Clinical trial results:
A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety and Efficacy of Denosumab in Pediatric Subjects With Glucocorticoid-induced Osteoporosis

Summary

EudraCT number	2016-003083-39
Trial protocol	BE BG Outside EU/EEA IT
Global end of trial date	20 December 2023

Results information

Result version number	v1 (current)
This version publication date	19 June 2024
First version publication date	19 June 2024

Trial information

Trial identification

Sponsor protocol code	20140444

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03164928
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States,
Public contact	Amgen (EUROPE) GmbH, IHQ Medical Info-Clinical Trials, MedInfoInternational@amgen.com
Scientific contact	Amgen (EUROPE) GmbH, IHQ Medical Info-Clinical Trials, MedInfoInternational@amgen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000145-PIP02-12
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 February 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 December 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of denosumab on lumbar spine bone mineral density (BMD) Z-score as assessed by dual-energy X-ray absorptiometry (DXA) at 12 months in children 5 to 17 year of age with Glucocorticoid (GC)-induced osteoporosis (GiOP).

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. Essential documents will be retained in accordance with ICH GCP. The study sponsor declares that the information provided in this report is an accurate representation of the data captured and analyses performed for this study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 May 2018
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	India: 2
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	Türkiye: 1
Country: Number of subjects enrolled	Ukraine: 4
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	United States: 2
Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	Peru: 1
Worldwide total number of subjects	24
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	6
Adolescents (12-17 years)	18
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 12 centers in Australia, Canada, Columbia, India, Peru, Russia, Turkey, Ukraine, and the United States between May 2018 and December 2023.

Pre-assignment

Screening details:

Participants were randomized in a 2:1 allocation ratio to receive either denosumab or placebo respectively, in a double-blind manner during the 12-month placebo-controlled double-blind Treatment Period. This was followed by a 12-month denosumab Open-label Treatment Period and a 12- month Off-treatment Observation Period.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Denosumab/Denosumab

Arm description:

Participants received 1 mg/kg Denosumab by subcutaneous injection (SC), up to a maximum of 60 mg, every 6 months (Q6M) for 24 months during the Treatment Period. Participants were then followed for an additional 12 months during the Off-treatment Observation Period.

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

Dosage and administration details:

1 mg/kg up to a maximum of 60 mg by SC injection.

Arm title	Placebo/Denosumab

Arm description:

Participants received matching placebo by SC injection Q6M for the first 12 months of the Treatment Period. This was followed by 1 mg/kg Denosumab administered by SC injection, up to a maximum of 60 mg, Q6M for the second 12 months of the Treatment Period. Participants were then followed for an additional 12 months during the Off-treatment Observation Period.

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

Dosage and administration details:

1 mg/kg up to a maximum of 60 mg by SC injection.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection

Routes of administration	Subcutaneous use

Dosage and administration details:

1 mg/kg by SC injection.

Number of subjects in period 1	Denosumab/Denosumab	Placebo/Denosumab
Started	16	8
Completed	15	8
Not completed	1	0
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Denosumab/Denosumab
Reporting group description:	
Participants received 1 mg/kg Denosumab by subcutaneous injection (SC), up to a maximum of 60 mg, every 6 months (Q6M) for 24 months during the Treatment Period. Participants were then followed for an additional 12 months during the Off-treatment Observation Period.	
Reporting group title	Placebo/Denosumab
Reporting group description:	
Participants received matching placebo by SC injection Q6M for the first 12 months of the Treatment Period. This was followed by 1 mg/kg Denosumab administered by SC injection, up to a maximum of 60 mg, Q6M for the second 12 months of the Treatment Period. Participants were then followed for an additional 12 months during the Off-treatment Observation Period.	

Reporting group values	Denosumab/Denosumab	Placebo/Denosumab	Total
Number of subjects	16	8	24
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	3	3	6
Adolescents (12-17 years)	13	5	18
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	13.8	12.8	
standard deviation	± 2.3	± 2.1	-
Sex: Female, Male Units: participants			
Female	6	4	10
Male	10	4	14
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	3	4
Not Hispanic or Latino	15	5	20
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	3	0	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	13	5	18

More than one race	0	0	0
Other	0	3	3

Lumbar Spine Bone Mineral Density (BMD) Z-score at Baseline			
Units: Z-score			
arithmetic mean	-1.95	-3.60	
standard deviation	± 1.03	± 1.77	-
Femoral Neck BMD Z-score at Baseline			
Units: Z-score			
arithmetic mean	-3.35	-4.78	
standard deviation	± 1.91	± 2.80	-
Total Hip BMD Z-score at Baseline			
Units: Z-score			
arithmetic mean	-3.14	-4.56	
standard deviation	± 1.70	± 2.08	-

End points

End points reporting groups

Reporting group title	Denosumab/Denosumab
Reporting group description:	
Participants received 1 mg/kg Denosumab by subcutaneous injection (SC), up to a maximum of 60 mg, every 6 months (Q6M) for 24 months during the Treatment Period. Participants were then followed for an additional 12 months during the Off-treatment Observation Period.	
Reporting group title	Placebo/Denosumab
Reporting group description:	
Participants received matching placebo by SC injection Q6M for the first 12 months of the Treatment Period. This was followed by 1 mg/kg Denosumab administered by SC injection, up to a maximum of 60 mg, Q6M for the second 12 months of the Treatment Period. Participants were then followed for an additional 12 months during the Off-treatment Observation Period.	

Primary: Change From Baseline in Lumbar Spine BMD Z-score as Assessed by DXA at 12 Months

End point title	Change From Baseline in Lumbar Spine BMD Z-score as Assessed by DXA at 12 Months
End point description:	
Lumbar spine BMD was assessed by DXA and analyzed by analysis of covariance (ANCOVA) including treatment (denosumab vs placebo), baseline age, and baseline BMD z-score. DXA results were converted to z-scores, indicating number of standard deviations from the reference population's mean, with 0 denoting the mean. Positive changes from baseline signify lumbar spine BMD improvement. Primary DXA Analysis Set: all participants in the FAS with baseline and ≥ 1 postbaseline DXA of lumbar spine provided by the central imaging vendor during the first 12 months.	
End point type	Primary
End point timeframe:	
Baseline and 12 Months	

End point values	Denosumab/Denosumab	Placebo/Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	8		
Units: Z-score				
least squares mean (confidence interval 95%)	0.23 (-0.054 to 0.506)	0.11 (-0.304 to 0.532)		

Statistical analyses

Statistical analysis title	ANCOVA Primary DXA Analysis Set
Comparison groups	Denosumab/Denosumab v Placebo/Denosumab

Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.68
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	0.673

Notes:

[1] - Analysis of covariance (ANCOVA) model including treatment (denosumab vs placebo), baseline age, and baseline BMD Z-score, with no imputation for missing data.

Secondary: Change From Baseline in Lumbar Spine BMD Z-score as Assessed by DXA at 6, 18, 24, and 36 Months

End point title	Change From Baseline in Lumbar Spine BMD Z-score as Assessed by DXA at 6, 18, 24, and 36 Months

End point description:

Lumbar spine BMD was assessed by DXA and analyzed by repeated measures analysis with randomization group, visit, baseline age, and baseline BMD z-score as fixed effects. Treatment-by-visit was included as an interaction term. DXA results were converted to z-scores, indicating number of standard deviations from the reference population's mean, with 0 denoting the mean. Positive changes from baseline signify lumbar spine BMD improvement.

DXA Analysis Set: all participants in the FAS with baseline and ≥ 1 postbaseline valid DXA assessment for lumbar spine as provided by the central imaging vendor.

End point type	Secondary

End point timeframe:

Baseline and 6, 18, 24, and 36 Months

End point values	Denosumab/Denosumab	Placebo/Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	8		
Units: Z-score				
least squares mean (confidence interval 95%)				
Month 6 n= 14, 6	0.28 (0.095 to 0.468)	0.11 (-0.176 to 0.391)		
Month 18 n= 15, 7	0.32 (-0.034 to 0.679)	0.30 (-0.206 to 0.800)		
Month 24 n= 13, 7	0.37 (-0.017 to 0.755)	0.26 (-0.285 to 0.801)		
Month 36 n= 9, 5	-0.23 (-0.833 to 0.372)	0.57 (-0.268 to 1.416)		

Statistical analyses

Statistical analysis title	Repeated Measures Model DXA Analysis Set
Statistical analysis description: Month 6	
Comparison groups	Denosumab/Denosumab v Placebo/Denosumab
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.34
Method	Repeated Measures Model
Parameter estimate	Least Squares Mean Difference
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.194
upper limit	0.542

Statistical analysis title	Repeated Measures Model DXA Analysis Set
Statistical analysis description: Month 18	
Comparison groups	Denosumab/Denosumab v Placebo/Denosumab
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.93
Method	Repeated Measures Model
Parameter estimate	Least Squares Mean Difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.609
upper limit	0.661

