Clinical trial results:
Multicenter, Single-arm Open-label Extension Study to Assess Long-term Safety and Efficacy of Current or Prior Treatment With Denosumab in Children/Young Adults With Osteogenesis Imperfecta

Summary

EudraCT number	2018-000550-21
Trial protocol	HU PL BE DE GB ES CZ FR BG IT
Global end of trial date	28 March 2022

Results information

Result version number	v1 (current)
This version publication date	12 October 2022
First version publication date	12 October 2022

Trial information

Trial identification

Sponsor protocol code	20170534

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, 91320
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	28 March 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 March 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate long-term safety of denosumab in subjects with pediatric osteogenesis imperfecta (OI) who completed Study 20130173 (EudraCT Number: 2014-000184-40).

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.
The study protocol and all amendments, the informed consent form, and any accompanying materials provided to the subjects were reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) at each study center.
The investigator or his/her designee informed the subject of all aspects pertaining to the subject's participation in the study before any screening procedures were performed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 July 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Czechia: 2
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	75
EEA total number of subjects	50

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)	24
Adolescents (12-17 years)	42
Adults (18-64 years)	9
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 22 centers in North America, Europe, and Australia from July 2018 to March 2022.

Pre-assignment

Screening details:

Subjects enrolled in Study 20130173 were eligible for this study if they completed Study 20130173 end of study visit, did not reconsent/reassent to transition to the Q3M dosing regimen, or early terminated due to meeting BMD Z-score investigational product stopping criteria.

Period 1

Period 1 title	Open-label Extension (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Alternative Medications / Observational

Arm description:

Participants who received non-denosumab alternative therapy during the study or who were not receiving any medication at baseline.
Alternative osteoporosis medication(s) were determined at the investigator's discretion and per standard of care and local guidelines.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Denosumab 1 mg/kg Q6M

Arm description:

Participants who received at least 1 dose of 1 mg/kg denosumab administered once every 6 months (Q6M) administered by subcutaneous injection, but no Q3M denosumab during this study.

Arm type	Experimental
Investigational medicinal product name	Denosumab
Investigational medicinal product code	AMG 162
Other name	Prolia®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection once every 6 months

Arm title	Denosumab 1 mg/kg Q3M

Arm description:

Participants who received at least one dose of 1 mg/kg denosumab administered once every 3 months (Q3M) by subcutaneous injection during this study.

Arm type	Experimental
Investigational medicinal product name	Denosumab
Investigational medicinal product code	AMG 162
Other name	Prolia®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection once every 3 months

Number of subjects in period 1	Alternative Medications / Observational	Denosumab 1 mg/kg Q6M	Denosumab 1 mg/kg Q3M
Started	21	27	27
Completed	5	8	1
Not completed	16	19	26
Consent withdrawn by subject	1	7	6
Sponsor decision	15	12	19
Lost to follow-up	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Alternative Medications / Observational
Reporting group description:	
Participants who received non-denosumab alternative therapy during the study or who were not receiving any medication at baseline. Alternative osteoporosis medication(s) were determined at the investigator's discretion and per standard of care and local guidelines.	
Reporting group title	Denosumab 1 mg/kg Q6M
Reporting group description:	
Participants who received at least 1 dose of 1 mg/kg denosumab administered once every 6 months (Q6M) administered by subcutaneous injection, but no Q3M denosumab during this study.	
Reporting group title	Denosumab 1 mg/kg Q3M
Reporting group description:	
Participants who received at least one dose of 1 mg/kg denosumab administered once every 3 months (Q3M) by subcutaneous injection during this study.	

Reporting group values	Alternative Medications / Observational	Denosumab 1 mg/kg Q6M	Denosumab 1 mg/kg Q3M
Number of subjects	21	27	27
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	12.5	13.2	14.3
standard deviation	± 3.5	± 2.5	± 4.8
Gender Categorical Units: Subjects			
Female	8	9	13
Male	13	18	14
Race Units: Subjects			
Asian	0	0	1
Black or African American	1	1	0
White	20	25	23
Other	0	1	1
Multiple	0	0	2

Reporting group values	Total		
Number of subjects	75		
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		

Gender Categorical Units: Subjects			
Female	30		
Male	45		
Race Units: Subjects			
Asian	1		
Black or African American	2		
White	68		
Other	2		
Multiple	2		

Subject analysis sets

Subject analysis set title	Any Treatment
Subject analysis set type	Full analysis

Subject analysis set description:

Participants who were enrolled in the study and received denosumab Q3M or Q6M, alternative treatment or did not receive any treatment.

Reporting group values	Any Treatment		
Number of subjects	75		
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	13.4		
standard deviation	± 3.8		
Gender Categorical Units: Subjects			
Female	30		
Male	45		
Race Units: Subjects			
Asian	1		
Black or African American	2		
White	68		
Other	2		
Multiple	2		

End points

End points reporting groups

Reporting group title	Alternative Medications / Observational

Reporting group description:

Participants who received non-denosumab alternative therapy during the study or who were not receiving any medication at baseline.
Alternative osteoporosis medication(s) were determined at the investigator's discretion and per standard of care and local guidelines.

Reporting group title	Denosumab 1 mg/kg Q6M

Reporting group description:

Participants who received at least 1 dose of 1 mg/kg denosumab administered once every 6 months (Q6M) administered by subcutaneous injection, but no Q3M denosumab during this study.

Reporting group title	Denosumab 1 mg/kg Q3M

Reporting group description:

Participants who received at least one dose of 1 mg/kg denosumab administered once every 3 months (Q3M) by subcutaneous injection during this study.

Subject analysis set title	Any Treatment
Subject analysis set type	Full analysis

Subject analysis set description:

Participants who were enrolled in the study and received denosumab Q3M or Q6M, alternative treatment or did not receive any treatment.

Primary: Number of Participants with Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

End point title	Number of Participants with Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest[1]

End point description:

Adverse events of special interest included changes in growth plate morphology, severe or symptomatic hypocalcemia, hypersensitivity, bacterial cellulitis, osteonecrosis of the jaw (ONJ), abnormal molar eruption, hypercalcemia, and abnormal mandibular shaping.

End point type	Primary

End point timeframe:

From enrollment to end of study, including 24 weeks after last dose of denosumab for participants who received denosumab; the maximum time on study was 24 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: This study was descriptive in nature and did not involve testing formal hypotheses.

End point values	Alternative Medications / Observational	Denosumab 1 mg/kg Q6M	Denosumab 1 mg/kg Q3M	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	27	27	
Units: participants				
Any adverse event	18	22	19	
Serious adverse events	6	5	6	
Adverse events of special interest	5	5	9	
Hypocalcemia	0	0	1	
Hypercalcemia	3	4	9	
Hypersensitivity	0	0	0	
Bacterial cellulitis (skin infection)	0	0	0	
Typical osteogenesis imperfecta femur fractures	2	1	2	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Anti-denosumab Antibodies

End point title	Number of Participants with Anti-denosumab Antibodies[2][3]

End point description:

Blood samples were collected (from denosumab treated subjects only) for the measurement of anti-denosumab binding antibodies. Samples positive for anti-denosumab binding antibodies were further tested for neutralizing antibodies.

End point type	Primary

End point timeframe:

From enrollment to end of study, including 24 weeks after last dose of denosumab for participants who received denosumab; the maximum time on study was 24 months

Notes:

[2] - 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: This study was descriptive in nature and did not involve testing formal hypotheses.

[3] - 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: Participants in the Alternative Medications / Observational group were not tested for anti-denosumab antibodies.

End point values	Denosumab 1 mg/kg Q6M	Denosumab 1 mg/kg Q3M		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: participants				
Anti-denosumab binding antibodies	0	0		
Anti-denosumab neutralizing antibodies	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Clinical Laboratory Toxicities Grade ≥ 3

End point title	Number of Participants with Clinical Laboratory Toxicities Grade ≥ 3[4]

End point description:

Laboratory abnormalities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. The grades refer to the severity of the finding:
Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe or medically significant; Grade 4 = Life-threatening consequences, urgent intervention indicated.

End point type	Primary

End point timeframe:

From enrollment to end of study, including 24 weeks after last dose of denosumab for participants who

received denosumab; the maximum time on study was 24 months

Notes:

[4] - 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: This study was descriptive in nature and did not involve testing formal hypotheses.

End point values	Alternative Medications / Observational	Denosumab 1 mg/kg Q6M	Denosumab 1 mg/kg Q3M	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	27	27	
Units: participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Clinically Significant Vital Sign Findings

End point title	Number of Participants with Clinically Significant Vital Sign Findings[5]

End point description:

Vital sign measurements included systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature. The investigator assessed vital sign results and determined whether any abnormal changes represented a clinically significant change from the participant's baseline values.

End point type	Primary

End point timeframe:

From enrollment to end of study, including 24 weeks after last dose of denosumab for participants who received denosumab; the maximum time on study was 24 months

Notes:

[5] - 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: This study was descriptive in nature and did not involve testing formal hypotheses.

End point values	Alternative Medications / Observational	Denosumab 1 mg/kg Q6M	Denosumab 1 mg/kg Q3M	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	27	27	
Units: participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Metaphyseal Index Z-score Above Age-appropriate Normal Range

End point title	Number of Participants with Metaphyseal Index Z-score Above Age-appropriate Normal Range[6]

End point description:

Anteroposterior radiographs of both knees (unless prohibited by the presence of hardware such as implants) were used to calculate the metaphyseal index Z-score of each knee in participants with open

growth plates; the knee selected for assessment during the study was the knee with the higher Z-score at baseline. The metaphyseal index (MI) was calculated by the central imaging vendor as the ratio of femoral width over distal femoral growth plate width, and the Z-score for each subject, relative to the subject's age as:
MI Z-score = (subject value – mean)/SD, where mean and standard deviation (SD) are the corresponding values based on a reference population for the subject's age group at the time of the assessment.
Metaphyseal index Z-score above age-appropriate normal range is defined as a MI Z-score > 2.
The metaphyseal analysis set includes subjects with open growth plates and no hardware preventing accurate calculation of MI at baseline and knee X-ray at baseline and postbaseline.

End point type	Primary

End point timeframe:

Baseline, month 12 and month 24

Notes:

[6] - 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: This study was descriptive in nature and did not involve testing formal hypotheses.

End point values	Alternative Medications / Observational	Denosumab 1 mg/kg Q6M	Denosumab 1 mg/kg Q3M	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3[7]	4[8]	4[9]	
Units: participants				
Baseline (N = 3, 4, 4)	2	1	0	
Month 12 (N = 3, 4, 4)	2	1	0	
Month 24 (N = 1, 1, 0)	1	0	0	

Notes:

[7] - Metaphyseal analysis set; subjects with available data at each time point

[8] - Metaphyseal analysis set; subjects with available data at each time point

[9] - Metaphyseal analysis set ; subjects with available data at each time point

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Abnormal Molar Eruption of the First or Second Molar Based on Radiological Findings

End point title	Number of Participants with Abnormal Molar Eruption of the First or Second Molar Based on Radiological Findings[10]

End point description:

Participants underwent a visual inspection under natural light for the presence of the first and second molars. Participants were referred to a dentist to perform radiographic assessment of the unerupted molar(s) if:
- A participant was age 7 to 12 years and appeared to have an unerupted upper or lower first molar (ie, not all 4 first molars were visible/detectable).
- A participant was age 13 years or older and appeared to have an unerupted upper or lower (first or) second molar (ie, not all 4 first molars and all 4 second molars were visible/detectable).
Abnormal molar eruptions includes the number of participants 7 to 12 years of age with 1st unerupted or partially erupted molars and participants 13 years of age or older with 2nd unerupted or partially erupted molars.
The analysis at each time point includes participants with radiologic assessments.

End point type	Primary

End point timeframe:

Baseline, month 12, and month 24

Notes:

[10] - 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: This study was descriptive in nature and did not involve testing formal hypotheses.

End point values	Alternative Medications / Observational	Denosumab 1 mg/kg Q6M	Denosumab 1 mg/kg Q3M	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	27	27	
Units: participants				
Baseline (N = 19, 22, 17)	2	3	1	
Month 12 (N = 10, 8, 6)	0	0	2	
Month 24 (N = 2, 8, 1)	1	1	0	

Statistical analyses

No statistical analyses for this end point

Primary: Percent Change from Baseline in Mandibular Shaping Parameters

End point title	Percent Change from Baseline in Mandibular Shaping Parameters[11]

End point description:

Lateral cephalogram was performed to enable assessment of mandibular shaping. The lateral cephalogram is a profile X-ray of the skull and soft tissues and is used to assess the relation of the teeth in the jaws, the relation of the jaws to the skull, and the relation of the soft tissues to the teeth and jaws.
The following anatomical angles and dimensions were measured to evaluate the correct proportions of the mandible and its position relative to the skull/maxilla: Gonial angle; Sella-Nasion-A Point Angle (SNA angle); Sella-Nasion-B Point Angle (SNB angle); and A Point - Nasion-B Point Angle (ANB Angle).
The analysis at each time point includes participants with radiologic assessments. "99999" indicates Not Applicable.

End point type	Primary

End point timeframe:

Baseline and month 12 and month 24

Notes:

[11] - 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: This study was descriptive in nature and did not involve testing formal hypotheses.

End point values	Alternative Medications / Observational	Denosumab 1 mg/kg Q6M	Denosumab 1 mg/kg Q3M	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	27	27	
Units: percent change				
arithmetic mean (standard deviation)				
Gonial Angle at Month 12 (N = 8, 8, 1)	0.5 (± 2.4)	-1.4 (± 1.7)	-1.0 (± 99999)	
Gonial Angle at Month 24 (N = 2, 7, 0)	-2.1 (± 3.1)	-1.4 (± 2.2)	99999 (± 99999)	
SNA Angle at Month 12 (N = 8, 8, 1)	1.38 (± 2.09)	0.37 (± 2.41)	0.20 (± 99999)	
SNA Angle at Month 24 (N = 2, 7, 0)	-0.07 (± 0.73)	-1.70 (± 1.79)	99999 (± 99999)	
SNB Angle at Month 12 (N = 6, 8, 1)	0.98 (± 1.56)	1.75 (± 2.36)	0.70 (± 99999)	
SNB Angle at Month 24 (N = 1, 4, 0)	1.28 (± 99999)	-1.60 (± 3.18)	99999 (± 99999)	
ANB Angle at Month 12 (N = 6, 8, 1)	-81.06 (± 199.39)	127.48 (± 312.99)	-16.26 (± 99999)	
ANB Angle at Month 24 (N = 1, 4, 0)	-79.69 (± 99999)	15.65 (± 84.75)	99999 (± 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Lumbar Spine Bone Mineral Density (BMD) Z-score

End point title	Change from Baseline in Lumbar Spine Bone Mineral Density (BMD) Z-score

End point description:

Bone densitometry assessments of the lumbar spine were performed using dual X-ray absorptiometry (DXA).
The Z-score indicates the number of standard deviations away from the mean of an average person of the same age, sex, race, and weight. A Z-score of 0 is equal to the mean of the matched population, negative Z-scores indicate a BMD lower than the mean of the matched population, and positive Z-scores indicate a higher BMD than that of the matched population. A positive change from baseline indicates an improvement in lumbar spine BMD.
The DXA analysis set includes all subjects with baseline and ≥ 1 postbaseline valid DXA assessments for lumbar spine as provided by the central imaging vendor.

End point type	Secondary

End point timeframe:

Baseline and months 6, 12, and 24

End point values	Any Treatment			
Subject group type	Subject analysis set			
Number of subjects analysed	58[12]			
Units: Z-score				
arithmetic mean (standard deviation)				
Month 6 (N = 29)	-0.11 (± 0.60)			
Month 12 (N = 39)	-0.01 (± 0.48)			
Month 24 (N = 18)	0.21 (± 0.49)			

Notes:

[12] - DXA analysis set; subjects with available data at each time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Total Hip BMD Z-score

End point title	Change from Baseline in Total Hip BMD Z-score

End point description:

Bone densitometry assessments of the hip were performed using dual X-ray absorptiometry (DXA).
The Z-score indicates the number of standard deviations away from the mean of an average person of the same age, sex, race, and weight. A Z-score of 0 is equal to the mean of the matched population, negative Z-scores indicate a BMD lower than the mean of the matched population, and positive Z-scores indicate a higher BMD than that of the matched population. A positive change from baseline indicates

an improvement in total hip BMD.
The DXA analysis set includes all subjects with baseline and ≥ 1 postbaseline valid DXA assessments for the total hip as provided by the central imaging vendor.

End point type	Secondary

End point timeframe:

Baseline, months 6, 12, and 24

End point values	Any Treatment			
Subject group type	Subject analysis set			
Number of subjects analysed	35[13]			
Units: Z-score				
arithmetic mean (standard deviation)				
Month 6 (N = 16)	-0.07 (± 0.40)			
Month 12 (N = 25)	0.24 (± 0.42)			
Month 24 (N = 15)	0.50 (± 0.54)			

Notes:

[13] - DXA analysis set; subjects with available data at each time point

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Femoral Neck BMD Z-score

End point title	Change from Baseline in Femoral Neck BMD Z-score

End point description:

Bone densitometry assessments of the femoral neck were performed using dual X-ray absorptiometry (DXA).
The Z-score indicates the number of standard deviations away from the mean of an average person of the same age, sex, race, and weight. A Z-score of 0 is equal to the mean of the matched population, negative Z-scores indicate a BMD lower than the mean of the matched population, and positive Z-scores indicate a higher BMD than that of the matched population. A positive change from baseline indicates an improvement in femoral neck BMD.
The DXA analysis set includes all subjects with baseline and ≥ 1 postbaseline valid DXA assessments for the femoral neck as provided by the central imaging vendor.

End point type	Secondary

End point timeframe:

Baseline, month 6, 12, and 24

End point values	Any Treatment			
Subject group type	Subject analysis set			
Number of subjects analysed	35[14]			
Units: Z-score				
arithmetic mean (standard deviation)				
Month 6 (N = 16)	0.08 (± 0.44)			
Month 12 (N = 25)	0.24 (± 0.39)			
Month 24 (N = 15)	0.45 (± 0.58)			

Notes:
[14] - DXA analysis set; subjects with available data at each time point

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From enrollment to end of study, including 24 weeks after last dose of denosumab for participants who received denosumab; the maximum time on study was 24 months.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Alternative Medications / Observational

Reporting group description:

Participants who received non-denosumab alternative therapy during the study or who were not receiving any medication at baseline. Alternative osteoporosis medication(s) were determined at the investigator's discretion and per standard of care and local guidelines.

Reporting group title	Denosumab 1 mg/kg Q3M

Reporting group description:

Participants who received at least one dose of 1 mg/kg denosumab administered once every 3 months (Q3M) by subcutaneous injection during this study.

Reporting group title	Denosumab 1 mg/kg Q6M

Reporting group description:

Participants who received at least 1 dose of 1 mg/kg denosumab administered once every 6 months (Q6M) administered by subcutaneous injection, but no Q3M denosumab during this study.

Serious adverse events	Alternative Medications / Observational	Denosumab 1 mg/kg Q3M	Denosumab 1 mg/kg Q6M
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 21 (28.57%)	6 / 27 (22.22%)	5 / 27 (18.52%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	2 / 21 (9.52%)	1 / 27 (3.70%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			
subjects affected / exposed	0 / 21 (0.00%)	0 / 27 (0.00%)	2 / 27 (7.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			

subjects affected / exposed	2 / 21 (9.52%)	0 / 27 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 21 (0.00%)	0 / 27 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 21 (0.00%)	0 / 27 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	1 / 21 (4.76%)	0 / 27 (0.00%)	0 / 27 (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
Tibia fracture			
subjects affected / exposed	0 / 21 (0.00%)	0 / 27 (0.00%)	2 / 27 (7.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			
subjects affected / exposed	1 / 21 (4.76%)	0 / 27 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Surgical failure			
subjects affected / exposed	0 / 21 (0.00%)	0 / 27 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 21 (0.00%)	1 / 27 (3.70%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 21 (4.76%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 27 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 27 (0.00%)	0 / 27 (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
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 21 (0.00%)	5 / 27 (18.52%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	4 / 6	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	Alternative Medications / Observational	Denosumab 1 mg/kg Q3M	Denosumab 1 mg/kg Q6M
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 21 (71.43%)	13 / 27 (48.15%)	21 / 27 (77.78%)
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 21 (0.00%)	2 / 27 (7.41%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Fibula fracture			
subjects affected / exposed	0 / 21 (0.00%)	2 / 27 (7.41%)	1 / 27 (3.70%)
occurrences (all)	0	2	1
Ligament sprain			

subjects affected / exposed	1 / 21 (4.76%)	2 / 27 (7.41%)	0 / 27 (0.00%)
occurrences (all)	1	2	0
Tibia fracture			
subjects affected / exposed	0 / 21 (0.00%)	0 / 27 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 21 (14.29%)	2 / 27 (7.41%)	1 / 27 (3.70%)
occurrences (all)	6	2	2
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 21 (0.00%)	2 / 27 (7.41%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 21 (9.52%)	0 / 27 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Renal and urinary disorders			
Hypercalciuria			
subjects affected / exposed	11 / 21 (52.38%)	1 / 27 (3.70%)	15 / 27 (55.56%)
occurrences (all)	29	7	41
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 21 (28.57%)	4 / 27 (14.81%)	7 / 27 (25.93%)
occurrences (all)	6	4	17
Back pain			
subjects affected / exposed	3 / 21 (14.29%)	3 / 27 (11.11%)	4 / 27 (14.81%)
occurrences (all)	6	6	5
Pain in extremity			
subjects affected / exposed	3 / 21 (14.29%)	0 / 27 (0.00%)	7 / 27 (25.93%)
occurrences (all)	3	0	16
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 21 (4.76%)	2 / 27 (7.41%)	1 / 27 (3.70%)
occurrences (all)	1	2	1
Metabolism and nutrition disorders			

Hypercalcaemia subjects affected / exposed occurrences (all)	3 / 21 (14.29%) 3	5 / 27 (18.52%) 6	4 / 27 (14.81%) 4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 July 2019	Major changes to the protocol included: • included incidence of adverse events of special interest in the primary endpoint. • clarified the treatment options for the study. • updated dose modification language.
31 March 2020	Major changes to the protocol included: • defined denosumab Q3M as the investigational product for the study. • modified inclusion criteria to allow subjects who -did not reconsent to transition to Q3M dosing regimen in Study 20130173, or early terminated from Study 20130173 due to meeting BMD Z-score investigational product stopping criteria. • updated end of study definition. • updated dose modification language.
30 April 2020	Major changes to the protocol included: • clarified that day 10 and day 30 assessments are only required for subjects who started the Q3M dosing regimen for the first time.
17 November 2020	Major changes to the protocol included: • added additional serum calcium samples at days 10 and 30 after investigational product dosing at weeks 12 and 24. • updated definition of study day 1 and end of study.
14 January 2021	Major changes to the protocol included: • updated to harmonize content with Study 20130173 protocol after minor updates to Schedule of Activities and remove reference to the Safety Report Form.
09 November 2021	Major updates to the protocol included: • updated text throughout based on early study termination due to the risk of hypercalcemia. • added immediate discontinuation of all subjects from study treatment followed by a 24-week safety follow-up period.
02 February 2022	Major updates to the protocol included: • removed the secondary efficacy endpoints of fracture and growth velocity. • clarified that BMD Z-score and BTM will be assessed at 6, 12, and 24 months. • removed the exploratory endpoint of BMD and bone mineral content. • removed the subgroup analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported