH 2015). It uses a T-score metric in which 50 is the			



mean of a relevant reference population and 10 is the standard deviation (SD) of that population. For the Physical Function Mobility Domain, increases indicate greater mobility.			
n=20, 15 (active control, burosumab)			
Units: T-score			
arithmetic mean	45.5	45.2	
standard deviation	± 9.86	± 9.05	-
PROMIS Fatigue Domain			
The PROMIS was developed by the National Institutes of Health and uses domain specific measures to assess patient well-being (Broderick et al. 2013), (NIH 2015). It uses a T-score metric in which 50 is the mean of a relevant reference population and 10 is the standard deviation (SD) of that population. For the Fatigue Domain, decreases indicate less fatigue.			
n=20, 15 (active control, burosumab)			
Units: T-score			
arithmetic mean	47.0	48.8	
standard deviation	± 13.70	± 9.60	-
Faces Pain Scale- Revised (FPS-R)			
The FPS-R is a dimensionless 10 point Likert scale used to assess self-reported pain intensity on a scale from 0 (no pain) to 10 (most pain you can imagine). Greater pain scores are indicative of more severe pain.			
n=20, 15 (active control, burosumab)			
Units: score on a scale			
arithmetic mean	0.7	0.4	
standard deviation	± 1.17	± 1.12	-
Six Minute Walk Test (6MWT) Total Distance			
The total distance walked (meters) in a 6-minute period was measured, and the percent predicted distance based on normative data for age and gender was estimated.			
n=20, 15 (active control, burosumab)			
Units: meters			
arithmetic mean	450.50	365.93	
standard deviation	± 106.432	± 118.083	-
Percent of Predicted Normal in the 6MWT Total Distance			
The total distance walked (meters) in a 6-minute period was measured, and the percent predicted distance based on normative data for age and gender was estimated.			
n=20, 15 (active control, burosumab)			
Units: meters			
arithmetic mean	76.20	62.13	
standard deviation	± 14.838	± 18.629	-

## End points

### End points reporting groups

Reporting group title	Active Control
Reporting group description: Multiple daily doses of oral phosphate and one or more daily doses of active vitamin D therapy, titrated and individualized by the investigator based on published recommendations during the Treatment Period (up to Week 64).	
Reporting group title	Burosumab
Reporting group description: Burosumab 0.8 mg/kg starting dose, administered every 2 weeks by subcutaneous injection during the Treatment Period (up to Week 64).	
Reporting group title	Active Control
Reporting group description: During the Treatment Extension Period (Week 64 to Week 140), subjects crossed over to receive a starting dose of SC burosumab 0.8 mg/kg Q2W. Subjects in Japan and Korea did not enter the Treatment Extension Period.	
Reporting group title	Burosumab
Reporting group description: During the Treatment Extension Period (Week 64 to Week 140), subjects continued to receive a starting dose of SC burosumab 0.8 mg/kg Q2W. Subjects in Japan and Korea did not enter the Treatment Extension Period.	
Subject analysis set title	Full Analysis Set: Active Control
Subject analysis set type	Full analysis
Subject analysis set description: Full Analysis Set: all randomized subjects who received at least one dose of assigned medication and had at least one post-baseline assessment.	
Subject analysis set title	Full Analysis Set: Burosumab
Subject analysis set type	Full analysis
Subject analysis set description: Full Analysis Set: all randomized subjects who received at least one dose of assigned medication and had at least one post-baseline assessment.	
Subject analysis set title	Pharmacodynamic Analysis Set: Active Control
Subject analysis set type	Full analysis
Subject analysis set description: Pharmacodynamic (PD) Analysis Set: all subjects who received at least one dose of study therapy and had evaluable serum data.	
Subject analysis set title	Pharmacodynamic Analysis Set: Burosumab
Subject analysis set type	Full analysis
Subject analysis set description: Pharmacodynamic (PD) Analysis Set: all subjects who received at least one dose of study therapy and had evaluable serum data.	

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

End point title	Radiographic Global Impression of Change (RGI-C) Global Score at Week 40
End point description: Changes in the severity of rickets and bowing were assessed using a disease specific qualitative RGI-C scoring system. The RGI-C is a 7-point ordinal scale with possible values: +3 = very much better (complete or near complete healing of rickets), +2 = much better (substantial healing of rickets), +1 = minimally better (i.e., minimal healing of rickets), 0 = unchanged, -1 = minimally worse (minimal worsening of rickets), -2 = much worse (moderate worsening of rickets), -3 = very much worse (severe worsening of rickets).	
End point type	Primary

End point timeframe:

Week 40

End point values	Full Analysis Set: Active Control	Full Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	29		
Units: score on a scale				
least squares mean (standard error)	0.77 ( $\pm$ 0.107)	1.92 ( $\pm$ 0.110)		

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Least squares (LS) mean, standard error (SE), confidence interval (CI), and 2-sided p value per ANCOVA model, which included RGI-C as the dependent variable, treatment group and baseline age stratification factor as independent variables and baseline RSS score as a continuous covariate.	
Comparison groups	Full Analysis Set: Burosumab v Full Analysis Set: Active Control
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.45

## Secondary: Percentage of Participants With a Mean RGI-C Global Score $\geq$ +2.0 (Responders) at Week 40

End point title	Percentage of Participants With a Mean RGI-C Global Score $\geq$ +2.0 (Responders) at Week 40
End point description:	
RGI-C responders are defined as subjects with a mean RGI-C global score $\geq$ +2.0. The RGI-C is a 7-point ordinal scale with possible values: +3 = very much better (complete or near complete healing of rickets), +2 = much better (substantial healing of rickets), +1 = minimally better (i.e., minimal healing of rickets), 0 = unchanged, -1 = minimally worse (minimal worsening of rickets), -2 = much worse (moderate worsening of rickets), -3 = very much worse (severe worsening of rickets).	
End point type	Secondary
End point timeframe:	
Week 40	

<b>End point values</b>	Full Analysis Set: Active Control	Full Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	29		
Units: percentage of participants				
number (not applicable)	6.3	72.4		

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Full Analysis Set: Active Control v Full Analysis Set: Burosumab
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[1]</sup>
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	39.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.2
upper limit	211.7

Notes:

[1] - Odds ratio, CI, and 2-sided p-value were per logistic regression model, which included treatment group and baseline age stratification factor as independent variables and baseline RSS score as a continuous covariate.

## Secondary: Percentage of Participants With a Mean RGI-C Global Score $\geq$ +2.0 (Responders) at Week 64

End point title	Percentage of Participants With a Mean RGI-C Global Score $\geq$ +2.0 (Responders) at Week 64
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End point description:

RGI-C responders are defined as subjects with a mean RGI-C global score  $\geq$  +2.0. The RGI-C is a 7-point ordinal scale with possible values: +3 = very much better (complete or near complete healing of rickets), +2 = much better (substantial healing of rickets), +1 = minimally better (i.e., minimal healing of rickets), 0 = unchanged, -1 = minimally worse (minimal worsening of rickets), -2 = much worse (moderate worsening of rickets), -3 = very much worse (severe worsening of rickets).

End point type	Secondary
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End point timeframe:

Week 64

End point values	Full Analysis Set: Active Control	Full Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	29		
Units: percentage of subjects				
number (not applicable)	18.8	86.2		

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Full Analysis Set: Burosumab v Full Analysis Set: Active Control
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 <sup>[2]</sup>
Method	generalized linear mixed model
Parameter estimate	Odds ratio (OR)
Point estimate	34.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.6
upper limit	206.3

Notes:

[2] - Odds ratio, CI, and 2-sided p-value were per generalized linear mixed model, which includes treatment, visit, treatment by visit interaction and baseline age stratification factor as factors, baseline RSS total score as a continuous covariate.

## Secondary: RGI-C Global Score at Week 64

End point title	RGI-C Global Score at Week 64
End point description:	Changes in the severity of rickets and bowing were assessed using a disease specific qualitative RGI-C scoring system. The RGI-C is a 7-point ordinal scale with possible values: +3 = very much better (complete or near complete healing of rickets), +2 = much better (substantial healing of rickets), +1 = minimally better (i.e., minimal healing of rickets), 0 = unchanged, -1 = minimally worse (minimal worsening of rickets), -2 = much worse (moderate worsening of rickets), -3 = very much worse (severe worsening of rickets).
End point type	Secondary
End point timeframe:	
Week 64	

End point values	Full Analysis Set: Active Control	Full Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	29		
Units: score on a scale				
least squares mean (standard error)	1.03 (± 0.136)	2.06 (± 0.072)		

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Statistical analysis description:	
Per generalized estimating equation (GEE) model, which included RGI-C as the dependent variable, treatment, visit, treatment by visit interaction and baseline age stratification factor as factors, baseline RSS score as a continuous covariate, with exchangeable covariate structure.	
Comparison groups	Full Analysis Set: Active Control v Full Analysis Set: Burosumab
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	GEE model
Parameter estimate	difference in LS means
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.33

## Secondary: Change From Baseline in RSS Total Score at Week 40

End point title	Change From Baseline in RSS Total Score at Week 40
End point description:	
The RSS system is a 10-point radiographic scoring method that was developed to assess the severity of nutritional rickets in the wrists and knees based on the degree of metaphyseal fraying, cupping, lucency, separation, and the proportion of the growth plate affected. Scores are assigned for the unilateral wrist and knee X-rays deemed by the rater to be the more severe of the bilateral images. The maximum total score on the RSS is 10 points and the minimum score is 0, with a total possible score of 4 points for the wrists and 6 points for the knees (the total score is the sum of the wrist and knee score). Higher scores indicate greater rickets severity.	
End point type	Secondary
End point timeframe:	
Baseline, Week 40	

End point values	Full Analysis Set: Active Control	Full Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32 <sup>[3]</sup>	28 <sup>[4]</sup>		
Units: score on a scale				
least squares mean (standard error)	-0.71 (±	-2.04 (±		

Notes:

[3] - subjects who had at least one post-baseline RSS Total Score assessment

[4] - subjects who had at least one post-baseline RSS Total Score assessment

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Full Analysis Set: Active Control v Full Analysis Set: Burosumab
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[5]</sup>
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.74
upper limit	-0.94

Notes:

[5] - LS mean, SE, CI, and 2-sided p value per ANCOVA model, which included treatment group and baseline age stratification factor as independent variables and baseline RSS score as a continuous covariate.

## Secondary: Change From Baseline in RSS Total Score at Week 64

End point title	Change From Baseline in RSS Total Score at Week 64
End point description:	
The RSS system is a 10-point radiographic scoring method that was developed to assess the severity of nutritional rickets in the wrists and knees based on the degree of metaphyseal fraying, cupping, and the proportion of the growth plate affected. Scores are assigned for the unilateral wrist and knee X-rays deemed by the rater to be the more severe of the bilateral images. The maximum total score on the RSS is 10 points and the minimum score is 0, with a total possible score of 4 points for the wrists and 6 points for the knees. Higher scores indicate greater rickets severity.	
End point type	Secondary
End point timeframe:	
Baseline, Week 64	

End point values	Full Analysis Set: Active Control	Full Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32 <sup>[6]</sup>	29 <sup>[7]</sup>		
Units: score on a scale				
least squares mean (standard error)	-1.01 (± 0.151)	-2.23 (± 0.117)		

Notes:

[6] - subjects who had at least one post-baseline RSS Total Score assessment

[7] - subjects who had at least one post-baseline RSS Total Score assessment

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Full Analysis Set: Active Control v Full Analysis Set: Burosumab
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[8]</sup>
Method	GEE model
Parameter estimate	difference in LS means
Point estimate	-1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.59
upper limit	-0.83

Notes:

[8] - LS mean, SE, CI, and 2-sided p value per GEE model, which included treatment, visit, treatment by visit interaction and baseline age stratification factor as factors, baseline RSS score as a continuous covariate.

## Secondary: RGI-C Long Leg Score at Week 40

End point title	RGI-C Long Leg Score at Week 40
End point description:	Changes in the severity of lower extremity skeletal abnormalities, including genu varum and genu valgus, were assessed using a disease specific qualitative RGI-C scoring system. The RGI-C is a 7-point ordinal scale with possible values: +3 = very much better (complete or near complete healing), +2 = much better (substantial healing), +1 = minimally better (i.e., minimal healing), 0 = unchanged, -1 = minimally worse (minimal worsening), -2 = much worse (moderate worsening), -3 = very much worse (severe worsening).
End point type	Secondary
End point timeframe:	
Week 40	

End point values	Full Analysis Set: Active Control	Full Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	29		
Units: score on a scale				
least squares mean (standard error)	0.22 (± 0.080)	0.62 (± 0.153)		



## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Full Analysis Set: Active Control v Full Analysis Set: Burosumab
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0162 <sup>[9]</sup>
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	0.72

Notes:

[9] - LS mean, SE, CI, and 2-sided p value per GEE model, which included treatment, visit, treatment by visit interaction, and baseline age stratification factor as factors; and baseline RSS score as a continuous covariate.

## Secondary: RGI-C Long Leg Score at Week 64

End point title	RGI-C Long Leg Score at Week 64
End point description:	Changes in the severity of lower extremity skeletal abnormalities, including genu varum and genu valgus, were assessed using a disease specific qualitative RGI-C scoring system. The RGI-C is a 7-point ordinal scale with possible values: +3 = very much better (complete or near complete healing), +2 = much better (substantial healing), +1 = minimally better (i.e., minimal healing), 0 = unchanged, -1 = minimally worse (minimal worsening), -2 = much worse (moderate worsening), -3 = very much worse (severe worsening).
End point type	Secondary
End point timeframe:	
Week 64	

<b>End point values</b>	Full Analysis Set: Active Control	Full Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	29		
Units: score on a scale				
least squares mean (standard error)	0.29 (± 0.119)	1.25 (± 0.170)		

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Full Analysis Set: Active Control v Full Analysis Set: Burosumab

Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[10]</sup>
Method	GEE model
Parameter estimate	difference in LS means
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.37

Notes:

[10] - LS mean, SE, CI, and 2-sided p value per GEE model, which included treatment, visit, treatment by visit interaction, and baseline age stratification factor as factors; and baseline RSS score as a continuous covariate.

## Secondary: Change From Baseline in Height-For-Age Z-Scores to Week 40

End point title	Change From Baseline in Height-For-Age Z-Scores to Week 40
End point description:	
Recumbent length/Standing height z scores are measures of height adjusted for a child's age and sex. The Z-score indicates the number of standard deviations away from a reference population (from the Centers for Disease Control [CDC] growth charts) in the same age range and with the same sex. A Z-score of 0 is equal to the mean with negative numbers indicating values lower than the mean and positive values higher. Higher Z-scores indicate a better outcome.	
End point type	Secondary
End point timeframe:	
Baseline, Week 40	

End point values	Full Analysis Set: Active Control	Full Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	28 <sup>[11]</sup>		
Units: Z score				
least squares mean (standard error)	0.03 (± 0.031)	0.16 (± 0.052)		

Notes:

[11] - subjects with an assessment at Week 40

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
LS mean, SE, CI, and 2-sided p value per GEE model, which included change from baseline for recumbent length/standing height Z score as the dependent variable, treatment group, visit, interaction between treatment group by visit and baseline RSS stratification as factors, age and baseline recumbent length/standing height Z score as continuous covariates, with exchangeable covariance structure.	
Comparison groups	Full Analysis Set: Active Control v Full Analysis Set: Burosumab

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0408
Method	GEE model
Parameter estimate	LS Mean Difference
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.24

## Secondary: Change From Baseline in Height-For-Age Z-Scores to Week 64

End point title	Change From Baseline in Height-For-Age Z-Scores to Week 64
End point description:	
Recumbent length/Standing height z scores are measures of height adjusted for a child's age and sex. The Z-score indicates the number of standard deviations away from a reference population (from the CDC growth charts) in the same age range and with the same sex. A Z-score of 0 is equal to the mean with negative numbers indicating values lower than the mean and positive values higher. Higher Z-scores indicate a better outcome.	
End point type	Secondary
End point timeframe:	
Baseline, Week 64	

End point values	Full Analysis Set: Active Control	Full Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	28 <sup>[12]</sup>		
Units: Z score				
least squares mean (standard error)	0.02 (± 0.035)	0.17 (± 0.066)		

Notes:

[12] - subjects with an assessment at Week 64

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
LS mean, SE, CI, and 2-sided p value per GEE model, which included change from baseline for recumbent length/standing height Z score as the dependent variable, treatment group, visit, interaction between treatment group by visit and baseline RSS stratification as factors, age and baseline recumbent length/standing height Z score as continuous covariates, with exchangeable covariance structure.	
Comparison groups	Full Analysis Set: Active Control v Full Analysis Set: Burosumab

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.049
Method	GEE model
Parameter estimate	difference in LS means
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.29

## Secondary: Change in Growth Velocity Z Score From Baseline to Week 40

End point title	Change in Growth Velocity Z Score From Baseline to Week 40
End point description:	
<p>A growth velocity Z score was calculated based on Tanner's standard. The Z score indicates the number of standard deviations away from a reference population (from Tanner's standard) in the same age range and with the same sex. The baseline growth velocity was calculated for participants who had data available from within 1.5 years prior to baseline. The Week 64 growth velocity was calculated using data between baseline and Week 64. The mid-point of the age interval was used to locate the closest reference age provided by Tanner's Standard. Children with a mid-point age under 2.25 years were excluded, because younger ages are not available in Tanner's standard. To smoothly transition from recumbent length to standing height, 0.8 cm was subtracted from recumbent length before pooling with standing height. A Z score of 0 is equal to the mean with negative numbers indicating values lower than the mean and positive values higher. Higher Z scores indicate a better outcome.</p>	
End point type	Secondary
End point timeframe:	
Baseline, Week 40	

End point values	Full Analysis Set: Active Control	Full Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22 <sup>[13]</sup>	22 <sup>[14]</sup>		
Units: Z score				
least squares mean (standard error)	0.73 (± 0.339)	1.76 (± 0.337)		

Notes:

[13] - subjects with Baseline growth velocity

[14] - subjects with Baseline growth velocity

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
<p>LS mean, SE, CI, and 2-sided p value per ANCOVA model, which included change from baseline for growth velocity Z score as the dependent variable, treatment group and baseline RSS total score stratification as factors, baseline Z score and age as continuous covariates.</p>	
Comparison groups	Full Analysis Set: Active Control v Full Analysis Set: Burosumab

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0386
Method	ANCOVA
Parameter estimate	difference in LS means
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	1.99

## Secondary: Change in Growth Velocity Z Score From Baseline to Week 64

End point title	Change in Growth Velocity Z Score From Baseline to Week 64
End point description:	
<p>A growth velocity Z score was calculated based on Tanner's standard. The Z score indicates the number of standard deviations away from a reference population (from Tanner's standard) in the same age range and with the same sex. The baseline growth velocity was calculated for participants who had data available from within 1.5 years prior to baseline. The Week 64 growth velocity was calculated using data between baseline and Week 64. The mid-point of the age interval was used to locate the closest reference age provided by Tanner's Standard. Children with a mid-point age under 2.25 years were excluded, because younger ages are not available in Tanner's standard. To smoothly transition from recumbent length to standing height, 0.8 cm was subtracted from recumbent length before pooling with standing height. A Z score of 0 is equal to the mean with negative numbers indicating values lower than the mean and positive values higher. Higher Z scores indicate a better outcome.</p>	
End point type	Secondary
End point timeframe:	
Baseline, Week 64	

End point values	Full Analysis Set: Active Control	Full Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22 <sup>[15]</sup>	22 <sup>[16]</sup>		
Units: Z score				
least squares mean (standard error)	0.41 (± 0.265)	1.53 (± 0.264)		

Notes:

[15] - subjects with Baseline growth velocity

[16] - subjects with Baseline growth velocity

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
<p>LS mean, SE, CI, and 2-sided p value per ANCOVA model, which included change from baseline for growth velocity Z score as the dependent variable, treatment group and baseline RSS total score stratification as factors, baseline Z score and age as continuous covariates.</p>	
Comparison groups	Full Analysis Set: Active Control v Full Analysis Set: Burosumab

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0047
Method	ANCOVA
Parameter estimate	difference in LS means
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	1.88

### Secondary: Change From Baseline Over Time in Serum Phosphorus Concentration, up to Week 64

End point title	Change From Baseline Over Time in Serum Phosphorus Concentration, up to Week 64
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End point description:

The generalized estimation equation (GEE) model includes change from baseline for serum phosphorous measurement as the dependent variable, treatment group, visit, interaction between treatment group by visit, baseline age and Baseline RSS stratification as factors, baseline phosphorous measure as a covariate, with exchangeable covariance structure. The GEE model included data up to Week 64.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 1, 2, 4, 8, 12, 16, 24, 32, 33, 40, 52, 64

End point values	Pharmacodynamic Analysis Set: Active Control	Pharmacodynamic Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32 <sup>[17]</sup>	29 <sup>[18]</sup>		
Units: mg/dL				
least squares mean (standard error)				
Week 1; n=31, 28	0.22 (± 0.072)	1.26 (± 0.094)		
Week 2; n=0, 26	99999 (± 99999)	1.14 (± 0.098)		
Week 4; n=32, 29	0.18 (± 0.061)	1.21 (± 0.102)		
Week 8; n=32, 29	0.21 (± 0.064)	0.99 (± 0.074)		
Week 12; n=0, 26	99999 (± 99999)	1.01 (± 0.072)		
Week 16; n=29, 29	0.24 (± 0.063)	0.87 (± 0.072)		
Week 24; n=32, 29	0.27 (± 0.073)	0.78 (± 0.077)		
Week 32; n=32, 29	0.23 (± 0.063)	0.93 (± 0.073)		
Week 33; n=0, 27	99999 (± 99999)	1.23 (± 0.106)		
Week 40; n=32, 29	0.20 (± 0.062)	0.92 (± 0.080)		
Week 52; n=32, 29	0.30 (± 0.082)	0.91 (± 0.075)		
Week 64; n=32, 29	0.21 (± 0.062)	0.91 (± 0.078)		

Notes:

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

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

<b>Attachments (see zip file)</b>	Change From Baseline Over Time in Serum Phosphorus
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### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline Over Time in Serum Phosphorus Concentration, Weeks 66-112

End point title	Change From Baseline Over Time in Serum Phosphorus Concentration, Weeks 66-112
End point description:	
End point type	Secondary
End point timeframe:	
Baseline, Weeks 66, 68, 76, 88, 100, 112	

End point values	Pharmacodynamic Analysis Set: Active Control	Pharmacodynamic Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26 <sup>[19]</sup>	22 <sup>[20]</sup>		
Units: mg/dL				
arithmetic mean (standard deviation)				
Week 66; n=26, 0	0.05 (± 0.235)	99999 (± 99999)		
Week 68; n=26, 1	1.17 (± 0.472)	1.10 (± 999999)		
Week 76; n=22, 22	0.90 (± 0.324)	0.92 (± 0.324)		
Week 88; n=16, 11	0.98 (± 0.433)	1.00 (± 0.576)		
Week 100; n=7, 2	0.99 (± 0.445)	1.00 (± 0.424)		
Week 112; n=5, 2	1.26 (± 0.508)	1.10 (± 0.283)		

Notes:

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

[20] - n=subjects with an assessment at given time point; 99999=not applicable (NA; n=0); 999999=NA (n=1)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Mean Post-Baseline Serum Phosphorus Level to Week 64

End point title	Change From Baseline in Mean Post-Baseline Serum Phosphorus Level to Week 64
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End point description:

The ANCOVA model includes change in serum phosphorus from baseline to mean post-baseline as the dependent variable, treatment group, baseline age and baseline RSS stratification as factors, baseline phosphorous measure as a covariate.

End point type	Secondary
End point timeframe:	
Baseline, Weeks 1, 4, 8, 16, 24, 32, 40, 52, 64	

<b>End point values</b>	Pharmacodynamic Analysis Set: Active Control	Pharmacodynamic Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	29		
Units: mg/dL				
least squares mean (standard error)	0.24 ( $\pm$ 0.058)	0.98 ( $\pm$ 0.061)		

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Pharmacodynamic Analysis Set: Active Control v Pharmacodynamic Analysis Set: Burosumab
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	difference in LS means
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	0.91

## Secondary: Change From Baseline in Mean Post-Baseline Serum Phosphorus Level to Week 140 (During Treatment with Burosumab)

End point title	Change From Baseline in Mean Post-Baseline Serum Phosphorus Level to Week 140 (During Treatment with Burosumab)
End point description:	
End point type	Secondary
End point timeframe:	
Burosumab arm: Baseline, Week 1, 4, 8, 16, 24, 32, 40, 52, 64, 66, 68, 76, 88, 100, 112, 124, 140; Active Control arm: Baseline, Week 68, 76, 88, 100, 112, 124, 140	



End point values	Pharmacodynamic Analysis Set: Active Control	Pharmacodynamic Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	29		
Units: mg/dL				
arithmetic mean (standard deviation)	1.05 ( $\pm$ 0.310)	0.93 ( $\pm$ 0.336)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants Reaching the Normal Range of Serum Phosphorus Concentration (3.2 - 6.1 mg/dL)

End point title	Percentage of Participants Reaching the Normal Range of Serum Phosphorus Concentration (3.2 - 6.1 mg/dL)
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End point description:

End point type	Secondary
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End point timeframe:

Burosumab arm: Baseline, up to Week 140; Active Control arm: Baseline, Week 68 up to Week 140

End point values	Pharmacodynamic Analysis Set: Active Control	Pharmacodynamic Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	29		
Units: percentage of subjects				
number (not applicable)	75.0	96.6		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline Over Time in 1,25-Dihydroxyvitamin D, up to Week 64

End point title	Change From Baseline Over Time in 1,25-Dihydroxyvitamin D, up to Week 64
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End point description:

The GEE model includes change from baseline for 1, 25-Dihydroxyvitamin D measurement as the dependent variable, treatment group, visit, interaction between treatment group by visit, baseline age

and baseline RSS stratification as factors, baseline 1, 25-Dihydroxyvitamin D measure as a covariate, with exchangeable covariance structure. The GEE model included data up to Week 64.

End point type	Secondary
End point timeframe:	
Baseline, Weeks 1, 2, 4, 8, 12, 16, 24, 32, 33, 40, 52, 64	

End point values	Pharmacodynamic Analysis Set: Active Control	Pharmacodynamic Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30 <sup>[21]</sup>	28 <sup>[22]</sup>		
Units: pg/mL				
least squares mean (standard error)				
Week 1; n=29, 27	19.81 (± 2.758)	68.09 (± 5.251)		
Week 2; n=0, 24	99999 (± 99999)	31.78 (± 5.130)		
Week 4; n=30, 27	12.77 (± 2.998)	33.86 (± 3.561)		
Week 8; n=30, 28	15.10 (± 2.528)	30.85 (± 3.830)		
Week 12; n=0, 24	99999 (± 99999)	33.43 (± 3.176)		
Week 16; n=27, 28	19.41 (± 3.757)	32.38 (± 3.032)		
Week 24; n=28, 27	17.46 (± 2.905)	28.35 (± 3.113)		
Week 32; n=29, 28	17.25 (± 3.156)	23.49 (± 2.439)		
Week 33; n=0, 24	99999 (± 99999)	31.50 (± 3.423)		
Week 40; n=27, 25	18.42 (± 3.594)	29.63 (± 3.721)		
Week 52; n=29, 27	8.74 (± 3.866)	13.75 (± 2.862)		
Week 64; n=29, 27	1.19 (± 2.785)	9.89 (± 2.235)		

Notes:

[21] - n=subjects with an assessment at given time point; 99999=NA (n=0)

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

<b>Attachments (see zip file)</b>	Change From Baseline Over Time in 1,25-Dihydroxyvitamin D,
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## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline Over Time in 1,25-Dihydroxyvitamin D, Weeks 68 to 112

End point title	Change From Baseline Over Time in 1,25-Dihydroxyvitamin D, Weeks 68 to 112
End point description:	
End point type	Secondary

End point timeframe:

Baseline, Weeks 68, 76, 88, 100, 112

End point values	Pharmacodynamic Analysis Set: Active Control	Pharmacodynamic Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25 <sup>[23]</sup>	21 <sup>[24]</sup>		
Units: pg/mL				
arithmetic mean (standard deviation)				
Week 68; n=25, 1	22.12 (± 23.950)	-9.80 (± 99999)		
Week 76; n=21, 21	19.05 (± 22.612)	12.80 (± 20.093)		
Week 88; n=14, 10	24.58 (± 17.787)	11.76 (± 22.874)		
Week 100; n=6, 2	33.57 (± 16.591)	13.25 (± 1.061)		
Week 112; n=5, 2	29.94 (± 15.402)	31.05 (± 33.729)		

Notes:

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

[24] - n=subjects with an assessment at given time point; 99999=NA (n=1)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline Over Time in TmP/GFR, up to Week 64

End point title	Change From Baseline Over Time in TmP/GFR, up to Week 64
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End point description:

Serum phosphorus and TRP measurements were used in the calculation of TmP/GFR.

The GEE model includes change from baseline for TmP/GFR measurement as the dependent variable, treatment group, visit, interaction between treatment group by visit, baseline age and baseline RSS stratification as factors, baseline TmP/GFR measure as a covariate, with exchangeable covariance structure. The GEE model included data up to Week 64.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 4, 8, 16, 24, 32, 40, 52, 64

End point values	Pharmacodynamic Analysis Set: Active Control	Pharmacodynamic Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed				
Units: mg/dL				
least squares mean (standard error)				

Week 4; n=28, 23	-0.17 (± 0.065)	1.48 (± 0.173)		
Week 8; n=27, 24	-0.20 (± 0.057)	1.22 (± 0.101)		
Week 16; n=26, 24	-0.15 (± 0.085)	1.00 (± 0.139)		
Week 24; n=29, 23	-0.12 (± 0.072)	0.99 (± 0.134)		
Week 32; n=29, 22	-0.10 (± 0.062)	1.14 (± 0.115)		
Week 40; n=28, 23	-0.15 (± 0.053)	1.20 (± 0.113)		
Week 52; n=28, 22	-0.12 (± 0.069)	1.13 (± 0.124)		
Week 64; n=30, 23	-0.09 (± 0.070)	1.16 (± 0.127)		

<b>Attachments (see zip file)</b>	Change From Baseline Over Time in TmP_GFR, up to Week 64
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### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline Over Time in TmP/GFR, Week 68 to 112

End point title	Change From Baseline Over Time in TmP/GFR, Week 68 to 112
End point description:	Serum phosphorus and TRP measurements were used in the calculation of TmP/GFR.
End point type	Secondary
End point timeframe:	Baseline, Weeks 68, 76, 88, 112

End point values	Pharmacodynamic Analysis Set: Active Control	Pharmacodynamic Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24 <sup>[25]</sup>	7 <sup>[26]</sup>		
Units: mg/dL				
arithmetic mean (standard deviation)				
Week 68; n=24, 1	1.61 (± 0.705)	1.65 (± 99999)		
Week 76; n=4, 4	1.18 (± 0.758)	0.59 (± 0.429)		
Week 88; n=14, 7	1.33 (± 0.480)	0.95 (± 0.620)		
Week 112; n=3, 2	1.56 (± 0.233)	1.32 (± 0.233)		

Notes:

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

[26] - n=subjects with an assessment at given time point; 99999=NA (n=1)

### Statistical analyses

**Secondary: Change From Baseline Over Time in Serum ALP, up to Week 64**

End point title	Change From Baseline Over Time in Serum ALP, up to Week 64
End point description: The GEE model includes change from baseline for ALP measurement as the dependent variable, treatment group, visit, interaction between treatment group by visit, baseline age and baseline RSS stratification as factors, baseline ALP measure as a covariate, with exchangeable covariance structure. The GEE model included data up to Week 64.	
End point type	Secondary
End point timeframe: Baseline, Weeks 16, 24, 40, 52, 64	

End point values	Pharmacodynamic Analysis Set: Active Control	Pharmacodynamic Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	29		
Units: U/L				
least squares mean (standard error)				
Week 16	-5.43 (± 17.885)	-97.97 (± 11.281)		
Week 24	-22.43 (± 15.074)	-108.00 (± 16.225)		
Week 40	-34.78 (± 18.132)	-130.72 (± 12.365)		
Week 52	-50.03 (± 18.641)	-161.31 (± 11.674)		
Week 64	-28.06 (± 19.980)	-174.62 (± 13.427)		

**Statistical analyses**

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Week 16	
Comparison groups	Pharmacodynamic Analysis Set: Active Control v Pharmacodynamic Analysis Set: Burosumab
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	GEE model
Parameter estimate	difference
Point estimate	-92.53

Confidence interval	
level	95 %
sides	2-sided
lower limit	-131.4
upper limit	-53.66

<b>Statistical analysis title</b>	Statistical Analysis 2
Statistical analysis description:	
Week 24	
Comparison groups	Pharmacodynamic Analysis Set: Active Control v Pharmacodynamic Analysis Set: Burosumab
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	GEE model
Parameter estimate	difference
Point estimate	-85.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-126.37
upper limit	-44.76

<b>Statistical analysis title</b>	Statistical Analysis 3
Statistical analysis description:	
Week 40	
Comparison groups	Pharmacodynamic Analysis Set: Active Control v Pharmacodynamic Analysis Set: Burosumab
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	GEE model
Parameter estimate	difference
Point estimate	-95.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-136.05
upper limit	-55.84

<b>Statistical analysis title</b>	Statistical Analysis 4
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**Statistical analysis description:****Week 52**

Comparison groups	Pharmacodynamic Analysis Set: Active Control v Pharmacodynamic Analysis Set: Burosumab
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	GEE model
Parameter estimate	difference
Point estimate	-111.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-152.08
upper limit	-70.49

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**Statistical analysis title**

Statistical Analysis 5

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**Statistical analysis description:****Week 64**

Comparison groups	Pharmacodynamic Analysis Set: Active Control v Pharmacodynamic Analysis Set: Burosumab
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	GEE model
Parameter estimate	difference
Point estimate	-146.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-191.61
upper limit	-101.52

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**Secondary: Change From Baseline Over Time in Serum ALP, Week 68 to 112**

End point title	Change From Baseline Over Time in Serum ALP, Week 68 to 112
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End point description:

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End point type	Secondary
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End point timeframe:

Baseline, Weeks 68, 76, 88, 100, 112

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End point values	Pharmacodynamic Analysis Set: Active Control	Pharmacodynamic Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26 <sup>[27]</sup>	22 <sup>[28]</sup>		
Units: U/L				
arithmetic mean (standard deviation)				
Week 68; n=26, 1	-82.73 (± 83.683)	-184.00 (± 99999)		
Week 76; n=22, 22	-106.73 (± 73.316)	-166.73 (± 87.700)		
Week 88; n=16, 11	-146.56 (± 73.120)	-154.55 (± 48.148)		
Week 100; n=7, 2	-83.14 (± 104.675)	-184.00 (± 48.083)		
Week 112; n=5, 2	-104.80 (± 80.350)	-172.00 (± 26.870)		

Notes:

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

[28] - n=subjects with an assessment at given time point; 99999=NA (n=1)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Change From Baseline Over Time in Serum ALP, up to Week 112

End point title	Percent Change From Baseline Over Time in Serum ALP, up to Week 112
End point description:	
Decreases indicate improvement.	
End point type	Secondary
End point timeframe:	
Baseline, Weeks 16, 24, 40, 52, 64, 68, 76, 88, 100, 112	

End point values	Pharmacodynamic Analysis Set: Active Control	Pharmacodynamic Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32 <sup>[29]</sup>	29 <sup>[30]</sup>		
Units: percent change				
arithmetic mean (standard deviation)				
Week 16; n=29, 29	0.41 (± 21.021)	-18.39 (± 10.815)		
Week 24; n=32, 29	-3.21 (± 15.827)	-19.88 (± 17.642)		
Week 40; n=32, 29	-6.85 (± 16.493)	-24.38 (± 13.498)		
Week 52; n=32, 29	-8.60 (± 19.027)	-30.60 (± 11.852)		
Week 64; n=32, 29	-4.60 (± 20.711)	-32.78 (± 13.095)		
Week 68; n=26, 1	-14.66 (± 14.760)	-38.02 (± 99999)		



Week 76; n=22, 22	-20.49 ( $\pm$ 13.926)	-31.42 ( $\pm$ 13.422)		
Week 88; n=16, 11	-28.77 ( $\pm$ 12.201)	-32.02 ( $\pm$ 10.610)		
Week 100; n=7, 2	-16.06 ( $\pm$ 23.703)	-39.29 ( $\pm$ 11.460)		
Week 112; n=5, 2	-21.00 ( $\pm$ 15.053)	-36.67 ( $\pm$ 6.868)		

Notes:

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

[30] - n=subjects with an assessment at given time point; 99999=NA (n=1)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in the PROMIS Pediatric Pain Interference, Physical Function Mobility and Fatigue Domain Scores (For Participants $\geq$ 5 Years of Age at the Screening Visit) at Week 40

End point title	Change From Baseline in the PROMIS Pediatric Pain Interference, Physical Function Mobility and Fatigue Domain Scores (For Participants $\geq$ 5 Years of Age at the Screening Visit) at Week 40
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End point description:

The PROMIS was developed by the National Institutes of Health and uses domain-specific measures to assess patient well-being (Broderick et al. 2013), (NIH 2015). It uses a T-score metric in which 50 is the mean of a relevant reference population and 10 is the standard deviation (SD) of that population. For the Pain Interference Domain, decreases indicate less pain, for the Physical Function Mobility Domain, increases indicate greater mobility and for the Fatigue Domain, decreases indicate less fatigue.

End point type	Secondary
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End point timeframe:

Baseline, Week 40

End point values	Full Analysis Set: Active Control	Full Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20 <sup>[31]</sup>	15 <sup>[32]</sup>		
Units: T-score				
least squares mean (standard error)				
Pain Interference Domain Score	-0.29 ( $\pm$ 1.539)	-5.31 ( $\pm$ 1.705)		
Physical Function Mobility Domain Score	0.10 ( $\pm$ 0.966)	2.78 ( $\pm$ 1.336)		
Fatigue Domain Score	-1.05 ( $\pm$ 1.754)	-4.29 ( $\pm$ 1.709)		

Notes:

[31] - subjects with an assessment at Week 40

[32] - subjects with an assessment at Week 40

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Pain Interference Domain. 2-sided p value per GEE model, which included change from baseline for the parameter as the dependent variable, treatment group, visit, interaction between treatment group by

visit, baseline age and baseline RSS stratification as factors, baseline parameter measure as a covariate, with exchangeable covariance structure.

Comparison groups	Full Analysis Set: Active Control v Full Analysis Set: Burosumab
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0212
Method	GEE model
Parameter estimate	difference in LS means
Point estimate	-5.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.29
upper limit	-0.75

<b>Statistical analysis title</b>	Statistical Analysis 2
Statistical analysis description:	
Physical Function Mobility Domain. 2-sided p value per GEE model, which included change from baseline for the parameter as the dependent variable, treatment group, visit, interaction between treatment group by visit, baseline age and baseline RSS stratification as factors, baseline parameter measure as a covariate, with exchangeable covariance structure.	
Comparison groups	Full Analysis Set: Burosumab v Full Analysis Set: Active Control
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1009
Method	GEE model
Parameter estimate	difference in LS means
Point estimate	2.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.52
upper limit	5.89

<b>Statistical analysis title</b>	Statistical Analysis 3
Statistical analysis description:	
Fatigue Domain. 2-sided p value per GEE model, which included change from baseline for the parameter as the dependent variable, treatment group, visit, interaction between treatment group by visit, baseline age and baseline RSS stratification as factors, baseline parameter measure as a covariate, with exchangeable covariance structure.	
Comparison groups	Full Analysis Set: Active Control v Full Analysis Set: Burosumab

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1676
Method	GEE model
Parameter estimate	difference in LS means
Point estimate	-3.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.86
upper limit	1.37

### Secondary: Change From Baseline in the PROMIS Pediatric Pain Interference, Physical Function Mobility and Fatigue Domain Scores (For Participants $\geq$ 5 Years of Age at the Screening Visit) at Week 64

End point title	Change From Baseline in the PROMIS Pediatric Pain Interference, Physical Function Mobility and Fatigue Domain Scores (For Participants $\geq$ 5 Years of Age at the Screening Visit) at Week 64
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End point description:

The PROMIS was developed by the National Institutes of Health and uses domain-specific measures to assess patient well-being (Broderick et al. 2013), (NIH 2015). It uses a T-score metric in which 50 is the mean of a relevant reference population and 10 is the standard deviation (SD) of that population. For the Pain Interference Domain, decreases indicate less pain, for the Physical Function Mobility Domain, increases indicate greater mobility and for the Fatigue Domain, decreases indicate less fatigue.

End point type	Secondary
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End point timeframe:

Baseline, Week 64

End point values	Full Analysis Set: Active Control	Full Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20 <sup>[33]</sup>	15 <sup>[34]</sup>		
Units: T-score				
least squares mean (standard error)				
Pain Interference Domain Score	-1.29 ( $\pm$ 1.267)	-3.55 ( $\pm$ 1.873)		
Physical Function Mobility Domain Score	0.92 ( $\pm$ 0.962)	2.82 ( $\pm$ 1.648)		
Fatigue Domain Score	-2.57 ( $\pm$ 1.547)	-3.65 ( $\pm$ 2.119)		

Notes:

[33] - subjects with an assessment at Week 64

[34] - subjects with an assessment at Week 64

### Statistical analyses

Statistical analysis title	Statistical Analysis 1
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**Statistical analysis description:**

Pain Interference Domain. 2-sided p value per GEE model, which included change from baseline for the parameter as the dependent variable, treatment group, visit, interaction between treatment group by visit, baseline age and baseline RSS stratification as factors, baseline parameter measure as a covariate, with exchangeable covariance structure.

Comparison groups	Full Analysis Set: Active Control v Full Analysis Set: Burosumab
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3091
Method	GEE model
Parameter estimate	difference in LS means
Point estimate	-2.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.61
upper limit	2.09

**Statistical analysis title**

Statistical Analysis 2

**Statistical analysis description:**

Physical Function Mobility Domain. 2-sided p value per GEE model, which included change from baseline for the parameter as the dependent variable, treatment group, visit, interaction between treatment group by visit, baseline age and baseline RSS stratification as factors, baseline parameter measure as a covariate, with exchangeable covariance structure.

Comparison groups	Full Analysis Set: Active Control v Full Analysis Set: Burosumab
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3145
Method	GEE model
Parameter estimate	difference in LS means
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	5.59

**Statistical analysis title**

Statistical Analysis 3

**Statistical analysis description:**

Fatigue Domain. 2-sided p value per GEE model, which included change from baseline for the parameter as the dependent variable, treatment group, visit, interaction between treatment group by visit, baseline age and baseline RSS stratification as factors, baseline parameter measure as a covariate, with exchangeable covariance structure.

Comparison groups	Full Analysis Set: Active Control v Full Analysis Set: Burosumab
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Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.681
Method	GEE model
Parameter estimate	difference in LS means
Point estimate	-1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.21
upper limit	4.06

### Secondary: Change From Baseline in the FPS-R (For Participants ≥ 5 Years of Age at the Screening Visit) at Week 40

End point title	Change From Baseline in the FPS-R (For Participants ≥ 5 Years of Age at the Screening Visit) at Week 40
End point description:	
The FPS-R is a dimensionless 10 point Likert scale used to assess self-reported pain intensity on a scale from 0 (no pain) to 10 (most pain you can imagine). Greater pain scores are indicative of more severe pain.	
End point type	Secondary
End point timeframe:	
Baseline, Week 40	

End point values	Full Analysis Set: Active Control	Full Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20 <sup>[35]</sup>	15 <sup>[36]</sup>		
Units: units on a scale				
least squares mean (standard error)	0.02 (± 0.323)	0.03 (± 0.323)		

Notes:

[35] - subjects with an assessment at Week 40

[36] - subjects with an assessment at Week 40

### Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
GEE model includes change from baseline for FPS-R as the dependent variable, treatment group, visit, interaction between treatment group by visit and baseline RSS stratification as factors, baseline FPS-R as a covariate, with exchangeable covariance structure. The LS Mean, SE, 95% CI and 2-sided p-value are from the GEE model.	
Comparison groups	Full Analysis Set: Active Control v Full Analysis Set: Burosumab

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9862
Method	GEE model
Parameter estimate	difference in LS means
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.79
upper limit	0.8

### Secondary: Change From Baseline in the FPS-R (For Participants ≥ 5 Years of Age at the Screening Visit) at Week 64

End point title	Change From Baseline in the FPS-R (For Participants ≥ 5 Years of Age at the Screening Visit) at Week 64
End point description:	
The FPS-R is a dimensionless 10 point Likert scale used to assess self-reported pain intensity on a scale from 0 (no pain) to 10 (most pain you can imagine). Greater pain scores are indicative of more severe pain.	
End point type	Secondary
End point timeframe:	
Baseline, Week 64	

End point values	Full Analysis Set: Active Control	Full Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19 <sup>[37]</sup>	15 <sup>[38]</sup>		
Units: units on a scale				
least squares mean (standard error)	0.04 (± 0.270)	-0.01 (± 0.234)		

Notes:

[37] - subjects with an assessment at Week 64

[38] - subjects with an assessment at Week 64

### Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
GEE model includes change from baseline for FPS-R as the dependent variable, treatment group, visit, interaction between treatment group by visit and baseline RSS stratification as factors, baseline FPS-R as a covariate, with exchangeable covariance structure. The LS Mean, SE, 95% CI and 2-sided p-value are from the GEE model.	
Comparison groups	Full Analysis Set: Active Control v Full Analysis Set: Burosumab

Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8786
Method	GEE model
Parameter estimate	difference in LS means
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	0.68

## Secondary: Change From Baseline in the 6MWT Total Distance at Week 40

End point title	Change From Baseline in the 6MWT Total Distance at Week 40
End point description:	
The total distance walked (meters) in a 6-minute period was measured in participants $\geq 5$ years of age at the Screening Visit who were able to complete the test.	
End point type	Secondary
End point timeframe:	
Baseline, Week 40	

End point values	Full Analysis Set: Active Control	Full Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20 <sup>[39]</sup>	13 <sup>[40]</sup>		
Units: meters				
least squares mean (standard error)	3.65 ( $\pm$ 14.060)	47.10 ( $\pm$ 15.768)		

Notes:

[39] - subjects with an assessment at Week 40 in subjects  $\geq 5$  years who were able to complete the test

[40] - subjects with an assessment at Week 40 in subjects  $\geq 5$  years who were able to complete the test

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
2-sided p value per GEE model, which included change from baseline for the parameter as the dependent variable, treatment group, visit, interaction between treatment group by visit, baseline age and baseline RSS stratification as factors, baseline parameter measure as a covariate, with exchangeable covariance structure.	
Comparison groups	Full Analysis Set: Burosumab v Full Analysis Set: Active Control

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0514
Method	GEE model
Parameter estimate	difference in LS means
Point estimate	43.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	87.17

## Secondary: Change From Baseline in the 6MWT Total Distance at Week 64

End point title	Change From Baseline in the 6MWT Total Distance at Week 64
End point description:	The total distance walked (meters) in a 6-minute period was measured in participants $\geq 5$ years of age at the Screening Visit who were able to complete the test.
End point type	Secondary
End point timeframe:	Baseline, Week 64

End point values	Full Analysis Set: Active Control	Full Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20 <sup>[41]</sup>	13 <sup>[42]</sup>		
Units: meters				
least squares mean (standard error)	29.28 ( $\pm$ 16.834)	74.83 ( $\pm$ 12.513)		

Notes:

[41] - subjects with an assessment at Week 64

[42] - subjects with an assessment at Week 64

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	2-sided p value per GEE model, which included change from baseline for the parameter as the dependent variable, treatment group, visit, interaction between treatment group by visit, baseline age and baseline RSS stratification as factors, baseline parameter measure as a covariate, with exchangeable covariance structure.
Comparison groups	Full Analysis Set: Active Control v Full Analysis Set: Burosumab



Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0399
Method	GEE model
Parameter estimate	difference in LS means
Point estimate	45.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.09
upper limit	89.02

## Secondary: Percent of Predicted Normal in the 6MWT Total Distance at Week 40

End point title	Percent of Predicted Normal in the 6MWT Total Distance at Week 40
End point description:	
The total distance walked (meters) in a 6-minute period was measured in participants $\geq 5$ years of age at the Screening Visit who were able to complete the test, and the percent predicted distance based on normative data for age and gender was estimated.	
End point type	Secondary
End point timeframe:	
Baseline, Week 40	

End point values	Full Analysis Set: Active Control	Full Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20 <sup>[43]</sup>	13 <sup>[44]</sup>		
Units: percent of predicted meters				
least squares mean (standard error)	-1.14 ( $\pm$ 2.224)	5.59 ( $\pm$ 2.633)		

Notes:

[43] - subjects with an assessment at Week 40

[44] - subjects with an assessment at Week 40

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
2-sided p value per GEE model, which included change from baseline for the parameter as the dependent variable, treatment group, visit, interaction between treatment group by visit, baseline age and baseline RSS stratification as factors, baseline parameter measure as a covariate, with exchangeable covariance structure.	
Comparison groups	Full Analysis Set: Active Control v Full Analysis Set: Burosumab

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0633
Method	GEE model
Parameter estimate	difference in LS means
Point estimate	6.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	13.82

## Secondary: Percent of Predicted Normal in the 6MWT Total Distance at Week 64

End point title	Percent of Predicted Normal in the 6MWT Total Distance at Week 64
End point description:	
The total distance walked (meters) in a 6-minute period was measured in participants $\geq 5$ years of age at the Screening Visit who were able to complete the test, and the percent predicted distance based on normative data for age and gender was estimated.	
End point type	Secondary
End point timeframe:	
Baseline, Week 64	

End point values	Full Analysis Set: Active Control	Full Analysis Set: Burosumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20 <sup>[45]</sup>	13 <sup>[46]</sup>		
Units: percent of predicted meters				
least squares mean (standard error)	1.88 ( $\pm$ 2.789)	9.15 ( $\pm$ 2.056)		

Notes:

[45] - subjects with an assessment at Week 64

[46] - subjects with an assessment at Week 64

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
2-sided p value per GEE model, which included change from baseline for the parameter as the dependent variable, treatment group, visit, interaction between treatment group by visit, baseline age and baseline RSS stratification as factors, baseline parameter measure as a covariate, with exchangeable covariance structure.	
Comparison groups	Full Analysis Set: Burosumab v Full Analysis Set: Active Control

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0496
Method	GEE model
Parameter estimate	difference in LS means
Point estimate	7.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	14.52

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to Week 64 in the Treatment Period and up to Week 140 in the Long Term Extension Period, plus up to 12 weeks  $\pm$  1 week after the last dose of study drug.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

### Reporting groups

Reporting group title	Oral Phosphate/Active Vitamin D (Treatment Period)
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Reporting group description:

Multiple daily doses of oral phosphate and one or more daily doses of active vitamin D therapy, titrated and individualized by the investigator based on published recommendations during the Treatment Period (up to Week 64).

Reporting group title	Burosumab (Treatment Period)
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Reporting group description:

Burosumab 0.8 mg/kg starting dose, administered Q2W by SC injection during the Treatment Period (up to Week 64).

Reporting group title	Oral Phosphate/Active Vitamin D->Burosumab (Extension Period)
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Reporting group description:

Multiple daily doses of oral phosphate and one or more daily doses of active vitamin D therapy, titrated and individualized by the investigator based on published recommendations during the Treatment Period (up to Week 64). During the Treatment Extension Period (Week 64 to Week 140), subjects crossed over to receive a starting dose of SC burosumab 0.8 mg/kg Q2W. Subjects in Japan and Korea did not enter the Treatment Extension Period.

Reporting group title	Burosumab->Burosumab (Treatment Period and Extension Period)
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Reporting group description:

Burosumab 0.8 mg/kg starting dose, administered Q2W by SC injection during the Treatment Period (up to Week 64). During the Treatment Extension Period (Week 64 to Week 140), subjects continued to receive a starting dose of SC burosumab 0.8 mg/kg Q2W. Subjects in Japan and Korea did not enter the Treatment Extension Period.

Reporting group title	Total Burosumab (Treatment Period and Extension Period)
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Reporting group description:

Burosumab 0.8 mg/kg starting dose, administered Q2W by SC injection at any time during the study.

Serious adverse events	Oral Phosphate/Active Vitamin D (Treatment Period)	Burosumab (Treatment Period)	Oral Phosphate/Active Vitamin D->Burosumab (Extension Period)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 32 (9.38%)	3 / 29 (10.34%)	0 / 26 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Congenital, familial and genetic disorders			
Craniosynostosis			

subjects affected / exposed	1 / 32 (3.13%)	1 / 29 (3.45%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Nervous system disorders</b>			
Migraine			
subjects affected / exposed	0 / 32 (0.00%)	1 / 29 (3.45%)	0 / 26 (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
<b>Eye disorders</b>			
Papilloedema			
subjects affected / exposed	0 / 32 (0.00%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Renal and urinary disorders</b>			
Haematuria			
subjects affected / exposed	1 / 32 (3.13%)	0 / 29 (0.00%)	0 / 26 (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
<b>Musculoskeletal and connective tissue disorders</b>			
Knee Deformity			
subjects affected / exposed	1 / 32 (3.13%)	0 / 29 (0.00%)	0 / 26 (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
<b>Infections and infestations</b>			
Viral Infection			
subjects affected / exposed	0 / 32 (0.00%)	1 / 29 (3.45%)	0 / 26 (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

<b>Serious adverse events</b>	Burosumab- >Burosumab (Treatment Period and Extension Period)	Total Burosumab (Treatment Period and Extension Period)	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 29 (13.79%)	4 / 55 (7.27%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Congenital, familial and genetic disorders Craniosynostosis	subjects affected / exposed	1 / 29 (3.45%)	1 / 55 (1.82%)	
	occurrences causally related to treatment / all	0 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders Migraine	subjects affected / exposed	1 / 29 (3.45%)	1 / 55 (1.82%)	
	occurrences causally related to treatment / all	0 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders Papilloedema	subjects affected / exposed	1 / 29 (3.45%)	1 / 55 (1.82%)	
	occurrences causally related to treatment / all	1 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders Haematuria	subjects affected / exposed	0 / 29 (0.00%)	0 / 55 (0.00%)	
	occurrences causally related to treatment / all	0 / 0	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders Knee Deformity	subjects affected / exposed	0 / 29 (0.00%)	0 / 55 (0.00%)	
	occurrences causally related to treatment / all	0 / 0	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations Viral Infection	subjects affected / exposed	1 / 29 (3.45%)	1 / 55 (1.82%)	
	occurrences causally related to treatment / all	0 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	<b>Oral Phosphate/Active Vitamin D (Treatment Period)</b>	<b>Burosumab (Treatment Period)</b>	<b>Oral Phosphate/Active Vitamin D- &gt;Burosumab (Extension Period)</b>
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 32 (71.88%)	21 / 29 (72.41%)	9 / 26 (34.62%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 32 (6.25%)	1 / 29 (3.45%)	1 / 26 (3.85%)
occurrences (all)	3	1	1
Injection Site Bruising			
subjects affected / exposed	0 / 32 (0.00%)	0 / 29 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Injection Site Erosion			
subjects affected / exposed	0 / 32 (0.00%)	2 / 29 (6.90%)	0 / 26 (0.00%)
occurrences (all)	0	3	0
Injection Site Erythema			
subjects affected / exposed	0 / 32 (0.00%)	9 / 29 (31.03%)	6 / 26 (23.08%)
occurrences (all)	0	26	12
Injection Site Pruritus			
subjects affected / exposed	0 / 32 (0.00%)	3 / 29 (10.34%)	2 / 26 (7.69%)
occurrences (all)	0	10	2
Injection Site Rash			
subjects affected / exposed	0 / 32 (0.00%)	3 / 29 (10.34%)	0 / 26 (0.00%)
occurrences (all)	0	4	0
Injection Site Reaction			
subjects affected / exposed	0 / 32 (0.00%)	7 / 29 (24.14%)	2 / 26 (7.69%)
occurrences (all)	0	10	2
Injection Site Swelling			
subjects affected / exposed	0 / 32 (0.00%)	3 / 29 (10.34%)	1 / 26 (3.85%)
occurrences (all)	0	4	3
Injection Site Urticaria			
subjects affected / exposed	0 / 32 (0.00%)	2 / 29 (6.90%)	0 / 26 (0.00%)
occurrences (all)	0	5	0
Pain			
subjects affected / exposed	0 / 32 (0.00%)	2 / 29 (6.90%)	0 / 26 (0.00%)
occurrences (all)	0	3	0

Pyrexia subjects affected / exposed occurrences (all)	7 / 32 (21.88%) 13	16 / 29 (55.17%) 35	7 / 26 (26.92%) 8
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	1 / 29 (3.45%) 1	0 / 26 (0.00%) 0
Seasonal Allergy subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 3	4 / 29 (13.79%) 6	1 / 26 (3.85%) 1
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 2	4 / 29 (13.79%) 7	0 / 26 (0.00%) 0
Cough subjects affected / exposed occurrences (all)	6 / 32 (18.75%) 7	15 / 29 (51.72%) 31	4 / 26 (15.38%) 4
Nasal Congestion subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	5 / 29 (17.24%) 6	1 / 26 (3.85%) 1
Oropharyngeal Pain subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 3	5 / 29 (17.24%) 8	3 / 26 (11.54%) 3
Rhinitis Allergic subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	2 / 29 (6.90%) 3	0 / 26 (0.00%) 0
Rhinorrhoea subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	7 / 29 (24.14%) 16	3 / 26 (11.54%) 5
Wheezing subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 29 (3.45%) 1	0 / 26 (0.00%) 0
Psychiatric disorders Attention Deficit/Hyperactivity Disorder subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	0 / 29 (0.00%) 0	0 / 26 (0.00%) 0



Investigations Vitamin D Decreased subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	6 / 29 (20.69%) 6	1 / 26 (3.85%) 1
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)  Fall subjects affected / exposed occurrences (all)  Procedural Pain subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0  0 / 32 (0.00%) 0  0 / 32 (0.00%) 0	4 / 29 (13.79%) 4  3 / 29 (10.34%) 3  2 / 29 (6.90%) 2	0 / 26 (0.00%) 0  0 / 26 (0.00%) 0  0 / 26 (0.00%) 0
Congenital, familial and genetic disorders Tooth Hypoplasia subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	2 / 29 (6.90%) 2	0 / 26 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)  Migraine subjects affected / exposed occurrences (all)	6 / 32 (18.75%) 42  2 / 32 (6.25%) 2	10 / 29 (34.48%) 23  1 / 29 (3.45%) 1	3 / 26 (11.54%) 24  1 / 26 (3.85%) 1
Ear and labyrinth disorders Ear Discomfort subjects affected / exposed occurrences (all)  Ear Pain subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0  1 / 32 (3.13%) 3	1 / 29 (3.45%) 1  4 / 29 (13.79%) 6	0 / 26 (0.00%) 0  2 / 26 (7.69%) 3
Gastrointestinal disorders Abdominal Discomfort subjects affected / exposed occurrences (all)  Abdominal Pain	2 / 32 (6.25%) 2	2 / 29 (6.90%) 2	1 / 26 (3.85%) 1

subjects affected / exposed	1 / 32 (3.13%)	2 / 29 (6.90%)	1 / 26 (3.85%)
occurrences (all)	1	3	1
Abdominal Pain Upper			
subjects affected / exposed	3 / 32 (9.38%)	3 / 29 (10.34%)	2 / 26 (7.69%)
occurrences (all)	5	3	2
Constipation			
subjects affected / exposed	0 / 32 (0.00%)	5 / 29 (17.24%)	2 / 26 (7.69%)
occurrences (all)	0	7	2
Dental Caries			
subjects affected / exposed	2 / 32 (6.25%)	9 / 29 (31.03%)	0 / 26 (0.00%)
occurrences (all)	3	25	0
Diarrhoea			
subjects affected / exposed	2 / 32 (6.25%)	7 / 29 (24.14%)	1 / 26 (3.85%)
occurrences (all)	3	7	1
Haematochezia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 29 (3.45%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	1 / 32 (3.13%)	3 / 29 (10.34%)	2 / 26 (7.69%)
occurrences (all)	1	3	3
Teething			
subjects affected / exposed	0 / 32 (0.00%)	2 / 29 (6.90%)	1 / 26 (3.85%)
occurrences (all)	0	2	1
Tooth Loss			
subjects affected / exposed	0 / 32 (0.00%)	1 / 29 (3.45%)	1 / 26 (3.85%)
occurrences (all)	0	2	1
Toothache			
subjects affected / exposed	1 / 32 (3.13%)	4 / 29 (13.79%)	1 / 26 (3.85%)
occurrences (all)	1	6	1
Vomiting			
subjects affected / exposed	8 / 32 (25.00%)	12 / 29 (41.38%)	5 / 26 (19.23%)
occurrences (all)	10	25	8
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 32 (0.00%)	2 / 29 (6.90%)	0 / 26 (0.00%)
occurrences (all)	0	2	0

Rash			
subjects affected / exposed	2 / 32 (6.25%)	3 / 29 (10.34%)	0 / 26 (0.00%)
occurrences (all)	2	3	0
Skin Lesion			
subjects affected / exposed	0 / 32 (0.00%)	1 / 29 (3.45%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Swelling Face			
subjects affected / exposed	0 / 32 (0.00%)	1 / 29 (3.45%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 32 (0.00%)	2 / 29 (6.90%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 32 (31.25%)	13 / 29 (44.83%)	3 / 26 (11.54%)
occurrences (all)	28	39	6
Back Pain			
subjects affected / exposed	3 / 32 (9.38%)	2 / 29 (6.90%)	0 / 26 (0.00%)
occurrences (all)	3	2	0
Pain In Extremity			
subjects affected / exposed	10 / 32 (31.25%)	11 / 29 (37.93%)	3 / 26 (11.54%)
occurrences (all)	29	33	4
Infections and infestations			
Ear Infection			
subjects affected / exposed	3 / 32 (9.38%)	2 / 29 (6.90%)	1 / 26 (3.85%)
occurrences (all)	5	2	1
Gastroenteritis			
subjects affected / exposed	3 / 32 (9.38%)	2 / 29 (6.90%)	0 / 26 (0.00%)
occurrences (all)	4	2	0
Gastroenteritis Viral			
subjects affected / exposed	3 / 32 (9.38%)	2 / 29 (6.90%)	0 / 26 (0.00%)
occurrences (all)	3	2	0
Influenza			
subjects affected / exposed	6 / 32 (18.75%)	4 / 29 (13.79%)	0 / 26 (0.00%)
occurrences (all)	8	5	0

Nasopharyngitis			
subjects affected / exposed	14 / 32 (43.75%)	11 / 29 (37.93%)	6 / 26 (23.08%)
occurrences (all)	22	23	8
Otitis Externa			
subjects affected / exposed	3 / 32 (9.38%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	3	0	0
Otitis Media			
subjects affected / exposed	4 / 32 (12.50%)	2 / 29 (6.90%)	0 / 26 (0.00%)
occurrences (all)	4	5	0
Pharyngitis Streptococcal			
subjects affected / exposed	1 / 32 (3.13%)	1 / 29 (3.45%)	1 / 26 (3.85%)
occurrences (all)	2	1	1
Pneumonia			
subjects affected / exposed	0 / 32 (0.00%)	2 / 29 (6.90%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Rhinitis			
subjects affected / exposed	2 / 32 (6.25%)	2 / 29 (6.90%)	0 / 26 (0.00%)
occurrences (all)	6	7	0
Tooth Abscess			
subjects affected / exposed	3 / 32 (9.38%)	8 / 29 (27.59%)	2 / 26 (7.69%)
occurrences (all)	4	12	2
Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 32 (9.38%)	3 / 29 (10.34%)	0 / 26 (0.00%)
occurrences (all)	3	4	0
Varicella			
subjects affected / exposed	0 / 32 (0.00%)	2 / 29 (6.90%)	1 / 26 (3.85%)
occurrences (all)	0	2	1
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 32 (6.25%)	0 / 29 (0.00%)	0 / 26 (0.00%)
occurrences (all)	2	0	0
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	2 / 32 (6.25%)	1 / 29 (3.45%)	0 / 26 (0.00%)
occurrences (all)	2	1	0
Vitamin D Deficiency			

subjects affected / exposed	1 / 32 (3.13%)	5 / 29 (17.24%)	0 / 26 (0.00%)
occurrences (all)	1	5	0

<b>Non-serious adverse events</b>	Burosumab- >Burosumab (Treatment Period and Extension Period)	Total Burosumab (Treatment Period and Extension Period)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 29 (86.21%)	34 / 55 (61.82%)	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 29 (6.90%)	3 / 55 (5.45%)	
occurrences (all)	2	3	
Injection Site Bruising			
subjects affected / exposed	1 / 29 (3.45%)	3 / 55 (5.45%)	
occurrences (all)	1	3	
Injection Site Erosion			
subjects affected / exposed	2 / 29 (6.90%)	2 / 55 (3.64%)	
occurrences (all)	3	3	
Injection Site Erythema			
subjects affected / exposed	9 / 29 (31.03%)	15 / 55 (27.27%)	
occurrences (all)	29	41	
Injection Site Pruritus			
subjects affected / exposed	3 / 29 (10.34%)	5 / 55 (9.09%)	
occurrences (all)	11	13	
Injection Site Rash			
subjects affected / exposed	3 / 29 (10.34%)	3 / 55 (5.45%)	
occurrences (all)	4	4	
Injection Site Reaction			
subjects affected / exposed	8 / 29 (27.59%)	10 / 55 (18.18%)	
occurrences (all)	13	15	
Injection Site Swelling			
subjects affected / exposed	3 / 29 (10.34%)	4 / 55 (7.27%)	
occurrences (all)	7	10	
Injection Site Urticaria			
subjects affected / exposed	2 / 29 (6.90%)	2 / 55 (3.64%)	
occurrences (all)	5	5	

Pain			
subjects affected / exposed	3 / 29 (10.34%)	3 / 55 (5.45%)	
occurrences (all)	4	4	
Pyrexia			
subjects affected / exposed	17 / 29 (58.62%)	24 / 55 (43.64%)	
occurrences (all)	42	50	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 29 (3.45%)	1 / 55 (1.82%)	
occurrences (all)	1	1	
Seasonal Allergy			
subjects affected / exposed	4 / 29 (13.79%)	5 / 55 (9.09%)	
occurrences (all)	7	8	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	4 / 29 (13.79%)	4 / 55 (7.27%)	
occurrences (all)	7	7	
Cough			
subjects affected / exposed	15 / 29 (51.72%)	19 / 55 (34.55%)	
occurrences (all)	35	39	
Nasal Congestion			
subjects affected / exposed	7 / 29 (24.14%)	8 / 55 (14.55%)	
occurrences (all)	9	10	
Oropharyngeal Pain			
subjects affected / exposed	6 / 29 (20.69%)	9 / 55 (16.36%)	
occurrences (all)	10	13	
Rhinitis Allergic			
subjects affected / exposed	2 / 29 (6.90%)	2 / 55 (3.64%)	
occurrences (all)	4	4	
Rhinorrhoea			
subjects affected / exposed	8 / 29 (27.59%)	11 / 55 (20.00%)	
occurrences (all)	17	22	
Wheezing			
subjects affected / exposed	2 / 29 (6.90%)	2 / 55 (3.64%)	
occurrences (all)	2	2	
Psychiatric disorders			

<p>Attention Deficit/Hyperactivity Disorder</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 29 (6.90%)</p> <p>2</p>	<p>2 / 55 (3.64%)</p> <p>2</p>	
<p>Investigations</p> <p>Vitamin D Decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>6 / 29 (20.69%)</p> <p>6</p>	<p>7 / 55 (12.73%)</p> <p>7</p>	
<p>Injury, poisoning and procedural complications</p> <p>Contusion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Fall</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Procedural Pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 29 (13.79%)</p> <p>4</p> <p>3 / 29 (10.34%)</p> <p>4</p> <p>2 / 29 (6.90%)</p> <p>2</p>	<p>4 / 55 (7.27%)</p> <p>4</p> <p>3 / 55 (5.45%)</p> <p>4</p> <p>2 / 55 (3.64%)</p> <p>2</p>	
<p>Congenital, familial and genetic disorders</p> <p>Tooth Hypoplasia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 29 (6.90%)</p> <p>2</p>	<p>2 / 55 (3.64%)</p> <p>2</p>	
<p>Nervous system disorders</p> <p>Headache</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Migraine</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>10 / 29 (34.48%)</p> <p>25</p> <p>1 / 29 (3.45%)</p> <p>1</p>	<p>13 / 55 (23.64%)</p> <p>49</p> <p>2 / 55 (3.64%)</p> <p>2</p>	
<p>Ear and labyrinth disorders</p> <p>Ear Discomfort</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Ear Pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 29 (6.90%)</p> <p>2</p> <p>4 / 29 (13.79%)</p> <p>6</p>	<p>2 / 55 (3.64%)</p> <p>2</p> <p>6 / 55 (10.91%)</p> <p>9</p>	
Gastrointestinal disorders			

Abdominal Discomfort		
subjects affected / exposed	2 / 29 (6.90%)	3 / 55 (5.45%)
occurrences (all)	2	3
Abdominal Pain		
subjects affected / exposed	2 / 29 (6.90%)	3 / 55 (5.45%)
occurrences (all)	3	4
Abdominal Pain Upper		
subjects affected / exposed	4 / 29 (13.79%)	6 / 55 (10.91%)
occurrences (all)	4	6
Constipation		
subjects affected / exposed	5 / 29 (17.24%)	7 / 55 (12.73%)
occurrences (all)	8	10
Dental Caries		
subjects affected / exposed	10 / 29 (34.48%)	10 / 55 (18.18%)
occurrences (all)	26	26
Diarrhoea		
subjects affected / exposed	7 / 29 (24.14%)	8 / 55 (14.55%)
occurrences (all)	8	9
Haematochezia		
subjects affected / exposed	2 / 29 (6.90%)	2 / 55 (3.64%)
occurrences (all)	2	2
Nausea		
subjects affected / exposed	5 / 29 (17.24%)	7 / 55 (12.73%)
occurrences (all)	5	8
Teething		
subjects affected / exposed	2 / 29 (6.90%)	3 / 55 (5.45%)
occurrences (all)	2	3
Tooth Loss		
subjects affected / exposed	2 / 29 (6.90%)	3 / 55 (5.45%)
occurrences (all)	3	4
Toothache		
subjects affected / exposed	5 / 29 (17.24%)	6 / 55 (10.91%)
occurrences (all)	8	9
Vomiting		
subjects affected / exposed	14 / 29 (48.28%)	19 / 55 (34.55%)
occurrences (all)	29	37



Skin and subcutaneous tissue disorders	Erythema			
	subjects affected / exposed	2 / 29 (6.90%)	2 / 55 (3.64%)	
	occurrences (all)	2	2	
	Rash			
	subjects affected / exposed	4 / 29 (13.79%)	4 / 55 (7.27%)	
	occurrences (all)	4	4	
	Skin Lesion			
	subjects affected / exposed	2 / 29 (6.90%)	2 / 55 (3.64%)	
	occurrences (all)	3	3	
	Swelling Face			
	subjects affected / exposed	2 / 29 (6.90%)	2 / 55 (3.64%)	
	occurrences (all)	2	2	
Renal and urinary disorders				
	Dysuria			
	subjects affected / exposed	2 / 29 (6.90%)	2 / 55 (3.64%)	
	occurrences (all)	2	2	
Musculoskeletal and connective tissue disorders				
	Arthralgia			
	subjects affected / exposed	13 / 29 (44.83%)	16 / 55 (29.09%)	
	occurrences (all)	42	48	
	Back Pain			
	subjects affected / exposed	2 / 29 (6.90%)	2 / 55 (3.64%)	
	occurrences (all)	2	2	
	Pain In Extremity			
	subjects affected / exposed	11 / 29 (37.93%)	14 / 55 (25.45%)	
	occurrences (all)	37	41	
Infections and infestations				
	Ear Infection			
	subjects affected / exposed	3 / 29 (10.34%)	4 / 55 (7.27%)	
	occurrences (all)	3	4	
	Gastroenteritis			
	subjects affected / exposed	2 / 29 (6.90%)	2 / 55 (3.64%)	
	occurrences (all)	2	2	
	Gastroenteritis Viral			

subjects affected / exposed	2 / 29 (6.90%)	2 / 55 (3.64%)
occurrences (all)	2	2
Influenza		
subjects affected / exposed	4 / 29 (13.79%)	4 / 55 (7.27%)
occurrences (all)	5	5
Nasopharyngitis		
subjects affected / exposed	15 / 29 (51.72%)	21 / 55 (38.18%)
occurrences (all)	28	36
Otitis Externa		
subjects affected / exposed	0 / 29 (0.00%)	0 / 55 (0.00%)
occurrences (all)	0	0
Otitis Media		
subjects affected / exposed	3 / 29 (10.34%)	3 / 55 (5.45%)
occurrences (all)	6	6
Pharyngitis Streptococcal		
subjects affected / exposed	2 / 29 (6.90%)	3 / 55 (5.45%)
occurrences (all)	2	3
Pneumonia		
subjects affected / exposed	2 / 29 (6.90%)	2 / 55 (3.64%)
occurrences (all)	2	2
Rhinitis		
subjects affected / exposed	2 / 29 (6.90%)	2 / 55 (3.64%)
occurrences (all)	8	8
Tooth Abscess		
subjects affected / exposed	9 / 29 (31.03%)	11 / 55 (20.00%)
occurrences (all)	13	15
Upper Respiratory Tract Infection		
subjects affected / exposed	3 / 29 (10.34%)	3 / 55 (5.45%)
occurrences (all)	4	4
Varicella		
subjects affected / exposed	2 / 29 (6.90%)	3 / 55 (5.45%)
occurrences (all)	2	3
Viral Upper Respiratory Tract Infection		
subjects affected / exposed	0 / 29 (0.00%)	0 / 55 (0.00%)
occurrences (all)	0	0

Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 29 (3.45%)	1 / 55 (1.82%)	
occurrences (all)	1	1	
Vitamin D Deficiency			
subjects affected / exposed	5 / 29 (17.24%)	5 / 55 (9.09%)	
occurrences (all)	5	5	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 November 2017	<p>1. Overall Study Design and Plan</p> <p>a. Treatment Periods and Treatment Duration: A Treatment Extension Period was added to the study for subjects in Europe, the US, Canada, and Australia. All subjects who continue into the Treatment Extension Period will receive burosumab (refer to Summary of Change Item #1b). The total treatment duration will vary by region. For subjects at study sites in Japan and Korea, the final visit for the study (ie, the end of the Treatment Period) will be Week 64 (final dose of burosumab at Week 62); subjects in these countries will be enrolled into a separate clinical trial of burosumab or will receive burosumab through another mechanism. For subjects in Europe, the US, Canada, and Australia, the study consists of the Treatment Period (last study visit Week 64) and the Treatment Extension Period (Weeks 66-140) for a total treatment duration of up to 140 weeks. For subjects in Europe and Australia, the Treatment Extension Period will end in September 2018; subjects will be enrolled into separate clinical trials of burosumab or will receive burosumab through another mechanism. For subjects in the US and Canada, the Treatment Extension Period will end in September 2018 and June 2019, respectively, when commercial burosumab is expected to be available; subjects will receive commercial burosumab or will receive burosumab through another mechanism. The total duration of treatment in this study for subjects in Europe, the US, Canada, and Australia will vary based on the subjects' initial date of enrollment but will not exceed 140 weeks</p>
03 November 2017	<p>(continued)</p> <p>b. Treatment in Treatment Extension Period (subjects in Europe, the US, Canada, and Australia only). After completion of the Treatment Period, subjects who were randomized to burosumab will continue treatment with burosumab, and subjects randomized to active control will cross over to receive open-label burosumab at the starting dose and regimen administered to subjects in the burosumab group. Subjects in the active control group will discontinue treatment the day after the Week 64 visit to allow washout of oral phosphate and active vitamin D treatments before their first dose of burosumab at Week 66</p> <p>c. Procedures: Evaluation of PD parameters, rickets, growth, and safety will continue in the Treatment Extension Period. The description of the timing of the planned analyses was clarified, and additional analyses time points were added for the Treatment Extension Period at Week 88, Week 112, and EOS. All AEs will be recorded from the time the informed consent is signed through 12 weeks following the last dose of study drug, unless the subject enrolls in another clinical study of burosumab, is treated with commercially available burosumab, or is treated with burosumab through another mechanism, at which point the collection of AEs within this study is no longer applicable (however, AEs will continue to be reported either under another burosumab protocol or per postapproval requirements for safety monitoring, as applicable)</p> <p>d. EOS: The description of the study periods was updated to describe the EOS procedures for different regions. For subjects in Japan and Korea, the EOS (EOS) Visit is Week 64 (referred to as "Week 64/EOS I"). Subjects in Europe, the US, Canada, and Australia will have an EOS visit that includes efficacy assessments (EOS II)</p>

03 November 2017	<p>(continued)</p> <p>e. Safety Follow-up: All subjects are expected to continue burosumab treatment poststudy in another clinical trial, through commercial use, or through another mechanism; poststudy safety follow-up calls and safety visits will occur only for subjects who are not documented to be continuing on burosumab at the EOS visits. A safety follow-up telephone call will occur at 5 weeks (+5 days) after the Week 64/EOS I or EOS II visit, as applicable, to determine if burosumab therapy has been started in another clinical trial, as commercial product, or through another mechanism; if burosumab therapy has not been started, information on any ongoing or new AEs, SAEs, or concomitant medications will be collected. For subjects who do not continue burosumab therapy, an additional safety visit will occur 12 weeks <math>\pm</math>1 week after the last dose of study drug. Every reasonable effort should be made to have required subjects return to the clinic for the final safety visit; however, subjects who are unable to return to the clinic for the final safety visit will be given the option of providing blood and urine samples as part of a HH visit. The end of the study is defined as the date of the last protocol-specified procedures (including telephone contact) for the last subject in the study</p> <p>f. Clarified that "at least" (rather than "approximately") 20 subjects age 1 to &lt; 5 years will be included</p> <p>g. The maximum proportion of female subjects was increased from 60% to 70% to better reflect the gender distribution of X-linked dominant disease and study experience</p> <p>h. Specified that the terms "study drug" and "investigational product" refer to burosumab, and "active control" and "active control arm" refer to oral phosphate/active vitamin D therapy</p>
03 November 2017	<p>(continued)</p> <p>i. Added a substudy to assess pre- and postprandial serum phosphorus and calcium concentrations. Assessments for this substudy will occur at a single clinic visit anytime 10 to 14 days after a burosumab dose; this clinic visit may take the place of a HH visit. Approximately 20 subjects, age <math>\geq</math> 3 years, will fast overnight for a minimum of 8 hours, and fasting serum will be collected prior to a breakfast of a standardized meal. Dietary phosphate will be estimated based on the calculated phosphate content and the amount of food consumed. Serum samples will be drawn 1 and 2 hours after the completion of the meal</p> <p>2. Selection of Study Population</p> <p>a. Inclusion Criterion #4 was revised to "Serum creatinine below age-adjusted upper normal limit"</p> <p>b. Inclusion Criterion #6 was revised to indicate that conventional therapy should be discontinued "...7 days prior to the Randomization Visit" rather than "...prior to the Screening Visit"</p> <p>c. Inclusion Criterion #10 was updated to require sexually active male subjects with female partners of childbearing potential to use a condom with spermicide or a highly effective method of contraception (rather than 2 methods) for the duration of the study plus 12 weeks after stopping the study drug</p> <p>d. Exclusion Criterion #1 was revised to specify that Tanner stage 4 or higher is assessed through physical examination in any of the following: genitals, breast, or pubic hair</p> <p>e. Exclusion Criterion #7 was corrected to "Planned orthopedic surgery, including osteotomy or implantation or removal of staples, 8-plates, or any other hardware, within the first 40 weeks of the study"</p>

03 November 2017	<p>(continued)</p> <p>3. Schedule of Events</p> <p>a. Added Table 2.3, Schedule of Events – Treatment Extension Period Weeks 66-140 to define assessments for the 76-week Treatment Extension Period</p> <p>b. Additional assessments at clinic visits at Weeks 52, 76, 88, 100, 112, 124, and 140 were added to Urine Pregnancy Test for females administered burosumab who have reached menarche</p> <p>c. Clarified that all study visits will be scheduled relative to the Baseline visit, with an allowable variance of <math>\pm 3</math> days for each visit (with the exception of the Screening and Safety Follow-up Visits) to accommodate scheduling; clarified that burosumab dosing should occur no sooner than 8 days after the last dose administered, and that the Safety Follow-up Visit has an allowable variance of <math>\pm 7</math> days</p> <p>d. Changed “within 7 days” to “after 7 days” to describe the time frame when subjects may return to the site after weaning from oral phosphate/active vitamin D therapy</p> <p>4. Study Drug</p> <p>a. Specified that subjects may resume burosumab at half of the last dose received (ie, half the dose of either 0.8 or 1.2 mg/kg) following withdrawal from burosumab due to increased serum phosphorus concentrations above the ULN, with a maximum dose of 40 mg. The maximum allowable dose of burosumab was defined as 90 mg per administration. Additional language was added to define the term “unscheduled serum phosphorus assessment”</p> <p>b. Changed criterion 2 for dose escalation, from “serum phosphorus has increased by <math>&lt; 0.5</math> mg/dL from Baseline” to “serum phosphorus has increased by <math>\leq 0.5</math> mg/dL from Baseline”</p> <p>c. Buttocks are included as a potential injection site for the administration of burosumab, and guidance provided to clarify the rotation of injection sites</p>
03 November 2017	<p>(continued)</p> <p>5. Prohibited Medications</p> <p>a. Clarified that active vitamin D, not vitamin D supplementation, is prohibited in the burosumab treatment group</p> <p>6. Efficacy Assessments</p> <p>a. Provided additional information regarding the collection of historical radiograph images and standing height/recumbent length data prior to Screening</p> <p>b. A new section, Change in Lower Extremity Abnormalities, was added to describe how this endpoint will be evaluated</p> <p>c. Provided greater clarity about how growth will be assessed. At each time point, height will be assessed 3 times; an average of the 3 measurements will be calculated. For subjects <math>&lt; 2</math> years old, recumbent length will be used as the growth measurement. For subjects <math>\geq 2</math> years old, standing and sitting heights will be collected for growth measurement</p> <p>d. The method used to calculate the ratio of the maximum renal tubular reabsorption rate of phosphate to the glomerular filtration rate (TmP/GFR) was updated to (Payne 1998)</p> <p>e. Version 2.0 of the PROMIS instrument will be used (rather than Version 1.0)</p> <p>f. Clarified the process for a subject <math>\geq 8</math> years old at Screening who has difficulty completing the PROMIS self-report</p> <p>7. PK and ADA Assessments</p> <p>a. Specified that subjects randomized to receive active control during the study will not have a blood sample drawn for these assessments</p> <p>8. Safety Assessments</p> <p>a. Clarified the acceptable method for measuring blood pressure and updated the literature reference. The National Heart, Lung, and Blood Institute (NHBLI) guidelines specifically recommend auscultation as the preferred method for measuring blood pressure and have reported that automated devices do not always closely match with those obtained by auscultation</p> <p>b. Specified that the genitourinary exam should be non-invasive, age appropriate, and consistent with the Investigator’s standard of care, and that the purpose of the exam is establish and monitor Tanner staging</p>

03 November 2017	(continued) c. Added the definition of a highly effective contraceptive method d. Clarified “dental events” as “dental caries, tooth extraction, root canal, dental abscesses, and gingivitis” to specify the events to be evaluated for the assessment of dental health e. Clarified SAE reporting for the active control group and added Appendix 1, which serves as reference safety information (RSI) for the oral phosphate and active vitamin D products used in the active control group of this study f. Clarified the visits at which subject weight is determined g. Section 8.5.5.3, Pregnancy Reporting, was deleted because it was redundant with text in Section 8.5.4.3, Pregnancy in Subject or Partner, and Requirements for Immediate Reporting 9. Investigators and Study Administrative Structure a. Included a requirement for a Coordinating Investigator.
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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