Statistical analysis title	Repeated Measures Model DXA Analysis Set
Statistical analysis description: Month 24	
Comparison groups	Denosumab/Denosumab v Placebo/Denosumab
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.74
Method	Repeated Measures Model
Parameter estimate	Least Squares Mean Difference
Point estimate	0.11

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.572
upper limit	0.795

Statistical analysis title	Repeated Measures Model DXA Analysis Set
Statistical analysis description:	
Month 36	
Comparison groups	Denosumab/Denosumab v Placebo/Denosumab
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.12
Method	Repeated Measures Model
Parameter estimate	Least Squares Means Difference
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.848
upper limit	0.239

Secondary: Change From Baseline in Proximal Femur BMD Z-score as Assessed by DXA at 6, 12, 18, 24, and 36 Months

End point title	Change From Baseline in Proximal Femur BMD Z-score as Assessed by DXA at 6, 12, 18, 24, and 36 Months

End point description:

Proximal femur (total hip and femoral neck) BMD was assessed by DXA and analyzed by repeated measures analysis with randomization group, visit, baseline age, and baseline BMD z-score as fixed effects. Treatment-by-visit was included as an interaction term. DXA results were converted to z-scores, indicating number of standard deviations from the reference population's mean, with 0 denoting the mean. Positive changes from baseline signify proximal femur BMD improvement.

DXA Analysis Set: all participants in the FAS with baseline and ≥ 1 postbaseline valid DXA assessment for total hip and femoral neck as provided by the central imaging vendor.

End point type	Secondary

End point timeframe:

Baseline and 6, 12, 18, 24, and 36 Months

End point values	Denosumab/Denosumab	Placebo/Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	7		
Units: Z-score				
least squares mean (confidence interval 95%)				
Month 6 (Total Hip) n= 13, 5	0.22 (-0.103 to 0.552)	0.64 (0.104 to 1.171)		
Month 12 (Total Hip) n= 14, 7	0.24 (-0.079 to 0.554)	0.30 (-0.168 to 0.759)		
Month 18 (Total Hip) n= 15, 6	0.48 (0.015 to 0.937)	0.75 (0.061 to 1.434)		
Month 24 (Total Hip) n= 13, 6	0.52 (0.000 to 1.033)	0.69 (-0.062 to 1.447)		
Month 36 (Total Hip) n= 9, 5	0.64 (-0.149 to 1.436)	0.73 (-0.384 to 1.850)		
Month 6 (Femoral Neck) n= 13, 5	0.42 (0.000 to 0.849)	0.60 (-0.037 to 1.241)		
Month 12 (Femoral Neck) n= 14, 7	0.53 (0.029 to 1.030)	0.43 (-0.294 to 1.161)		
Month 18 (Femoral Neck) n= 15, 6	0.85 (0.261 to 1.446)	0.48 (-0.387 to 1.350)		
Month 24 (Femoral Neck) n= 13, 6	0.75 (0.000 to 1.495)	0.64 (-0.449 to 1.724)		
Month 36 (Femoral Neck) n= 9, 5	1.00 (-0.008 to 2.012)	0.63 (-0.798 to 2.050)		

Statistical analyses

Statistical analysis title	Repeated Measures Model DXA Analysis Set
Statistical analysis description: Month 18 (Total Hip)	
Comparison groups	Denosumab/Denosumab v Placebo/Denosumab
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.51
Method	Repeated Measures Model
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.108
upper limit	0.565

Statistical analysis title	Repeated Measures Model DXA Analysis Set
Statistical analysis description: Month 12 (Total Hip)	
Comparison groups	Denosumab/Denosumab v Placebo/Denosumab

Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.83
Method	Repeated Measures Model
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.631
upper limit	0.515

Statistical analysis title	Repeated Measures Model DXA Analysis Set
Statistical analysis description: Month 6 (Total Hip)	
Comparison groups	Denosumab/Denosumab v Placebo/Denosumab
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.19
Method	Repeated Measures Model
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.05
upper limit	0.223

Statistical analysis title	Repeated Measures Model DXA Analysis Set
Statistical analysis description: Month 12 (Femoral Neck)	
Comparison groups	Denosumab/Denosumab v Placebo/Denosumab
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.83
Method	Repeated Measures Model
Parameter estimate	Least Squares Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.808
upper limit	1

Statistical analysis title	Repeated Measures Model DXA Analysis Set
Statistical analysis description: Month 18 (Femoral Neck)	
Comparison groups	Denosumab/Denosumab v Placebo/Denosumab
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.48
Method	Repeated Measures Model
Parameter estimate	Least Squares Mean Difference
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.697
upper limit	1.442

Statistical analysis title	Repeated Measures Model DXA Analysis Set
Statistical analysis description: Month 24 (Femoral Neck)	
Comparison groups	Denosumab/Denosumab v Placebo/Denosumab
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.86
Method	Repeated Measures Model
Parameter estimate	Least Squares Mean Difference
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.222
upper limit	1.443

Statistical analysis title	Repeated Measures Model DXA Analysis Set
Statistical analysis description: Month 6 (Femoral Neck)	
Comparison groups	Denosumab/Denosumab v Placebo/Denosumab

Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.64
Method	Repeated Measures Model
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.969
upper limit	0.614

Statistical analysis title	Repeated Measures Model DXA Analysis Set
Statistical analysis description: Month 36 (Femoral Neck)	
Comparison groups	Denosumab/Denosumab v Placebo/Denosumab
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.66
Method	Repeated Measures Model
Parameter estimate	Least Squares Mean Difference
Point estimate	0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.378
upper limit	2.13

Statistical analysis title	Repeated Measures Model DXA Analysis Set
Statistical analysis description: Month 24 (Total Hip)	
Comparison groups	Denosumab/Denosumab v Placebo/Denosumab
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.69
Method	Repeated Measures Model
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.098
upper limit	0.746

Statistical analysis title	Repeated Measures Model DXA Analysis Set
Statistical analysis description: Month 36 (Total Hip)	
Comparison groups	Denosumab/Denosumab v Placebo/Denosumab
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.89
Method	Repeated Measures Model
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.465
upper limit	1.286

Secondary: Number of Participants with X-ray Confirmed Long-bone Fractures and/or Vertebral Fractures at 12, 24, and 36 Months

End point title	Number of Participants with X-ray Confirmed Long-bone Fractures and/or Vertebral Fractures at 12, 24, and 36 Months

End point description:

Number of participants who have at least one long bone fracture or vertebral fracture, and number of participants who have more than one long bone fracture or vertebral fracture.

FAS: all participants randomized into the study.

End point type	Secondary

End point timeframe:

Month 12, 24, and 36

End point values	Denosumab/Denosumab	Placebo/Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	8		
Units: Participants				
Month 12 (at least 1 fracture)	2	2		
Month 24 (at least 1 fracture)	3	3		
Month 36 (at least 1 fracture)	3	3		
Month 12 (more than 1 fracture)	2	1		
Month 24 (more than 1 fracture)	2	0		
Month 36 (more than 1 fracture)	3	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Improving Vertebral Fractures at 12, 24, and 36 Months

End point title	Number of Participants with Improving Vertebral Fractures at 12, 24, and 36 Months

End point description:

Vertebral Fracture Analysis Set: all participants in the FAS who have a non-missing baseline and ≥ 1 non missing postbaseline X-ray vertebral evaluation as provided by the central imaging vendor, on or before the time point under consideration.

End point type	Secondary

End point timeframe:

Month 12, 24, and 36

End point values	Denosumab/Denosumab	Placebo/Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	7		
Units: Participants				
Month 12	3	1		
Month 24	2	1		
Month 36	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with New and Worsening Vertebral and Non-vertebral Fractures at 12, 24, and 36 Months

End point title	Number of Participants with New and Worsening Vertebral and Non-vertebral Fractures at 12, 24, and 36 Months

End point description:

Number of participants who have at least one vertebral fracture or non-vertebral fracture, and number of participants who have more than one vertebral fracture or non-vertebral fracture.

FAS: all participants randomized into the study.

End point type	Secondary

End point timeframe:

Month 12, 24, and 36

End point values	Denosumab/Denosumab	Placebo/Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	8		
Units: Participants				
Month 12 (at least 1 fracture)	2	2		
Month 24 (at least 1 fracture)	3	3		
Month 36 (at least 1 fracture)	3	3		
Month 12 (more than 1 fracture)	2	1		
Month 24 (more than 1 fracture)	2	0		
Month 36 (more than 1 fracture)	3	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Child Health Questionnaire-Parent Form-50 (CHQ-PF-50) Physical Summary Score at 12, 24, and 36 Months

End point title	Change From Baseline in Child Health Questionnaire-Parent Form-50 (CHQ-PF-50) Physical Summary Score at 12, 24, and 36 Months

End point description:

The CHQ-PF-50 is a 5O-item questionnaire to be completed by the parents or guardians of children between 5 and 18 years of age. The physical summary score ranges from 0-100 with higher scores indicating better physical health.

Patient Reported Outcomes (PRO) Analysis Set: all participants in the FAS with baseline and at least one valid CHQ-PF-50 response at postbaseline.

End point type	Secondary

End point timeframe:

Baseline and Month 12, 24, and 36

End point values	Denosumab/Denosumab	Placebo/Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	7		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Month 12 n= 12, 7	5.26 (± 8.88)	8.53 (± 16.39)		
Month 24 n= 13, 5	5.62 (± 7.39)	19.88 (± 15.20)		
Month 36 n= 9, 5	4.48 (± 8.89)	14.18 (± 8.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CHQ-PF-50 Psychological Summary Score at 12, 24, and 36 Months

End point title	Change From Baseline in CHQ-PF-50 Psychological Summary Score at 12, 24, and 36 Months

End point description:

The CHQ-PF-50 is a 5O-item questionnaire to be completed by the parents or guardians of children between 5 and 18 years of age. The psychological summary score ranges from 0-100 with higher scores indicating better psychological health.

PRO Analysis Set: all participants in the FAS with baseline and at least one valid CHQ-PF-50 response at postbaseline.

End point type	Secondary

End point timeframe:

Baseline and Month 12, 24, and 36

End point values	Denosumab/Denosumab	Placebo/Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	7		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Month 12 n= 12, 7	0.71 (± 9.15)	-0.10 (± 12.52)		
Month 24 n= 13, 5	2.58 (± 12.58)	1.90 (± 9.76)		
Month 36 n= 9, 5	5.20 (± 10.09)	2.00 (± 9.33)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Childhood Health Assessment Questionnaire (CHAQ) Disability Index Score at 12, 24, and 36 Months

End point title	Change From Baseline in Childhood Health Assessment Questionnaire (CHAQ) Disability Index Score at 12, 24, and 36 Months

End point description:

The CHAQ was developed to measure the physical functioning in children 6 months to 18 years of age. It consists of 54 questions related to the child's ability to perform various activities of daily living. Depending on the question asked, each question is scored either 0 to 3 based on the level of difficulty experienced by the child or 0-1 based on whether the child required assistance from another person or used an aid or other device. All CHAQ questions were scored and converted to a total index score ranging from 0-3, where higher scores indicate greater disability.

PRO Analysis Set: all participants in the FAS with baseline and at least one valid CHAQ response at postbaseline.

End point type	Secondary

End point timeframe:

Baseline and Month 12, 24, and 36

End point values	Denosumab/Denosumab	Placebo/Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	7		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Month 12 n= 12, 7	-0.06 (± 0.32)	-0.29 (± 0.44)		
Month 24 n= 13, 5	-0.09 (± 0.33)	-0.30 (± 0.49)		
Month 36 n= 8, 5	-0.12 (± 0.45)	-0.43 (± 0.45)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Wong-Baker FACES Pain Rating Scale (WBFPRS) at 12, 24, and 36 Months

End point title	Change From Baseline in Wong-Baker FACES Pain Rating Scale (WBFPRS) at 12, 24, and 36 Months

End point description:

WBFPRS is a horizontal pain scale for children from 3 to 18 years, which consists of 6 hand-drawn faces that range from a smiling "no hurt" face with a score of 0 to a crying "hurts most" face with a score of 10.

PRO Analysis Set: all participants in the FAS with baseline and at least one valid WBFPRS response at postbaseline.

End point type	Secondary

End point timeframe:

Baseline and Month 12, 24, and 36

End point values	Denosumab/Denosumab	Placebo/Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	7		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Month 12 n= 11, 7	-0.7 (± 3.3)	-0.3 (± 3.9)		
Month 24 n= 13, 5	-0.6 (± 2.9)	-2.4 (± 0.9)		
Month 36 n= 8, 5	-2.5 (± 1.8)	0.0 (± 1.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Growth Velocity Z-score (height) at 12, 24, and 36 Months

End point title	Change From Baseline in Growth Velocity Z-score (height) at 12, 24, and 36 Months

End point description:

Growth velocity was determined by calculating age-adjusted z-scores for height, weight, and body mass index (BMI). Z-scores represent the number of standard deviations from the reference population's mean, with 0 denoting the mean. Positive changes from baseline signify increased growth velocity.

Growth Velocity Analysis Set: all participants in the FAS who have non-missing height and age in total months at baseline and postbaseline. Only participants with available data for growth velocity (height) are included. All participants included in the Overall Number of Participants Analyzed contributed data to this outcome measure.

End point type	Secondary

End point timeframe:

Baseline and Month 12, 24, and 36

End point values	Denosumab/Denosumab	Placebo/Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	8		
Units: Z-score				
arithmetic mean (standard deviation)				
Month 12 n= 13, 8	-0.18 (± 0.46)	-0.07 (± 0.84)		
Month 24 n= 12, 7	-0.11 (± 0.90)	-0.27 (± 1.17)		
Month 36 n= 12, 7	-0.33 (± 0.84)	0.01 (± 1.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Growth Velocity Z-score (weight) at 12, 24, and 36 Months

End point title	Change From Baseline in Growth Velocity Z-score (weight) at 12, 24, and 36 Months

End point description:

Growth velocity was determined by calculating age-adjusted z-scores for height, weight, and BMI. Z-scores represent the number of standard deviations from the reference population's mean, with 0 denoting the mean. Positive changes from baseline signify increased growth velocity.

Growth Velocity Analysis Set: all participants in the FAS who have non-missing weight and age in total months at baseline and postbaseline. Only participants with available data for growth velocity (weight) are included.

End point type	Secondary

End point timeframe:

Baseline and Month 12, 24, and 36

End point values	Denosumab/Denosumab	Placebo/Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	8		
Units: Z-score				
arithmetic mean (standard deviation)				
Month 12 n= 15, 8	-0.12 (± 0.44)	-0.10 (± 0.49)		
Month 24 n= 12, 7	-0.22 (± 0.73)	-0.68 (± 0.62)		
Month 36 n= 12, 7	-0.32 (± 0.90)	-0.44 (± 0.60)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Growth Velocity Z-score (BMI) at 12, 24, and 36 Months

End point title	Change From Baseline in Growth Velocity Z-score (BMI) at 12, 24, and 36 Months

End point description:

Growth velocity was determined by calculating age-adjusted z-scores for height, weight, and BMI. Z-scores represent the number of standard deviations from the reference population's mean, with 0 denoting the mean. Positive changes from baseline signify increased growth velocity.

Growth Velocity Analysis Set: all participants in the FAS who have non-missing BMI and age in total months at baseline and postbaseline. Only participants with available data for growth velocity (BMI) are included. All participants included in the Overall Number of Participants Analyzed contributed data to this outcome measure

End point type	Secondary

End point timeframe:

Baseline and Month 12, 24, and 36

End point values	Denosumab/Denosumab	Placebo/Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	8		
Units: Z-score				
arithmetic mean (standard deviation)				
Month 12 n= 13, 8	-0.03 (± 0.53)	-0.14 (± 0.54)		
Month 24 n= 12, 7	-0.12 (± 0.80)	-0.75 (± 1.02)		
Month 36 n= 12, 7	-0.12 (± 0.84)	-0.72 (± 0.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Denosumab

End point title	Serum Concentration of Denosumab[2]

End point description:

Participants were randomized to receive 1 mg/kg Denosumab or Placebo by SC injection up to a maximum of 60 mg, Q6M for 12 months during the Treatment Period. All participants then received 1 mg/kg Denosumab, up to a maximum of 60 mg, Q6M, for the second 12 months of the Treatment Period. Participants were then followed for an additional 12 months during the Off-treatment Observation Period.

PK Analysis Set: all participants in the FAS who have ≥ 1 denosumab reported result.

End point type	Secondary

End point timeframe:

Day 1, Day 10, Day 30, Month 3, and Month 6

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Arms were pooled for serum concentration analysis.

End point values	Denosumab/Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1 n= 14	0.00 (± 0.00)			
Day 10 n= 11	10300 (± 7900)			
Day 30 n= 9	6830 (± 4770)			
Month 3 n= 10	1100 (± 935)			
Month 6 n= 12	141 (± 338)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From enrollment through last dose, up to 36 months.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups	
Reporting group title	Baseline-Month 12: Placebo
Reporting group description:	
Participants received placebo by SC injection during the first 12 months of the Treatment Period.	
Reporting group title	Baseline-Month 12: Denosumab
Reporting group description:	
Participants received 1 mg/kg Denosumab up to a maximum of 60 mg, Q6M by SC injection during the first 12 months of the Treatment Period.	
Reporting group title	Baseline-Month 36: Denosumab/Denosumab
Reporting group description:	
Participants received 1 mg/kg Denosumab by SC injection up to a maximum of 60 mg, Q6M for 24 months during the Treatment Period. Participants were then followed for an additional 12 months during the Off-treatment Observation Period.	
Reporting group title	Baseline-Month 24: Denosumab/Denosumab
Reporting group description:	
Participants received 1 mg/kg Denosumab by SC injection up to a maximum of 60 mg, Q6M for 24 months during the Treatment Period.	
Reporting group title	Baseline-Month 36: Placebo/Denosumab
Reporting group description:	
Participants received matching placebo by SC injection Q6M for the first 12 months of the Treatment Period. This was followed by 1 mg/kg Denosumab up to a maximum of 60 mg, Q6M administered by SC injection for the second 12 months of the Treatment Period. Participants were then followed for an additional 12 months during the Off-treatment Observation Period.	
Reporting group title	Baseline-Month 24: Placebo/Denosumab
Reporting group description:	
Participants received matching placebo by SC injection Q6M for the first 12 months of the Treatment Period. This was followed by 1 mg/kg Denosumab administered by SC injection Q6M for the second 12 months of the Treatment Period.	

Serious adverse events	Baseline-Month 12: Placebo	Baseline-Month 12: Denosumab	Baseline-Month 36: Denosumab/Denosumab
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 8 (12.50%)	3 / 16 (18.75%)	4 / 16 (25.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Tibia fracture			

subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain contusion			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiomyopathy			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	0 / 16 (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
Reproductive system and breast disorders			
Uterine haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Ureterolithiasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 16 (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
Infections and infestations			
Urinary tract infection			

subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Baseline-Month 24: Denosumab/Denosumab	Baseline-Month 36: Placebo/Denosumab	Baseline-Month 24: Placebo/Denosumab
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 16 (18.75%)	2 / 8 (25.00%)	1 / 8 (12.50%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Tibia fracture			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (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
Femur fracture			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (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
Brain contusion			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (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
Cardiac disorders			
Cardiomyopathy			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Uterine haemorrhage			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (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
Hepatobiliary disorders			
Autoimmune hepatitis			

subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Ureterolithiasis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 8 (0.00%)	0 / 8 (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

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

Non-serious adverse events	Baseline-Month 12: Placebo	Baseline-Month 12: Denosumab	Baseline-Month 36: Denosumab/Denosumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 8 (62.50%)	11 / 16 (68.75%)	13 / 16 (81.25%)
General disorders and administration site conditions			
Hyperthermia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Asthenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Injection site pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Pyrexia			

subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	2 / 16 (12.50%)
occurrences (all)	0	1	2
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Central sleep apnoea syndrome			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Cough			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Nasal septum deviation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Obstructive sleep apnoea syndrome			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Pleural effusion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Vasomotor rhinitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			

Anxiety			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Investigations			
Bone density decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Tooth fracture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Congenital, familial and genetic disorders			
Intracranial lipoma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Cardiomyopathy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	2 / 16 (12.50%)
occurrences (all)	0	1	2
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 8 (12.50%)	2 / 16 (12.50%)	3 / 16 (18.75%)
occurrences (all)	1	5	8
Hypoaesthesia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Myelopathy			

subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Syncope			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 16 (12.50%)	2 / 16 (12.50%)
occurrences (all)	0	2	2
Iron deficiency anaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Cataract subcapsular			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Cataract			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Astigmatism			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Constipation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Gastrointestinal disorder			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	2 / 16 (12.50%)
occurrences (all)	0	1	2
Duodenogastric reflux			

subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	2 / 16 (12.50%)
occurrences (all)	0	1	2
Duodenal bulb deformity			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Dental caries			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Oesophagitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Biliary tract disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Dermal cyst			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Acne			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Chronic spontaneous urticaria			

subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Erythema			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Eczema			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Ingrowing nail			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Renal and urinary disorders			
Metabolic nephropathy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Delayed puberty			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	2 / 16 (12.50%)
occurrences (all)	0	1	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Autoimmune arthritis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Back pain			
subjects affected / exposed	0 / 8 (0.00%)	2 / 16 (12.50%)	2 / 16 (12.50%)
occurrences (all)	0	2	2
Costochondritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Dwarfism			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			

subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Osteonecrosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Infections and infestations			
Balanitis candida			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
COVID-19			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Hordeolum			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Chronic tonsillitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Coronavirus infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Gingivitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Gastrointestinal infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Fungal skin infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Epstein-Barr virus infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1

COVID-19 pneumonia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	3 / 16 (18.75%)
occurrences (all)	1	0	4
Respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Skin infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Varicella			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Viral tonsillitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Vulvitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Iron deficiency			
subjects affected / exposed	1 / 8 (12.50%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Vitamin D deficiency			

subjects affected / exposed	0 / 8 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1

Non-serious adverse events	Baseline-Month 24: Denosumab/Denosumab	Baseline-Month 36: Placebo/Denosumab	Baseline-Month 24: Placebo/Denosumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 16 (75.00%)	5 / 8 (62.50%)	5 / 8 (62.50%)
General disorders and administration site conditions			
Hyperthermia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Fatigue			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Asthenia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Injection site pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Central sleep apnoea syndrome			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Epistaxis			

subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Nasal septum deviation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Obstructive sleep apnoea syndrome			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Rhinorrhoea			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Vasomotor rhinitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Investigations			
Bone density decreased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Tooth fracture			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Congenital, familial and genetic disorders			

Intracranial lipoma			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Cardiomyopathy			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Tachycardia			
subjects affected / exposed	2 / 16 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 16 (12.50%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	6	1	1
Hypoaesthesia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Myelopathy			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Syncope			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 16 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Iron deficiency anaemia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Eye disorders			
Cataract subcapsular			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	0	1	1

Cataract			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Astigmatism			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorder			
subjects affected / exposed	2 / 16 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Duodenogastric reflux			
subjects affected / exposed	2 / 16 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Duodenal bulb deformity			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Dental caries			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Oesophagitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Vomiting			

subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Biliary tract disorder			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Dermal cyst			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Acne			
subjects affected / exposed	0 / 16 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Chronic spontaneous urticaria			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Eczema			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Ingrowing nail			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Metabolic nephropathy			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			

Delayed puberty			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Autoimmune arthritis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	2 / 16 (12.50%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Costochondritis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Dwarfism			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Osteonecrosis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Balanitis candida			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
COVID-19			
subjects affected / exposed	1 / 16 (6.25%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	1	1	1
Hordeolum			

subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Chronic tonsillitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Coronavirus infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Gingivitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Fungal skin infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Epstein-Barr virus infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
COVID-19 pneumonia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Influenza			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	0	2	1
Nasopharyngitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Respiratory tract infection			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	0	2	2
Rhinitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Skin infection			

subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Varicella			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Viral tonsillitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Vulvitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Iron deficiency			
subjects affected / exposed	0 / 16 (0.00%)	1 / 8 (12.50%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Vitamin D deficiency			
subjects affected / exposed	1 / 16 (6.25%)	0 / 8 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 February 2017	Amendment 1: - Updated placebo arm to transition to open-label denosumab at 12 months and continue open-label denosumab for an additional 12 months. - Updated primary analysis to be conducted at the time of the final analysis. - Updated primary analysis to use an ANCOVA model, replacing the repeated measures analysis, which was updated to be included as a sensitivity analysis. - Updated protocol to include imputation rules for primary endpoint analysis.
25 May 2018	Amendment 2: - Updated exclusion criteria to include any causes of primary or secondary osteoporosis (other than GC use), or previous exposure to non-GC medications, which the investigator considers to have been a major factor contributing to the patient’s fracture(s). - Updated schedule of assessments to include blood sampling for immunogenicity assessments at months 1, 3, and 6. - Added description of additional sensitivity analysis to assess impact of short stature on BMD Z-scores in response to FDA. - Changed description of placebo to reflect the fact that with the new XGEVA formulation, the placebo will no longer be identical in composition.
20 April 2021	Amendment 3: - Updated the number of subjects enrolled in the study to 24 from an initial plan to enroll 150 subjects. - Updated close of enrollment to January 2021 because too few children with disease or condition to study.
10 July 2023	Amendment 4: - Updated "from pre-treatment to post-treatment" to "compared to baseline" to clarify that the determination of improving vertebral fracture is to compare with baseline spine X-ray. - Removed subgroup analyses because of low enrollment. - Updated language to clarify that new and worsening vertebral and non-vertebral fractures will be used to evaluate the effect of denosumab in children with GiOP.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported