Clinical trial results:
Prospective, Multicenter, Single-arm Study to Evaluate Efficacy, Safety, and Pharmacokinetics of Denosumab in Children With Osteogenesis Imperfecta

Summary

EudraCT number	2014-000184-40
Trial protocol	CZ DE GB HU ES Outside EU/EEA BG PL BE FR IT
Global end of trial date	26 March 2022

Results information

Result version number	v1 (current)
This version publication date	11 October 2022
First version publication date	11 October 2022

Trial information

Trial identification

Sponsor protocol code	20130173

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03638128
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	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, 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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 March 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the effect of denosumab in lumbar spine bone mineral density (BMD) Z-score at 12 months, as assessed by dual-energy X-ray absorptiometry (DXA), in children 2 to 17 years of age (at the time of screening) with osteogenesis imperfecta (OI) on a 3-month dosing regimen.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation Good Clinical Practice regulations/guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 June 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	Czechia: 5
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 40
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	Italy: 13
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	United States: 30
Worldwide total number of subjects	153
EEA total number of subjects	95

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)	106
Adolescents (12-17 years)	46
Adults (18-64 years)	1
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 32 centers in North America, Europe, and Australia from June 2015 to March 2022.

Pre-assignment

Screening details:

Participants were screened within 35 days or rescreened within 42 days prior to receiving the initial dose of investigational product.

Period 1

Period 1 title	6-Month Dosing Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Denosumab

Arm description:

Participants received denosumab 1 mg/kg (up to a maximum of 60 mg) subcutaneously every 6 months (Q6M) for up to 36 months. Participants were dose adjusted from Q6M to every 3 months (Q3M) after early efficacy and pharmacokinetic (PK) data were analyzed. Participants enrolled and still receiving denosumab were transitioned from Q6M to Q3M dosing schedule. Participants could transition to Q3M dosing schedule up to and including the date they attended for their Month 36 visit under the Q6M dosing regimen. Those participants received denosumab during the Q3M dosing regimen for 12 months. Participants who transitioned to Q3M at month 18 of the Q6M dosing regimen received denosumab Q3M for up to 18 months.

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

Dosage and administration details:

Subcutaneous (SC) denosumab 1mg/kg (up to a maximum of 60 mg).

Number of subjects in period 1	Denosumab
Started	153
Received investigational product	153
Completed	115
Not completed	38
Consent withdrawn by subject	34
Lost to follow-up	2
Decision by sponsor	2

Period 2

Period 2 title	3-Month Dosing Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Denosumab

Arm description:

Participants received denosumab 1 mg/kg (up to a maximum of 60 mg) subcutaneously every 6 months (Q6M) for up to 36 months. Participants were dose adjusted from Q6M to every 3 months (Q3M) after early efficacy and pharmacokinetic (PK) data were analyzed. Participants enrolled and still receiving denosumab were transitioned from Q6M to Q3M dosing schedule. Participants could transition to Q3M dosing schedule up to and including the date they attended for their Month 36 visit under the Q6M dosing regimen. Those participants received denosumab during the Q3M dosing regimen for 12 months. Participants who transitioned to Q3M at month 18 of the Q6M dosing regimen received denosumab Q3M for up to 18 months.

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

Dosage and administration details:

Subcutaneous (SC) denosumab 1mg/kg (up to a maximum of 60 mg).

Number of subjects in period 2[1]	Denosumab
Started	60
Received Investigational Product	60
Completed	40
Not completed	20
Consent withdrawn by subject	6
Decision by sponsor	14

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: 55 participants completed Q6M and did not continue into the Q3M dosing regimen. Only 60 participants were transitioned to Q3M dosing regimen.

Baseline characteristics

Reporting groups	
Reporting group title	Denosumab
Reporting group description:	
Participants received denosumab 1 mg/kg (up to a maximum of 60 mg) subcutaneously every 6 months (Q6M) for up to 36 months. Participants were dose adjusted from Q6M to every 3 months (Q3M) after early efficacy and pharmacokinetic (PK) data were analyzed. Participants enrolled and still receiving denosumab were transitioned from Q6M to Q3M dosing schedule. Participants could transition to Q3M dosing schedule up to and including the date they attended for their Month 36 visit under the Q6M dosing regimen. Those participants received denosumab during the Q3M dosing regimen for 12 months. Participants who transitioned to Q3M at month 18 of the Q6M dosing regimen received denosumab Q3M for up to 18 months.	

Reporting group values	Denosumab	Total	
Number of subjects	153	153	
Age categorical Units: Subjects			
Children (2-11 years)	106	106	
Adolescents (12-17 years)	46	46	
Adults (18-64 years)	1	1	
From 65-84 years	0	0	
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
85 years and over	0	0	
Age Continuous			
Data presented is the age at Q6M dosing regimen enrolment.			
Units: Years			
arithmetic mean	9.3		
standard deviation	± 3.9	-	
Sex: Female, Male Units: Participants			
Female	73	73	
Male	80	80	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	15	15	
Not Hispanic or Latino	138	138	
Unknown or Not Reported	0	0	
Race/Ethnicity, Customized Units: Subjects			
Asian	4	4	
Black or African American	2	2	
White	135	135	
Other	8	8	
Multiple	4	4	

Subject analysis sets	
Subject analysis set title	6-Month Dosing Regimen Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

All participants who were enrolled in the study who received at least 1 dose of denosumab in the Q6M dosing regimen.

Subject analysis set title	3-Month Dosing Regimen Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

All participants who were enrolled in the study who received at least 1 dose of denosumab in the Q3M dosing regimen.

Reporting group values	6-Month Dosing Regimen Safety Analysis Set	3-Month Dosing Regimen Safety Analysis Set	
Number of subjects	153	60	
Age categorical Units: Subjects			
Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) 85 years and over			
Age Continuous			
Data presented is the age at Q6M dosing regimen enrolment.			
Units: Years arithmetic mean standard deviation	 9.3 ± 3.9	 11.0 ± 4.4	
Sex: Female, Male Units: Participants			
Female Male			
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported			
Race/Ethnicity, Customized Units: Subjects			
Asian Black or African American White Other Multiple			

End points

End points reporting groups

Reporting group title	Denosumab

Reporting group description:

Participants received denosumab 1 mg/kg (up to a maximum of 60 mg) subcutaneously every 6 months (Q6M) for up to 36 months. Participants were dose adjusted from Q6M to every 3 months (Q3M) after early efficacy and pharmacokinetic (PK) data were analyzed. Participants enrolled and still receiving denosumab were transitioned from Q6M to Q3M dosing schedule. Participants could transition to Q3M dosing schedule up to and including the date they attended for their Month 36 visit under the Q6M dosing regimen. Those participants received denosumab during the Q3M dosing regimen for 12 months. Participants who transitioned to Q3M at month 18 of the Q6M dosing regimen received denosumab Q3M for up to 18 months.

Reporting group title	Denosumab

Reporting group description:

Participants received denosumab 1 mg/kg (up to a maximum of 60 mg) subcutaneously every 6 months (Q6M) for up to 36 months. Participants were dose adjusted from Q6M to every 3 months (Q3M) after early efficacy and pharmacokinetic (PK) data were analyzed. Participants enrolled and still receiving denosumab were transitioned from Q6M to Q3M dosing schedule. Participants could transition to Q3M dosing schedule up to and including the date they attended for their Month 36 visit under the Q6M dosing regimen. Those participants received denosumab during the Q3M dosing regimen for 12 months. Participants who transitioned to Q3M at month 18 of the Q6M dosing regimen received denosumab Q3M for up to 18 months.

Subject analysis set title	6-Month Dosing Regimen Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

All participants who were enrolled in the study who received at least 1 dose of denosumab in the Q6M dosing regimen.

Subject analysis set title	3-Month Dosing Regimen Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

All participants who were enrolled in the study who received at least 1 dose of denosumab in the Q3M dosing regimen.

Primary: Change from Baseline in Lumbar Spine Bone Mineral Density (BMD) Z-Score at 12 Months

End point title	Change from Baseline in Lumbar Spine Bone Mineral Density (BMD) Z-Score at 12 Months[1]

End point description:

Lumbar spine BMD was measured by dual-energy X-ray absorptiometry (DXA) adjusted for age, sex, and race/ethnicity. The results were then converted to Z-scores. The Z-score indicated the number of standard deviations away from the reference population and a score of 0 is equal to the mean. Positive changes from Baseline indicated an improvement in lumbar spine BMD.

DXA Analysis Set included all participants in the FAS with Baseline and Month 12 DXA assessment on the Q3M dosing regimen for lumbar spine as provided by the central imaging vendor.

End point type	Primary

End point timeframe:

Baseline and 12 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistics were planned.

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Z-score				
least squares mean (standard error)	1.009 (± 0.119)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Lumbar Spine BMD Z-score at 6 Months

End point title	Change from Baseline in Lumbar Spine BMD Z-score at 6 Months

End point description:

Lumbar spine BMD was measured by DXA adjusted for age, sex, and race/ethnicity. The results were then converted to Z-scores. The Z-score indicated the number of standard deviations away from the reference population and a score of 0 is equal to the mean. Positive changes from Baseline indicated an improvement in lumbar spine BMD.

DXA Analysis Set included all participants in the FAS with Baseline and Month 12 DXA assessment on the Q3M dosing regimen for lumbar spine as provided by the central imaging vendor.

End point type	Secondary

End point timeframe:

Baseline and 6 months

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: Z-score				
least squares mean (standard error)	0.925 (± 0.078)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Proximal Femur BMD Z-score at 6 and 12 Months

End point title	Change from Baseline in Proximal Femur BMD Z-score at 6 and 12 Months

End point description:

Proximal femur (total hip and femoral neck) BMD Z-score was measured by DXA adjusted for age, sex, and race/ethnicity. The results were then converted to Z-scores. The Z-score indicated the number of standard deviations away from the reference population and a score of 0 is equal to the mean. Positive changes from Baseline indicated an improvement in lumbar spine BMD.

DXA Analysis Set included all participants in the FAS with Baseline, Month 6 and Month 12 DXA

assessment on the Q3M dosing regimen for lumbar spine as provided by the central imaging vendor. Only participants 5 years of age or older are included.

End point type	Secondary

End point timeframe:

Baseline, 6 and 12 months

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: Z score				
least squares mean (standard error)				
Total hip BMD Z-score - 6 Months	0.799 (± 0.082)			
Total hip BMD Z-score - 12 Months	0.793 (± 0.154)			
Femoral neck BMD Z-score - 6 Months	0.769 (± 0.067)			
Femoral neck BMD Z-score - 12 Months	0.689 (± 0.131)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with at least 1 X-ray Confirmed Long Bone or New and Worsening Vertebral Fracture

End point title	Percentage of Participants with at least 1 X-ray Confirmed Long Bone or New and Worsening Vertebral Fracture

End point description:

Q3M Dosing Regimen Safety Analysis Set: includes all participants in the FAS who received ≥ 1 dose of Q3M dosing regimen.

End point type	Secondary

End point timeframe:

Q6M Dosing Regimen: Last 12 months of treatment (median treatment duration was 730.0 days); Q3M Dosing Regimen: Day 1 up to 12 months

End point values	Denosumab	Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	60		
Units: Percentage of participants				
number (not applicable)	28.3	26.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with at least 1 X-ray Confirmed New and Worsening Vertebral Fracture

End point title	Percentage of Participants with at least 1 X-ray Confirmed New and Worsening Vertebral Fracture

End point description:

The Vertebral Fracture Analysis Set: includes all participants in the FAS who had a readable non-missing baseline and ≥1 non-missing postbaseline X-ray vertebral evaluation on the Q3M dosing regimen as provided by the central imaging vendor.

End point type	Secondary

End point timeframe:

Q6M Dosing Regimen: Last 12 months of treatment (median treatment duration was 730.0 days); Q3M Dosing Regimen: Day 1 up to 12 months

End point values	Denosumab	Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	60		
Units: Percentage of participants				
number (not applicable)	12.8	8.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants wth at least 1 X-ray Confirmed Improving Vertebral Fracture

End point title	Percentage of Participants wth at least 1 X-ray Confirmed Improving Vertebral Fracture

End point description:

The Vertebral Fracture Analysis Set: includes all participants in the FAS who had a readable non-missing baseline and ≥1 non-missing postbaseline X-ray vertebral evaluation on the Q3M dosing regimen as provided by the central imaging vendor.

End point type	Secondary

End point timeframe:

Q3M Dosing Regimen: Baseline up to 12 months

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: Percentage of participants				
number (not applicable)	27.7			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with at least 1 X-ray Confirmed New Vertebral Fracture

End point title	Percentage of Participants with at least 1 X-ray Confirmed New Vertebral Fracture

End point description:

The Vertebral Fracture Analysis Set: includes all participants in the FAS who had a readable non-missing baseline and ≥1 non-missing postbaseline X-ray vertebral evaluation on the Q3M dosing regimen as provided by the central imaging vendor.

End point type	Secondary

End point timeframe:

Q6M Dosing Regimen: Last 12 months of treatment (median treatment duration was 730.0 days); Q3M Dosing Regimen: Day 1 up to 12 months

End point values	Denosumab	Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Percentage of participants				
number (not applicable)	10.6	6.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with at least 1 Vertebral and Nonvertebral Fracture

End point title	Percentage of Participants with at least 1 Vertebral and Nonvertebral Fracture

End point description:

Q3M Dosing Regimen Safety Analysis Set: includes all participants in the FAS who received ≥ 1 dose of Q3M dosing regimen. Only participants 5 years of age or older are included.

End point type	Secondary

End point timeframe:

Q6M Dosing Regimen: Last 12 months of treatment (median treatment duration was 730.0 days); Q3M Dosing Regimen: Day 1 up to 12 months

End point values	Denosumab	Denosumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	56		
Units: Percentage of participants				
number (not applicable)	28.6	30.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Child Health Questionnaire–Parent Form Physical Summary Score (CHQ-PF-50) at 12 Months

End point title	Change from Baseline in Child Health Questionnaire–Parent Form Physical Summary Score (CHQ-PF-50) at 12 Months

End point description:

The CHQ-PF-50 was a 50-item questionnaire completed by the parents or guardians of children between 5 and 18 years of age. The 50 questions measure 14 domains which were summarized as the physical and psychological summary scores. Each summary score was transformed and could range from 0 to 100, with higher score indicating better physical and psychosocial health. A negative change from Baseline indicates decreased well-being.

Patient Reported Outcomes (PRO) Analysis Set: includes all participants in the FAS who had a baseline and ≥ 1 postbaseline valid PRO response on Q3M dosing regimen for the CHQ-PF-50. The CHQ-PF-50 analysis set only includes participants 5 years of age and older at screening.

End point type	Secondary

End point timeframe:

Baseline and 12 months

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Score on a scale				
arithmetic mean (standard deviation)	-0.98 (± 15.41)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in CHQ-PF-50 Psychological Summary Score at 12 Months

End point title	Change from Baseline in CHQ-PF-50 Psychological Summary Score at 12 Months

End point description:

The CHQ-PF-50 was a 50-item questionnaire completed by the parents or guardians of children between 5 and 18 years of age. The 50 questions measure 14 domains which were summarized as the physical and psychological summary scores. Each summary score was transformed and could range from 0 to

100, with higher score indicating better physical and psychosocial health. A positive change from Baseline indicates improved well-being.

Patient Reported Outcomes (PRO) Analysis Set: includes all participants in the FAS who had a baseline and ≥ 1 postbaseline valid PRO response on Q3M dosing regimen for the CHQ-PF-50. The CHQ-PF-50 analysis set only includes participants 5 years of age and older at screening.

PRO Analysis Set includes all participants in the FAS who had a baseline and ≥ 1 postbaseline valid PRO response on Q3M dosing regimen for the CHQ-PF-50. The CHQ-PF-50 analysis set only includes participants 5 years of age and older at screening

End point type	Secondary

End point timeframe:

Baseline and 12 months

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Score on a scale				
arithmetic mean (standard deviation)	0.85 (± 8.57)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Childhood Health Assessment Questionnaire (CHAQ) Disability Index Score at 12 Months

End point title	Change from Baseline in Childhood Health Assessment Questionnaire (CHAQ) Disability Index Score at 12 Months

End point description:

The disability domain (questions 1-54) of the CHAQ was used to measure the participant's assessment of physical functioning or the parent's assessment of the child's physical functioning. The disability index comprised of 8 categories (dressing and grooming, arising, eating, walking, hygiene, reaching, gripping, and activities). Scoring ranged from 1 to 5; 1 was "without any difficulty," 2 was "with some difficulty," 3 was "with much difficulty," and 4 was "unable to do." An answer of "not applicable" was scored as a 5, but was not counted. If a child required assistance from another person or used an aid or other device for any of the 8 categories, the minimum score for that category was recorded as a 3. The CHAQ questions were scored and converted to a total index score ranging from 0 to 3. Negative change from Baseline indicates an improvement.

PRO Analysis Set all participants in the FAS who had a baseline and ≥ 1 postbaseline valid PRO response on Q3M dosing regimen.

End point type	Secondary

End point timeframe:

Baseline and 12 months

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: Score on a scale				
arithmetic mean (standard deviation)	-0.06 (± 0.46)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Wong-Baker Faces Pain Rating Scale (WBFPRS) at 12 Months

End point title	Change from Baseline in Wong-Baker Faces Pain Rating Scale (WBFPRS) at 12 Months

End point description:

Participants were asked to report their level of pain by choosing a face that best described their own pain (the corresponding number: 0, 2, 4, 6, 8, 10) were then recorded. The WBFPRS ranged from 0, "no hurt," to 10, "hurts worst". A negative change from baseline indicates an improvement.

Patient Reported Outcomes (PRO) Analysis Set: includes all participants in the FAS who had a baseline and ≥ 1 postbaseline valid PRO response on Q3M dosing regimen for the WBFPRS.

End point type	Secondary

End point timeframe:

Baseline and 12 months

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: Score on a scale				
arithmetic mean (standard deviation)	0.0 (± 1.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Denosumab

End point title	Serum Concentration of Denosumab

End point description:

99999 represents data that were not evaluable.

PK Analysis Set includes all participants in the 3QM dosing regimen safety analysis set who had ≥ 1 serum denosumab reported result on 3QM dosing regimen.

End point type	Secondary

End point timeframe:

Days 1 (pre-dose), 10, 30, and 60 and Months 3, 6, 9, 12, 15, and 18

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: ng/mL				
arithmetic mean (standard deviation)				
Age 11-17; Day 1 (N = 15)	0.00 (± 0.00)			
Age 11-17; Day 10 (N = 10)	6580 (± 1350)			
Age 11-17; Day 30 (N = 12)	4380 (± 1360)			
Age 11-17; Day 60 (N = 13)	2280 (± 924)			
Age 11-17; Month 3 (N = 13)	1140 (± 772)			
Age 11-17; Month 6 (N = 13)	1380 (± 969)			
Age 11-17; Month 9 (N = 15)	1810 (± 1000)			
Age 11-17; Month 12 (N = 12)	1560 (± 1010)			
Age 11-17; Month 15 (N = 1)	956 (± 99999)			
Age 11-17; Month 18 (N = 0)	99999 (± 99999)			
Age 7-10; Day 1 (N = 19)	0.00 (± 0.00)			
Age 7-10; Day 10 (N = 11)	6580 (± 2020)			
Age 7-10; Day 30 (N = 18)	3980 (± 1320)			
Age 7-10; Day 60 (N = 16)	1300 (± 823)			
Age 7-10; Month 3 (N = 18)	222 (± 313)			
Age 7-10; Month 6 (N = 19)	561 (± 744)			
Age 7-10; Month 9 (N = 18)	655 (± 754)			
Age 7-10; Month 12 (N = 13)	691 (± 659)			
Age 7-10; Month 15 (N = 2)	1420 (± 99999)			
Age 7-10; Month 18 (N = 1)	1940 (± 99999)			
Age 2-6; Day 1 (N = 25)	0.00 (± 0.00)			
Age 2-6; Day 10 (N = 15)	7080 (± 2120)			
Age 2-6; Day 30 (N = 21)	3500 (± 1230)			
Age 2-6; Day 60 (N = 22)	699 (± 544)			
Age 2-6; Month 3 (N = 22)	159 (± 393)			
Age 2-6; Month 6 (N = 23)	196 (± 328)			
Age 2-6; Month 9 (N = 19)	237 (± 469)			
Age 2-6; Month 12 (N = 14)	278 (± 589)			
Age 2-6; Month 18 (N = 0)	99999 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Bone Turnover Marker (BTM) - Serum Type I Collagen C Telopeptide

End point title	Serum Bone Turnover Marker (BTM) - Serum Type I Collagen C Telopeptide

End point description:

99999 represents data that were not evaluable.

BTM Analysis Set: includes all participants in the 3QM dosing regimen safety analysis set who had baseline and ≥ 1 postbaseline assessment for the BTM endpoint of interest on Q3M dosing regimen.

End point type	Secondary

End point timeframe:

Baseline and Days 10 and 30, and Months 3, 6, 9, 12, 15 and 18

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: ng/L				
arithmetic mean (standard deviation)				
Baseline (N = 54)	1136.5 (± 569.7)			
Day 10 (N = 50)	174.4 (± 64.7)			
Day 30 (N = 48)	176.5 (± 87.9)			
Month 3 (N = 50)	498.47 (± 332.0)			
Month 6 (N = 49)	537.1 (± 427.1)			
Month 9 (N = 48)	539.0 (± 425.0)			
Month 12 (N = 42)	681.2 (± 563.1)			
Month 15 (N = 13)	1050.8 (± 758.8)			
Month 18 (N = 1)	1290.0 (± 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: BTM - Bone-specific Alkaline Phosphatase (BSAP)

End point title	BTM - Bone-specific Alkaline Phosphatase (BSAP)

End point description:

99999 represents data that were not evaluable. BTM Analysis Set: includes all participants in the 3QM dosing regimen safety analysis set who had baseline and ≥ 1 postbaseline assessment for the BTM endpoint of interest on Q3M dosing regimen.

End point type	Secondary

End point timeframe:

Baseline and Days 10 and 30, and Months 3, 6, 9, 12, and 15

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: µg/L				
arithmetic mean (standard deviation)				
Baseline; N = 59	69.22 (± 34.26)			
Day 10; N = 56	70.88 (± 32.77)			
Day 30; N = 53	56.28 (± 28.32)			
Month 3; N = 57	48.92 (± 25.45)			
Month 6; N = 54	40.30 (± 22.58)			
Month 9; N = 55	51.17 (± 106.27)			
Month 12; N = 47	40.02 (± 27.64)			
Month 15; N = 14	49.49 (± 31.20)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Growth Velocity at 12 Months

End point title	Change from Baseline in Growth Velocity at 12 Months

End point description:

Change from baseline in growth velocity was determined by calculating age-adjusted Z-scores for height, weight and BMI. Height-for-age Z-score was defined as the difference between the participant's height and the median height for the population with the same age and gender, divided by the population SD. The definitions of growth velocity based on weight and BMI were analogously calculated. To programmatically calculate the Z-scores, the National Center for Health Statistics percentiles growth charts, based on the 2000 Center for Disease Control and Prevention (CDC) (http://www.cdc.gov/growthcharts/c c_charts.htm), and the CDC Anthropometric Software Package 3.0 Z-scores were used. During normal growth, the change in z-score should equal 0. A positive change in any of the three = growth acceleration, whereas a negative change = deceleration.

Growth Velocity Analysis Set: all participants with non-missing height, weight, or BMI at baseline and postbaseline on the Q3M dosing regimen.

End point type	Secondary

End point timeframe:

Baseline and 12 months

End point values	Denosumab			
Subject group type	Reporting group			
Number of subjects analysed	48[2]			
Units: Z-score				
arithmetic mean (standard deviation)				
Height -for-age Z-score	-0.01 (± 0.43)			

Weight-for-age Z-score BMI-for-age Z-score	0.01 (± 0.53) -0.07 (± 0.52)			

Notes:

[2] - Only participants with observed data at Baseline and Month 12 are included.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

6QM dosing regimen: Day 1 up to 36 months
3QM dosing regimen: Day 1 up to 24 weeks after last dose (median duration of treatment was 253 days)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Denosumab 6-Month Dosing Regimen

Reporting group description:

Participants received denosumab 1 mg/kg (up to a maximum of 60 mg) subcutaneously every 6 months (Q6M) for up to 36 months.

Reporting group title	Denosumab3-Month Dosing Regimen

Reporting group description:

Early efficacy and PK data from Q6M dosing supported adjustment of the dosing regimen from Q6M to every 3 months (Q3M). Participants enrolled and still receiving denosumab were transitioned from Q6M to Q3M dosing schedule. Participants could transition to Q3M dosing schedule up to and including the date they attended for their month 36 visit under the Q6M dosing regimen. Those participants received denosumab during the Q3M dosing regimen for 12 months. Participants who transition to Q3M at month 18 of the Q6M dosing regimen received denosumab Q3M for up to 18 months.

Serious adverse events	Denosumab 6-Month Dosing Regimen	Denosumab3-Month Dosing Regimen	
Total subjects affected by serious adverse events			
subjects affected / exposed	52 / 153 (33.99%)	12 / 60 (20.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Testis cancer			
subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			

subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	7 / 153 (4.58%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 10	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	15 / 153 (9.80%)	2 / 60 (3.33%)	
occurrences causally related to treatment / all	3 / 22	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	8 / 153 (5.23%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	1 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	5 / 153 (3.27%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	1 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			

subjects affected / exposed	2 / 153 (1.31%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-traumatic pain			
subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	5 / 153 (3.27%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scapula fracture			
subjects affected / exposed	2 / 153 (1.31%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	10 / 153 (6.54%)	2 / 60 (3.33%)	
occurrences causally related to treatment / all	0 / 15	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			

subjects affected / exposed	4 / 153 (2.61%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Right ventricular dilatation			
subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Complex regional pain syndrome			
subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion complete			
subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 153 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural failure			

subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			
subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Adnexal torsion			
subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Knee deformity			
subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemarthrosis			
subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondrosis			
subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb deformity			

subjects affected / exposed	2 / 153 (1.31%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tenosynovitis			
subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scoliosis			
subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	2 / 153 (1.31%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis viral			
subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	4 / 153 (2.61%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device failure			
subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device loosening			
subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			

Hypercalcaemia			
subjects affected / exposed	0 / 153 (0.00%)	8 / 60 (13.33%)	
occurrences causally related to treatment / all	0 / 0	6 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 153 (0.65%)	0 / 60 (0.00%)	
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 %

Non-serious adverse events	Denosumab 6-Month Dosing Regimen	Denosumab3-Month Dosing Regimen	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	141 / 153 (92.16%)	38 / 60 (63.33%)	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	16 / 153 (10.46%)	0 / 60 (0.00%)	
occurrences (all)	21	0	
Fall			
subjects affected / exposed	25 / 153 (16.34%)	6 / 60 (10.00%)	
occurrences (all)	45	8	
Femur fracture			
subjects affected / exposed	16 / 153 (10.46%)	2 / 60 (3.33%)	
occurrences (all)	26	2	
Fibula fracture			
subjects affected / exposed	8 / 153 (5.23%)	3 / 60 (5.00%)	
occurrences (all)	9	3	
Hand fracture			
subjects affected / exposed	15 / 153 (9.80%)	1 / 60 (1.67%)	
occurrences (all)	23	1	
Foot fracture			

subjects affected / exposed	16 / 153 (10.46%)	2 / 60 (3.33%)	
occurrences (all)	20	2	
Humerus fracture			
subjects affected / exposed	12 / 153 (7.84%)	3 / 60 (5.00%)	
occurrences (all)	14	4	
Ligament sprain			
subjects affected / exposed	12 / 153 (7.84%)	1 / 60 (1.67%)	
occurrences (all)	12	1	
Post-traumatic pain			
subjects affected / exposed	6 / 153 (3.92%)	3 / 60 (5.00%)	
occurrences (all)	7	3	
Lumbar vertebral fracture			
subjects affected / exposed	11 / 153 (7.19%)	2 / 60 (3.33%)	
occurrences (all)	12	2	
Thoracic vertebral fracture			
subjects affected / exposed	10 / 153 (6.54%)	3 / 60 (5.00%)	
occurrences (all)	11	5	
Radius fracture			
subjects affected / exposed	14 / 153 (9.15%)	2 / 60 (3.33%)	
occurrences (all)	14	2	
Tibia fracture			
subjects affected / exposed	17 / 153 (11.11%)	3 / 60 (5.00%)	
occurrences (all)	26	3	
Ulna fracture			
subjects affected / exposed	16 / 153 (10.46%)	2 / 60 (3.33%)	
occurrences (all)	25	2	
Nervous system disorders			
Headache			
subjects affected / exposed	21 / 153 (13.73%)	4 / 60 (6.67%)	
occurrences (all)	28	5	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	12 / 153 (7.84%)	2 / 60 (3.33%)	
occurrences (all)	17	2	
Pyrexia			

subjects affected / exposed	18 / 153 (11.76%)	1 / 60 (1.67%)	
occurrences (all)	26	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	13 / 153 (8.50%)	0 / 60 (0.00%)	
occurrences (all)	16	0	
Abdominal pain upper			
subjects affected / exposed	9 / 153 (5.88%)	2 / 60 (3.33%)	
occurrences (all)	12	2	
Dental caries			
subjects affected / exposed	9 / 153 (5.88%)	1 / 60 (1.67%)	
occurrences (all)	27	1	
Vomiting			
subjects affected / exposed	13 / 153 (8.50%)	2 / 60 (3.33%)	
occurrences (all)	19	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	13 / 153 (8.50%)	2 / 60 (3.33%)	
occurrences (all)	19	2	
Epistaxis			
subjects affected / exposed	11 / 153 (7.19%)	2 / 60 (3.33%)	
occurrences (all)	16	3	
Renal and urinary disorders			
Hypercalciuria			
subjects affected / exposed	49 / 153 (32.03%)	5 / 60 (8.33%)	
occurrences (all)	87	8	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	70 / 153 (45.75%)	15 / 60 (25.00%)	
occurrences (all)	186	30	
Back pain			
subjects affected / exposed	50 / 153 (32.68%)	5 / 60 (8.33%)	
occurrences (all)	76	5	
Bone pain			
subjects affected / exposed	21 / 153 (13.73%)	1 / 60 (1.67%)	
occurrences (all)	31	4	

Myalgia			
subjects affected / exposed	8 / 153 (5.23%)	0 / 60 (0.00%)	
occurrences (all)	9	0	
Pain in extremity			
subjects affected / exposed	57 / 153 (37.25%)	11 / 60 (18.33%)	
occurrences (all)	125	20	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	8 / 153 (5.23%)	0 / 60 (0.00%)	
occurrences (all)	9	0	
Influenza			
subjects affected / exposed	13 / 153 (8.50%)	0 / 60 (0.00%)	
occurrences (all)	14	0	
Nasopharyngitis			
subjects affected / exposed	23 / 153 (15.03%)	7 / 60 (11.67%)	
occurrences (all)	30	7	
Upper respiratory tract infection			
subjects affected / exposed	9 / 153 (5.88%)	1 / 60 (1.67%)	
occurrences (all)	12	1	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	28 / 153 (18.30%)	15 / 60 (25.00%)	
occurrences (all)	39	23	
Hypocalcaemia			
subjects affected / exposed	15 / 153 (9.80%)	6 / 60 (10.00%)	
occurrences (all)	20	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 July 2014	• updated the exclusion criteria: - - added history of rare hereditary problems of fructose intolerance - - modified exclusion criteria related to HIV, hepatitis B, and hepatitis C - added serological tests for HIV, hepatitis B and hepatitis C to screening visit • clarified acceptable methods of contraception
28 August 2014	• updated the exclusion criteria regarding serum vitamin D levels at screening and duration of prior use of PTH or PTH derivatives • removed blood pressure measurement as a required procedure • added option for at-home blood collection for visits occurring on days 2 to 30
11 February 2015	• added additional visits to monitor serum calcium in the sentinel cohort
24 March 2016	• updated secondary objectives and endpoints and exclusion criteria to reflect approved modifications to the PIP • updated pregnancy and lactation reporting language and safety language to align with changes to the protocol template • clarified rescreening requirements and guidelines
11 March 2020	• changed the dosing regimen from Q6M to Q3M
19 November 2020	• added incidence of X-ray confirmed new and worsening vertebral fractures and incidence of new vertebral fractures from last 12 months on Q6M dosing regimen to 12 months on Q3M dosing regimen as secondary endpoints • added additional serum calcium samples at days 10 and 30 after investigational product dosing at weeks 12 and 24
14 January 2021	• corrected inconsistencies throughout
22 October 2021	• updated text throughout based on early study termination due to urgent safety measure • added immediate discontinuation of all subjects from study treatment followed by a 24-week safety follow-up period
26 November 2021	• added additional safety assessments to week 12 visit • removed PRO assessments from week 12 visit

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported