Clinical trial results:
A Phase 2b, Multicentre, Multinational, Double-blind, Dose-finding Study, incorporating an open label substudy, in Adult Patients with Type I, III or IV Osteogenesis Imperfecta Treated with setrusumab (BPS804)

Summary

EudraCT number	2016-005096-27
Trial protocol	DK GB FR
Global end of trial date	12 November 2020

Results information

Result version number	v1 (current)
This version publication date	01 March 2022
First version publication date	01 March 2022

Trial information

Trial identification

Sponsor protocol code	MBPS205

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03118570
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number: 113385

Notes:

Sponsors

Sponsor organisation name	Ultragenyx Pharmaceutical Inc.
Sponsor organisation address	60 Leveroni Court, Novato, United States, California 94949
Public contact	Medical Information, Ultragenyx Pharmaceutical Inc., 001 888-756-8567, medinfo@ultragenyx.com
Scientific contact	Medical Information, Ultragenyx Pharmaceutical Inc., 001 888-756-8567, medinfo@ultragenyx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 November 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that setrusumab increases radial trabecular volumetric bone mineral density (Tr. vBMD) on high resolution peripheral quantitative computed tomography (HRpQCT) and bone strength on finite element analysis (FEA) in patients with OI Type I, III or IV

Protection of trial subjects:

The investigator or his/her representative explained the nature of the study to the participant or his/her legally authorised representative and answered all questions regarding the study. Participants was informed that their participation was voluntary. Participants or their legally authorised representative were required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

Background therapy:

For the duration of the study participants receive a daily dose of 500 mg calcium and/or 800 I.U. vitamin D as background treatment.

Following the end of setrusumab therapy all participants had the option to receive a dose of zoledronic acid at 12 and 18 months, prescribed at the discretion of the treating physician and in line with local guidelines.

Evidence for comparator: -

Actual start date of recruitment	11 September 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	United States: 61
Country: Number of subjects enrolled	Canada: 8
Worldwide total number of subjects	112
EEA total number of subjects	26

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	105
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were randomized 1:1:1:1 to 3 doses of setrusumab (20 mg/kg, 8 mg/kg and 2 mg/kg) and placebo for a 12-month Treatment Period.

Pre-assignment

Screening details:

Per Protocol Amendment 4, participants originally randomized to the placebo group were reassigned to receive 20 mg/kg open-label setrusumab (1 discontinued study prior to the transition). Two participants in the setrusumab 20 mg/kg open-label group were randomized into this group after Amendment 4 and did not receive placebo.

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

Blinding implementation details:

With the exception of the open-label treatment arm, investigators and participants remained blinded to each participant’s assigned study treatment throughout the course of the study.

Arms

Are arms mutually exclusive?	No
Arm title	Setrusumab 20 mg/kg (Blinded)

Arm description:

Setrusumab 20 mg/kg intravenous (IV) infusion once a month for 12 months plus 500 mg calcium oral tablets and 800 IU vitamin D capsules.

Arm type	Experimental
Investigational medicinal product name	setrusumab
Investigational medicinal product code	BPS804
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

60-minute infusion

Investigational medicinal product name	zoledronic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

15-minute infusion

(Following the end of setrusumab therapy all participants had the option to receive a dose of zoledronic acid at 12 and 18 months, prescribed at the discretion of the treating physician and in line with local guidelines.)

Arm title	Setrusumab 8 mg/kg (Blinded)

Arm description:

Setrusumab 8 mg/kg IV infusion once a month for 12 months plus 500 mg calcium oral tablets and 800 IU vitamin D capsules.

Arm type	Experimental

Investigational medicinal product name	setrusumab
Investigational medicinal product code	BPS804
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

60-minute infusion

Investigational medicinal product name	zoledronic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

15-minute infusion

(Following the end of setrusumab therapy all participants had the option to receive a dose of zoledronic acid at 12 and 18 months, prescribed at the discretion of the treating physician and in line with local guidelines.)

Arm title	Setrusumab 2 mg/kg (Blinded)

Arm description:

Setrusumab 2 mg/kg IV infusion once a month for 12 months plus 500 mg calcium oral tablets and 800 IU vitamin D capsules.

Arm type	Experimental
Investigational medicinal product name	setrusumab
Investigational medicinal product code	BPS804
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

60-minute infusion

Investigational medicinal product name	zoledronic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

15-minute infusion

(Following the end of setrusumab therapy all participants had the option to receive a dose of zoledronic acid at 12 and 18 months, prescribed at the discretion of the treating physician and in line with local guidelines.)

Arm title	Setrusumab 20 mg/kg (Open-Label)

Arm description:

Setrusumab 20 mg/kg IV infusion once a month for 12 months plus 500 mg calcium oral tablets and 800 IU vitamin D capsules. Participants were randomized to this group after amendment 4.

Arm type	Experimental
Investigational medicinal product name	setrusumab
Investigational medicinal product code	BPS804
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

60-minute infusion

Investigational medicinal product name	zoledronic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

15-minute infusion

(Following the end of setrusumab therapy all participants had the option to receive a dose of zoledronic acid at 12 and 18 months, prescribed at the discretion of the treating physician and in line with local guidelines.)

Arm title	Placebo

Arm description:

Placebo IV infusion once a month for 12 months plus 500 mg calcium oral tablets and 800 IU vitamin D capsules. Due to a protocol amendment, placebo was actually received for an average of 5 months. Participants originally randomized to the placebo group were reassigned to receive 20 mg/kg open-label setrusumab after amendment 4.

Arm type	Experimental
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

60-minute infusion

Number of subjects in period 1	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)
Started	31	29	30
Completed	26	22	25
Not completed	5	7	5
Consent withdrawn by subject	-	1	4
Other, not specified	1	3	-
Transferred to other arm/group	-	-	-
Adverse event	2	-	-
Lost to follow-up	2	3	1
Joined	0	0	0
Transferred in from other group/arm	-	-	-

Number of subjects in period 1	Setrusumab 20 mg/kg (Open-Label)	Placebo
Started	2	20
Completed	17	0
Not completed	4	20
Consent withdrawn by subject	1	-
Other, not specified	-	-
Transferred to other arm/group	-	19

Adverse event	2	1
Lost to follow-up	1	-
Joined	19	0
Transferred in from other group/arm	19	-

Baseline characteristics

Reporting groups[1]	
Reporting group title	Setrusumab 20 mg/kg (Blinded)
Reporting group description:	
Setrusumab 20 mg/kg intravenous (IV) infusion once a month for 12 months plus 500 mg calcium oral tablets and 800 IU vitamin D capsules.	
Reporting group title	Setrusumab 8 mg/kg (Blinded)
Reporting group description:	
Setrusumab 8 mg/kg IV infusion once a month for 12 months plus 500 mg calcium oral tablets and 800 IU vitamin D capsules.	
Reporting group title	Setrusumab 2 mg/kg (Blinded)
Reporting group description:	
Setrusumab 2 mg/kg IV infusion once a month for 12 months plus 500 mg calcium oral tablets and 800 IU vitamin D capsules.	
Reporting group title	Setrusumab 20 mg/kg (Open-Label)
Reporting group description:	
Setrusumab 20 mg/kg IV infusion once a month for 12 months plus 500 mg calcium oral tablets and 800 IU vitamin D capsules. Participants were randomized to this group after amendment 4.	
Reporting group title	Placebo
Reporting group description:	
Placebo IV infusion once a month for 12 months plus 500 mg calcium oral tablets and 800 IU vitamin D capsules. Due to a protocol amendment, placebo was actually received for an average of 5 months. Participants originally randomized to the placebo group were reassigned to receive 20 mg/kg open-label setrusumab after amendment 4.	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: The 19 participants who transitioned from the Placebo arm to the Setrusumab 20 mg/kg Open-Label arm are "double-counted" for this analysis. (The total column represents the baseline values only for the n=112 enrolled participants.)

Reporting group values	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)
Number of subjects	31	29	30
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	40.6	40.4	47.2
standard deviation	± 13.73	± 14.34	± 12.42
Gender categorical Units: Subjects			
Female	17	20	21
Male	14	9	9
Ethnicity Units: Subjects			
Hispanic or Latino	3	1	2
Not Hispanic or Latino	27	27	28
Unknown or Not Reported	1	1	0
Race Units: Subjects			
Black or African American	2	1	1

White	29	27	29
Not Collected or Not Reported	0	1	0

Reporting group values	Setrusumab 20 mg/kg (Open-Label)	Placebo	Total
Number of subjects	21	20	112
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	41.6	40.9	
standard deviation	± 14.82	± 14.68	-
Gender categorical Units: Subjects			
Female	15	14	73
Male	6	6	39
Ethnicity Units: Subjects			
Hispanic or Latino	1	1	4
Not Hispanic or Latino	20	19	107
Unknown or Not Reported	0	0	1
Race Units: Subjects			
Black or African American	0	0	4
White	21	20	107
Not Collected or Not Reported	0	0	1

End points

End points reporting groups

Reporting group title	Setrusumab 20 mg/kg (Blinded)
Reporting group description:	
Setrusumab 20 mg/kg intravenous (IV) infusion once a month for 12 months plus 500 mg calcium oral tablets and 800 IU vitamin D capsules.	
Reporting group title	Setrusumab 8 mg/kg (Blinded)
Reporting group description:	
Setrusumab 8 mg/kg IV infusion once a month for 12 months plus 500 mg calcium oral tablets and 800 IU vitamin D capsules.	
Reporting group title	Setrusumab 2 mg/kg (Blinded)
Reporting group description:	
Setrusumab 2 mg/kg IV infusion once a month for 12 months plus 500 mg calcium oral tablets and 800 IU vitamin D capsules.	
Reporting group title	Setrusumab 20 mg/kg (Open-Label)
Reporting group description:	
Setrusumab 20 mg/kg IV infusion once a month for 12 months plus 500 mg calcium oral tablets and 800 IU vitamin D capsules. Participants were randomized to this group after amendment 4.	
Reporting group title	Placebo
Reporting group description:	
Placebo IV infusion once a month for 12 months plus 500 mg calcium oral tablets and 800 IU vitamin D capsules. Due to a protocol amendment, placebo was actually received for an average of 5 months. Participants originally randomized to the placebo group were reassigned to receive 20 mg/kg open-label setrusumab after amendment 4.	

Primary: Change From Baseline in Radial Trabecular Volumetric Bone Mineral Density (Tr vBMD) at Month 12

End point title	Change From Baseline in Radial Trabecular Volumetric Bone Mineral Density (Tr vBMD) at Month 12[1][2]
End point description:	
Assessed by high resolution peripheral quantitative computed tomography (HRpQCT). HRpQCT scans were performed on the participant's distal non-dominant arm. In cases of an arm that had been supported with rods or had significant deformity, the dominant limb was selected. Data presents the ratio of the means between the visit and Baseline from analysis of covariance (ANCOVA). Full Analysis Set: all participants who are randomized to one of the blinded treatment arms and took at least 1 dose of study treatment (per protocol almost all efficacy endpoints were to be analyzed only in the blinded treatment arms). Participants with an assessment at given time point.	
End point type	Primary
End point timeframe:	
Full Analysis Set: all participants who are randomized to one of the blinded treatment arms and took at least 1 dose of study treatment. Participants with an assessment at given time point.	

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: Statistical analyses are attached in a word document due to system limitations.

[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: Per protocol almost all efficacy endpoints were to be analyzed only in the blinded treatment arms.

End point values	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	29	30	
Units: ratio				
number (confidence interval 95%)	1.004 (0.987 to 1.021)	0.993 (0.975 to 1.012)	0.992 (0.974 to 1.011)	

Attachments (see zip file)	Endpoint 1 Stat Analyses.docx

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Radial Bone Strength (Failure Load) at Month 12

End point title	Change From Baseline in Radial Bone Strength (Failure Load) at Month 12[3][4]

End point description:

Assessed by finite element analysis (FEA) of models generated from HRpQCT images of the distal radius.

Full Analysis Set: all participants who are randomized to one of the blinded treatment arms and took at least 1 dose of study treatment. Participants with an assessment at given time point.

End point type	Primary

End point timeframe:

Baseline, Month 12 (EOT)

Notes:

[3] - 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: Statistical analyses are attached in a word document due to system limitations.

[4] - 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: Per protocol almost all efficacy endpoints were to be analyzed only in the blinded treatment arms.

End point values	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	22	25	
Units: newton (N)				
least squares mean (standard error)	61.25 (± 21.669)	32.25 (± 24.342)	8.86 (± 23.200)	

Attachments (see zip file)	Endpoint 2 Stat Analyses.docx

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Radial Bone Strength (Stiffness) at Month 12

End point title	Change From Baseline in Radial Bone Strength (Stiffness) at Month 12[5][6]

End point description:

Assessed by FEA of models generated from HRpQCT images of the distal radius.

Full Analysis Set: all participants who are randomized to one of the blinded treatment arms and took at least 1 dose of study treatment. Participants with an assessment at given time point.

End point type	Primary

End point timeframe:

Baseline, Month 12 (EOT)

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: Statistical analyses are attached in a word document due to system limitations.

[6] - 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: Per protocol almost all efficacy endpoints were to be analyzed only in the blinded treatment arms.

End point values	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	22	25	
Units: N/mm				
least squares mean (standard error)	1638.70 (± 625.808)	1422.00 (± 703.275)	209.89 (± 671.777)	

Attachments (see zip file)	Endpoint 3 Stat Analyses.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Radial and Tibial Tr VBMD Over Time: Full Analysis Set

End point title	Change From Baseline in Radial and Tibial Tr VBMD Over Time: Full Analysis Set[7]

End point description:

Assessed by HRpQCT. HRpQCT scans were performed on the participant's distal non-dominant arm. In cases of an arm that had been supported with rods or had significant deformity, the dominant limb was selected. Data presented is the ratio of the means between the Visit and Baseline from ANCOVA.

Full Analysis Set: all participants who are randomized to one of the blinded treatment arms and took at least 1 dose of study treatment. n=participants with an assessment at given time point.

End point type	Secondary

End point timeframe:

Baseline, Months 6, 12 (EOT), 18, 24

Notes:

[7] - 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: Per protocol almost all efficacy endpoints were to be analyzed only in the blinded treatment arms. Open-Label arm data for this endpoint are presented as a separate endpoint.

End point values	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	29	30	
Units: ratio				
number (confidence interval 95%)				
Radial: Month 6; n=26, 25, 25	1.007 (0.993 to 1.021)	1.000 (0.986 to 1.015)	0.998 (0.984 to 1.013)	
Radial: Month 12; n=28, 22, 24	1.004 (0.987 to 1.021)	0.993 (0.975 to 1.012)	0.992 (0.974 to 1.011)	
Radial: Month 18; n=23, 17, 23	1.002 (0.984 to 1.020)	0.992 (0.973 to 1.013)	0.979 (0.962 to 0.997)	
Radial: Month 24; n=21, 16, 16	0.997 (0.972 to 1.023)	0.998 (0.970 to 1.027)	0.979 (0.951 to 1.008)	
Tibial: Month 6; n=23, 20, 17	1.004 (0.986 to 1.022)	1.016 (0.996 to 1.036)	0.990 (0.969 to 1.012)	
Tibial: Month 12; n=24, 17, 15	0.991 (0.940 to 1.046)	1.018 (0.955 to 1.086)	0.973 (0.909 to 1.042)	
Tibial: Month 18; n=20, 13, 16	0.989 (0.945 to 1.035)	1.042 (0.985 to 1.102)	0.983 (0.933 to 1.036)	
Tibial: Month 24; n=19, 12, 11	1.000 (0.949 to 1.054)	1.062 (0.995 to 1.133)	1.017 (0.949 to 1.090)	

Attachments (see zip file)	Endpoint 4 Stat Analyses.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline in Radial and Tibial Tr VBMD at Months 6 and 12: Open-Label Arm

End point title	Changes From Baseline in Radial and Tibial Tr VBMD at Months 6 and 12: Open-Label Arm[8]

End point description:

Assessed by HRpQCT. HRpQCT scans were performed on the participant's distal non-dominant arm. In cases of an arm that had been supported with rods or had significant deformity, the dominant limb was selected. Data presented is the ratio of the means between the Visit and Baseline from ANCOVA.

Analysis Population: All participants in the open-label arm who took at least 1 dose of study treatment. n=participants with an assessment at given time point.

End point type	Secondary

End point timeframe:

Baseline, Months 6, 12 (EOT)

Notes:

[8] - 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: Per protocol almost all efficacy endpoints were to be analyzed only in the blinded treatment arms. Full Analysis Set data for this endpoint are presented as a separate endpoint.

End point values	Setrusumab 20 mg/kg (Open-Label)			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: ratio				
number (confidence interval 95%)				
Radial: Month 6; n=17	0.994 (0.972 to 1.017)			
Radial: Month 12; n=16	1.011 (0.986 to 1.036)			
Tibial: Month 6; n=15	1.013 (0.991 to 1.035)			
Tibial: Month 12; n=15	1.035 (0.975 to 1.099)			

Attachments (see zip file)	Endpoint 5 Stat Analyses.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline in Radial and Tibial Bone Strength (Failure Load) Over Time: Full Analysis Set

End point title	Changes From Baseline in Radial and Tibial Bone Strength (Failure Load) Over Time: Full Analysis Set[9]

End point description:

Assessed by FEA of models generated from HRpQCT images of the distal radius.

Full Analysis Set: all participants who are randomized to one of the blinded treatment arms and took at least 1 dose of study treatment. n=participants with an assessment at given time point.

End point type	Secondary

End point timeframe:

Baseline, Months 6, 12 (EOT), 18, 24

Notes:

[9] - 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: Per protocol almost all efficacy endpoints were to be analyzed only in the blinded treatment arms.

End point values	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	29	30	
Units: newton				
least squares mean (confidence interval 95%)				
Radial: Month 6; n=26, 25, 26	31.22 (-1.80 to 64.23)	39.95 (6.63 to 73.27)	-3.28 (-36.57 to 30.00)	
Radial: Month 12; n=28, 22, 25	61.25 (18.03 to 104.46)	32.25 (-16.30 to 80.80)	8.86 (-37.41 to 55.13)	
Radial: Month 18; n=23, 17, 24	50.39 (19.11 to 81.68)	43.11 (6.79 to 79.42)	-10.53 (-41.86 to 20.80)	

Radial: Month 24; n=21, 16, 17	-19.59 (-72.66 to 33.47)	45.03 (-14.40 to 104.47)	-50.65 (-108.69 to 7.39)	
Tibial: Month 6; n=23, 20, 17	46.00 (-24.91 to 116.92)	45.91 (-28.16 to 119.98)	-65.33 (-146.39 to 15.72)	
Tibial: Month 12; n=24, 17, 15	76.15 (-11.23 to 163.54)	60.20 (-42.63 to 163.04)	-65.96 (-175.43 to 43.51)	
Tibial: Month 18; n=20, 13, 16	50.69 (-34.55 to 135.93)	88.33 (-13.67 to 190.32)	-49.50 (-144.93 to 45.94)	
Tibial: Month 24; n=19, 12, 11	-24.75 (-126.76 to 77.27)	41.37 (-86.68 to 169.43)	-74.94 (-208.22 to 58.34)	

Attachments (see zip file)	Endpoint 6 Stat Analyses.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline in Radial and Tibial Bone Strength (Failure Load) at Months 6 and 12: Open-Label Arm

End point title	Changes From Baseline in Radial and Tibial Bone Strength (Failure Load) at Months 6 and 12: Open-Label Arm[10]

End point description:

Assessed by FEA of models generated from HRpQCT images of the distal radius.

All participants in the open-label arm who took at least 1 dose of study treatment. n=participants with an assessment at given time point.

End point type	Secondary

End point timeframe:

Baseline, Months 6, 12 (EOT)

Notes:

[10] - 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: Per protocol almost all efficacy endpoints were to be analyzed only in the blinded treatment arms.

End point values	Setrusumab 20 mg/kg (Open-Label)			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: newton				
least squares mean (confidence interval 95%)				
Radial: Month 6; n=16	110.16 (61.30 to 159.01)			
Radial: Month 12; n=15	88.32 (28.55 to 148.09)			
Tibial: Month 6; n=15	69.78 (-8.61 to 148.18)			

Tibial: Month 12; n=15	112.92 (10.76 to 215.07)			

Attachments (see zip file)	Endpoint 7 Stat Analyses.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline in Radial and Tibial Bone Strength (Stiffness) Over Time: Full Analysis Set

End point title	Changes From Baseline in Radial and Tibial Bone Strength (Stiffness) Over Time: Full Analysis Set[11]

End point description:

Assessed by FEA of models generated from HRpQCT images of the distal radius.

Full Analysis Set: all participants who are randomized to one of the blinded treatment arms and took at least 1 dose of study treatment. n=participants with an assessment at given time point.

End point type	Secondary

End point timeframe:

Baseline, Months 6, 12 (EOT), 18, 24

Notes:

[11] - 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: Per protocol almost all efficacy endpoints were to be analyzed only in the blinded treatment arms.

End point values	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	29	30	
Units: N/mm				
least squares mean (confidence interval 95%)				
Radial: Month 6; n=26, 25, 26	795.67 (-34.71 to 1626.04)	1048.61 (209.47 to 1887.75)	109.65 (-728.52 to 947.82)	
Radial: Month 12; n=28, 22, 25	1638.70 (390.57 to 2886.83)	1422.00 (19.37 to 2824.64)	209.89 (-1129.93 to 1549.71)	
Radial: Month 18; n=23, 17, 24	1295.98 (390.54 to 2201.42)	803.50 (-263.21 to 1870.21)	-215.92 (-1132.78 to 700.94)	
Radial: Month 24; n=21, 16, 17	-625.46 (-1888.53 to 637.60)	1172.45 (-265.87 to 2610.76)	-1258.55 (-2663.69 to 146.60)	
Tibial: Month 6; n=23, 20, 17	1344.84 (-296.83 to 2986.52)	1051.40 (-708.46 to 2811.25)	-1356.71 (-3284.14 to 570.73)	
Tibial: Month 12; n=24, 17, 15	2326.63 (221.71 to 4431.55)	1543.85 (-973.70 to 4061.40)	-1428.87 (-4118.78 to 1261.03)	

Tibial: Month 18; n=20, 13, 16	1047.16 (-1070.79 to 3165.11)	1697.21 (-861.80 to 4256.23)	-815.38 (-3247.85 to 1617.09)	
Tibial: Month 24; n=19, 12, 11	-1250.69 (-4131.64 to 1630.26)	622.77 (-2966.46 to 4212.01)	-1844.84 (-5695.04 to 2005.37)	

Attachments (see zip file)	Endpoint 8 Stat Analyses.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline in Radial and Tibial Bone Strength (Stiffness) at Months 6 and 12: Open-Label Arm

End point title	Changes From Baseline in Radial and Tibial Bone Strength (Stiffness) at Months 6 and 12: Open-Label Arm[12]

End point description:

Assessed by FEA of models generated from HRpQCT images of the distal radius.

All participants in the open-label arm who took at least 1 dose of study treatment. n=participants with an assessment at given time point.

End point type	Secondary

End point timeframe:

Baseline, Months 6, 12 (EOT)

Notes:

[12] - 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: Per protocol almost all efficacy endpoints were to be analyzed only in the blinded treatment arms.

End point values	Setrusumab 20 mg/kg (Open-Label)			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: N/mm				
least squares mean (confidence interval 95%)				
Radial: Month 6; n=16	5056.51 (3404.58 to 6708.45)			
Radial: Month 12; n=15	4992.82 (3056.80 to 6928.84)			
Tibial: Month 6; n=15	4225.92 (1840.16 to 6611.68)			
Tibial: Month 12; n=15	5827.81 (2601.54 to 9054.08)			

Attachments (see zip file)	Endpoint 9 Stat Analyses.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With at Least 1 New Fracture (Peripheral, Vertebral, Long-Bone, Any) at Month 12

End point title	Percentage of Participants With at Least 1 New Fracture (Peripheral, Vertebral, Long-Bone, Any) at Month 12[13]

End point description:

Fracture assessment, confirmed by central radiographic reading, was carried out for peripheral including all major long bones, minor bone (digits, ribs) and vertebral fractures. Fractures without clinical symptoms, detected only by means of radiographic investigations, were not included in the analysis.

Full Analysis Set: all participants who are randomized to one of the blinded treatment arms and took at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

Month 12 (EOT)

Notes:

[13] - 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: Per protocol almost all efficacy endpoints were to be analyzed only in the blinded treatment arms.

End point values	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	29	30	
Units: percentage of participants				
number (not applicable)				
Peripheral	6.5	17.2	13.3	
Vertebral	0	0	0	
Long-Bone	3.2	13.8	3.3	
Any	16.1	34.5	23.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Lumbar, Total Body, and Femoral Neck Bone Mineral Density (BMD) T-score at Month 6

End point title	Change From Baseline in Lumbar, Total Body, and Femoral Neck Bone Mineral Density (BMD) T-score at Month 6[14]

End point description:

BMD was evaluated by dual-energy x-ray absorptiometry (DXA). T-Score was calculated based on actual measured bone density value. T-scores are standardized scores that reflect the standard deviations (SDs) above/below the normal mean for young adults. A score of 50 indicates the population mean with a standard deviation of 10. A positive change in DXA T-score indicates an improvement in BMD.

Full Analysis Set: all participants who are randomized to one of the blinded treatment arms and took at least 1 dose of study treatment. n=participants with an assessment at given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Month 6

Notes:

[14] - 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: Per protocol almost all efficacy endpoints were to be analyzed only in the blinded treatment arms.

End point values	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	29	30	
Units: T-score				
least squares mean (confidence interval 95%)				
Lumbar; n=24, 25, 26	0.273 (0.142 to 0.405)	0.338 (0.213 to 0.464)	0.110 (-0.014 to 0.233)	
Total Body; n=23, 24, 27	0.072 (-0.049 to 0.194)	0.071 (-0.048 to 0.189)	0.122 (0.009 to 0.235)	
Femoral Neck; n=21, 19, 24	-0.024 (-0.143 to 0.095)	0.102 (-0.023 to 0.226)	0.087 (-0.026 to 0.199)	

Attachments (see zip file)	Endpoint 11 Stat Analyses.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Lumbar, Total Body, and Femoral Neck BMD at Month 6

End point title	Change From Baseline in Lumbar, Total Body, and Femoral Neck BMD at Month 6[15]

End point description:

BMD was evaluated by DXA.

Full Analysis Set: all participants who are randomized to one of the blinded treatment arms and took at least 1 dose of study treatment. n=participants with an assessment at given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Month 6

Notes:

[15] - 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: Per protocol almost all efficacy endpoints were to be analyzed only in the blinded treatment arms.

End point values	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	29	30	
Units: g/cm^2				
least squares mean (confidence interval 95%)				
Lumbar; n=24, 25, 26	4.06 (2.12 to 6.00)	4.70 (2.86 to 6.55)	1.58 (-0.24 to 3.40)	
Total Body; n=23, 24, 27	0.77 (-0.38 to 1.92)	0.83 (-0.29 to 1.94)	1.21 (0.14 to 2.28)	
Femoral Neck; n=21, 19, 24	-0.42 (-2.51 to 1.68)	1.64 (-0.57 to 3.84)	1.61 (-0.38 to 3.59)	

Attachments (see zip file)	Endpoint 12 Stat Analyses.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Lumbar, Total Body, and Femoral Neck BMD T-score at Month 12

End point title	Change From Baseline in Lumbar, Total Body, and Femoral Neck BMD T-score at Month 12[16]

End point description:

BMD was evaluated by DXA. T-Score was calculated based on actual measured bone density value. T-scores are standardized scores that reflect the standard deviations (SDs) above/below the normal mean for young adults. A score of 50 indicates the population mean with a standard deviation of 10. A positive change in DXA T-score indicates an improvement in BMD.

Full Analysis Set: all participants who are randomized to one of the blinded treatment arms and took at least 1 dose of study treatment. n=participants with an assessment at given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Month 12 (EOT)

Notes:

[16] - 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: Per protocol almost all efficacy endpoints were to be analyzed only in the blinded treatment arms.

End point values	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	29	30	
Units: T-score				
least squares mean (confidence interval 95%)				
Lumbar; n=24, 22, 25	0.587 (0.427 to 0.746)	0.486 (0.324 to 0.648)	0.174 (0.022 to 0.327)	
Total Body; n=23, 22, 26	0.181 (0.051 to 0.310)	0.199 (0.068 to 0.330)	0.108 (-0.015 to 0.231)	

Femoral Neck; n=21, 18, 22	0.163 (0.008 to 0.319)	0.159 (-0.007 to 0.326)	0.104 (-0.053 to 0.260)	

Attachments (see zip file)	Endpoint 13 Stat Analyses.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Lumbar, Total Body, and Femoral Neck BMD at Month 12

End point title	Change From Baseline in Lumbar, Total Body, and Femoral Neck BMD at Month 12[17]

End point description:

BMD was evaluated by DXA.

Full Analysis Set: all participants who are randomized to one of the blinded treatment arms and took at least 1 dose of study treatment. n=participants with an assessment at given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Month 12 (EOT)

Notes:

[17] - 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: Per protocol almost all efficacy endpoints were to be analyzed only in the blinded treatment arms.

End point values	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	29	30	
Units: g/cm^2				
least squares mean (confidence interval 95%)				
Lumbar; n=24, 22, 25	8.55 (6.13 to 10.97)	6.79 (4.34 to 9.25)	2.50 (0.19 to 4.81)	
Total Body; n=23, 22, 26	1.98 (0.70 to 3.25)	2.03 (0.73 to 3.33)	1.06 (-0.16 to 2.27)	
Femoral Neck; n= 21, 18, 22	3.30 (0.64 to 5.96)	2.65 (-0.20 to 5.51)	1.90 (-0.77 to 4.56)	

Attachments (see zip file)	Endpoint 14 Stat Analyses.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Total vBMD (Radial and Tibial) Over Time

End point title	Change From Baseline in Total vBMD (Radial and Tibial) Over Time[18]

End point description:

Assessed by HRpQCT. HRpQCT scans were performed on the participant's distal non-dominant arm. In cases of an arm that had been supported with rods or had significant deformity, the dominant limb was selected. Data presented is the ratio of the means between the Visit and Baseline from ANCOVA.

Full Analysis Set: all participants who are randomized to one of the blinded treatment arms and took at least 1 dose of study treatment. n=participants with an assessment at given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Months 6, 12 (EOT), 18, and 24

Notes:

[18] - 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: Per protocol almost all efficacy endpoints were to be analyzed only in the blinded treatment arms.

End point values	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	29	30	
Units: ratio				
number (confidence interval 95%)				
Radial, Month 6; n=26, 25, 26	1.011 (0.999 to 1.022)	0.995 (0.984 to 1.007)	1.000 (0.989 to 1.012)	
Radial, Month 12; n=28, 22, 25	1.017 (1.006 to 1.029)	1.008 (0.995 to 1.021)	0.999 (0.986 to 1.011)	
Radial, Month 18; n=23, 17, 24	1.013 (1.000 to 1.026)	0.992 (0.978 to 1.007)	0.996 (0.983 to 1.009)	
Radial, Month 24; n=21, 16, 17	0.998 (0.984 to 1.012)	1.009 (0.994 to 1.025)	0.985 (0.969 to 1.000)	
Tibial, Month 6; n=23, 20, 17	1.017 (1.001 to 1.033)	1.011 (0.995 to 1.028)	0.995 (0.977 to 1.031)	
Tibial, Month 12; n=24, 17, 15	1.024 (1.004 to 1.045)	1.011 (0.988 to 1.035)	0.989 (0.965 to 1.014)	
Tibial, Month 18; n=20, 13, 16	1.020 (0.997 to 1.045)	1.021 (0.992 to 1.050)	0.987 (0.961 to 1.014)	
Tibial, Month 24; n=19, 12, 11	1.001 (0.982 to 1.021)	1.025 (1.001 to 1.050)	0.994 (0.970 to 1.019)	

Attachments (see zip file)	Endpoint 15 Stat Analyses.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Cortical vBMD (Radial and Tibial) Over Time

End point title	Change From Baseline in Cortical vBMD (Radial and Tibial) Over Time[19]

End point description:

Assessed by HRpQCT. HRpQCT scans were performed on the participant's distal non-dominant arm. In

cases of an arm that had been supported with rods or had significant deformity, the dominant limb was selected. Data presented is the ratio of the means between the Visit and Baseline from ANCOVA.

Full Analysis Set: all participants who are randomized to one of the blinded treatment arms and took at least 1 dose of study treatment. n=participants with an assessment at given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Months 6, 12 (EOT), 18, and 24

Notes:

[19] - 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: Per protocol almost all efficacy endpoints were to be analyzed only in the blinded treatment arms.

End point values	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	29	30	
Units: ratio				
number (confidence interval 95%)				
Radial, Month 6; n=26, 25, 26	1.004 (0.997 to 1.010)	1.002 (0.996 to 1.009)	0.998 (0.992 to 1.005)	
Radial, Month 12; n=28, 22, 25	1.005 (0.998 to 1.012)	1.003 (0.995 to 1.010)	1.001 (0.993 to 1.008)	
Radial, Month 18; n=23, 17, 24	1.011 (1.001 to 1.021)	1.001 (0.989 to 1.012)	1.007 (0.997 to 1.017)	
Radial, Month 24; n=21, 16, 17	1.011 (0.999 to 1.022)	1.018 (1.005 to 1.031)	1.002 (0.989 to 1.015)	
Tibial, Month 6; n=23, 20, 17	1.012 (1.003 to 1.022)	0.997 (0.987 to 1.007)	0.998 (0.987 to 1.008)	
Tibial, Month 12; n=24, 17, 15	1.017 (1.008 to 1.026)	1.004 (0.993 to 1.014)	0.998 (0.987 to 1.009)	
Tibial, Month 18; n=20, 13, 16	1.024 (1.009 to 1.039)	1.004 (0.986 to 1.022)	0.993 (0.976 to 1.009)	
Tibial, Month 24; n=19, 12, 11	1.020 (1.004 to 1.035)	1.017 (0.998 to 1.036)	0.996 (0.976 to 1.017)	

Attachments (see zip file)	Endpoint 16 Stat Analyses.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Significant Changes From Baseline in Body Height, Weight and Body Mass Index (BMI) at 6 and 12 Months: Full Analysis Set

End point title	Number of Participants With Clinically Significant Changes From Baseline in Body Height, Weight and Body Mass Index (BMI) at 6 and 12 Months: Full Analysis Set[20]

End point description:

Full Analysis Set: all participants who are randomized to one of the blinded treatment arms and took at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline, Month 6, Month 12 (EOT)

Notes:

[20] - 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: Per protocol almost all efficacy endpoints were to be analyzed only in the blinded treatment arms.

End point values	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	29	30	
Units: participants				
Month 6: Body Height	0	0	0	
Month 6: Weight	0	0	0	
Month 6: BMI	0	0	0	
Month 12: Body Height	0	0	0	
Month 12: Weight	0	0	0	
Month 12: BMI	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Lean and Fat Body Mass From Whole Body at Months 6 and 12

End point title	Change From Baseline in Lean and Fat Body Mass From Whole Body at Months 6 and 12[21]

End point description:

Lean and fat body mass was evaluated using whole body DXA (including the head).

Full Analysis Set: all participants who are randomized to one of the blinded treatment arms and took at least 1 dose of study treatment. n=participants with an assessment at given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Months 6, 12 (EOT)

Notes:

[21] - 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: Per protocol almost all efficacy endpoints were to be analyzed only in the blinded treatment arms.

End point values	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	29	30	
Units: grams				
least squares mean (confidence interval 95%)				

Month 6: Lean; n=23, 24, 27	519.152 (13.020 to 1025.284)	-410.664 (-903.724 to 82.395)	168.206 (-306.981 to 643.393)	
Month 12: Lean; n=23, 22, 26	867.668 (204.535 to 1530.801)	-225.474 (-901.083 to 450.136)	184.164 (-448.625 to 816.953)	
Month 6: Fat; n=23, 24, 27	42.567 (-771.815 to 856.949)	105.420 (-676.720 to 887.561)	426.388 (-326.298 to 1179.074)	
Month 12: Fat; n=23, 22, 26	421.266 (-629.870 to 1472.401)	-85.495 (-1136.234 to 965.245)	792.485 (-191.238 to 1776.208)	

Attachments (see zip file)	Endpoint 18 Stat Analyses.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Amino-Terminal Propeptide of Type 1 Procollagen (P1NP) up to Month 12

End point title	Change From Baseline in Amino-Terminal Propeptide of Type 1 Procollagen (P1NP) up to Month 12[22]

End point description:

Full Analysis Set: all participants who are randomized to one of the blinded treatment arms and took at least 1 dose of study treatment. n=participants with an assessment at given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Months 1, 3, 6, 9, 12 (EOT)

Notes:

[22] - 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: Per protocol almost all efficacy endpoints were to be analyzed only in the blinded treatment arms.

End point values	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	29	30	
Units: µg/L				
least squares mean (confidence interval 95%)				
Month 1; n=30, 27, 29	24.349 (18.604 to 30.095)	14.288 (8.221 to 20.354)	0.060 (-5.827 to 5.948)	
Month 3; n=29, 27, 25	17.903 (11.412 to 24.395)	6.735 (0.015 to 13.455)	0.640 (-6.389 to 7.670)	
Month 6; n=27, 28, 27	13.096 (5.468 to 20.725)	6.665 (-0.788 to 14.118)	-0.429 (-8.116 to 7.258)	
Month 9; n=27, 25, 26	7.265 (-0.115 to 14.644)	0.238 (-7.353 to 7.830)	-2.254 (-9.820 to 5.312)	
Month 12; n=25, 20, 20	5.452 (-3.362 to 14.267)	4.172 (-5.529 to 13.874)	4.428 (-5.689 to 14.545)	

Attachments (see zip file)	Endpoint 19 Stat Analyses.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Carboxy-Terminal Telo-Peptide [CTX-1] up to Month 12

End point title	Change From Baseline in Carboxy-Terminal Telo-Peptide [CTX-1] up to Month 12[23]

End point description:

Full Analysis Set: all participants who are randomized to one of the blinded treatment arms and took at least 1 dose of study treatment. n=participants with an assessment at given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Months 1, 3, 6, 9, 12 (EOT)

Notes:

[23] - 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: Per protocol almost all efficacy endpoints were to be analyzed only in the blinded treatment arms.

End point values	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	29	30	
Units: µg/L				
least squares mean (confidence interval 95%)				
Month 1; n=30, 27, 29	-0.077 (-0.100 to -0.054)	-0.047 (-0.071 to -0.022)	-0.041 (-0.064 to -0.017)	
Month 3; n=29, 27, 25	-0.044 (-0.071 to -0.016)	-0.029 (-0.058 to 0.000)	-0.043 (-0.073 to -0.013)	
Month 6; n=27, 28, 27	-0.013 (-0.055 to 0.028)	-0.025 (-0.065 to 0.016)	-0.028 (-0.069 to 0.014)	
Month 9; n=27, 25, 26	-0.020 (-0.067 to 0.026)	-0.039 (-0.087 to 0.009)	-0.031 (-0.079 to 0.017)	
Month 12; n=25, 20, 20	-0.037 (-0.083 to 0.010)	-0.002 (-0.053 to 0.049)	-0.034 (-0.087 to 0.019)	

Attachments (see zip file)	Endpoint 20 Stat Analyses.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Short Form 12 Health Survey (SF-12) Physical Component Summary Score at Months 6 and 12

End point title	Change From Baseline in Short Form 12 Health Survey (SF-12) Physical Component Summary Score at Months 6 and 12[24]

End point description:

The SF-12 is a generic, 12-item survey that measures 8 domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. It yields scale scores for each of these 8 domains and 2 summary measures of physical and mental health: The Physical Component Summary and the Mental Component Summary. The total score for the Physical Component Summary ranges from 0 to 100, where higher scores reflect better physical functioning.

Full Analysis Set: all participants who are randomized to one of the blinded treatment arms and took at least 1 dose of study treatment. n=participants with an assessment at given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Months 6, 12 (EOT)

Notes:

[24] - 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: Per protocol almost all efficacy endpoints were to be analyzed only in the blinded treatment arms.

End point values	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	29	30	
Units: score on a scale				
least squares mean (confidence interval 95%)				
Month 6; n=27, 29, 27	0.672 (-1.788 to 3.132)	-0.463 (-2.821 to 1.895)	1.342 (-1.129 to 3.814)	
Month 12; n=26, 26, 26	-1.178 (-3.698 to 1.341)	-0.994 (-3.488 to 1.501)	2.171 (-0.352 to 4.695)	

Attachments (see zip file)	Endpoint 21 Stat Analyses.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in SF-12 Mental Component Summary Score at Months 6 and 12

End point title	Change From Baseline in SF-12 Mental Component Summary Score at Months 6 and 12[25]

End point description:

The SF-12 is a generic, 12-item survey that measures 8 domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. It yields scale scores for each of these 8 domains and 2 summary measures of physical and mental health: The Physical Component Summary and the Mental Component Summary. The total score for the Mental Component Summary ranges from

0 to 100, where higher scores reflect better mental health functioning.

Full Analysis Set: all participants who are randomized to one of the blinded treatment arms and took at least 1 dose of study treatment. n=participants with an assessment at given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Months 6, 12 (EOT)

Notes:

[25] - 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: Per protocol almost all efficacy endpoints were to be analyzed only in the blinded treatment arms.

End point values	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	29	30	
Units: score on a scale				
least squares mean (confidence interval 95%)				
Month 6; n=27, 29, 27	0.966 (-2.064 to 3.996)	-0.492 (-3.411 to 2.427)	-1.133 (-4.202 to 1.936)	
Month 12; n=26, 26, 26	2.807 (-0.216 to 5.831)	-1.473 (-4.457 to 1.511)	-1.664 (-4.694 to 1.366)	

Attachments (see zip file)	Endpoint 22 Stat Analyses.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Index (Utility) Score on EuroQol 5-Dimension 5-Level Descriptive System (EQ-5D-5L) Score at Months 6 and 12

End point title	Change From Baseline in Index (Utility) Score on EuroQol 5-Dimension 5-Level Descriptive System (EQ-5D-5L) Score at Months 6 and 12[26]

End point description:

The EQ-5D-5L is a standardised measure of health status comprised of a descriptive system of 5 health-related quality of life states (i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a Visual Analogue Scale (VAS) of overall health. Each dimension is rated on a 5-point response scale indicating severity of problems, where 1 is "no problems" and 5 is "extreme problems". The 5 questions are scored and together contribute to the EQ-5D index (utility) score between 0 and 1 (1 being perfect health).

Full Analysis Set: all participants who are randomized to one of the blinded treatment arms and took at least 1 dose of study treatment. n=participants with an assessment at given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Months 6 and 12 (EOT)

Notes:

[26] - 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: Per protocol almost all efficacy endpoints were to be analyzed only in the blinded treatment

arms.

End point values	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	29	30	
Units: score on a scale				
least squares mean (confidence interval 95%)				
Month 6; n=27, 28, 26	0.0627 (-0.0105 to 0.1359)	0.0362 (-0.0343 to 0.1067)	-0.0383 (-0.1121 to 0.0354)	
Month 12; n=26, 25, 26	0.0424 (-0.0163 to 0.1012)	0.0252 (-0.0332 to 0.0837)	0.0214 (-0.0365 to 0.0793)	

Attachments (see zip file)	Endpoint 23 Stat Analyses.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Osteogenesis Imperfecta Specific Quality of Life Questionnaire for Adults (OIQoL-A) Total Score at Months 6 and 12

End point title	Change From Baseline in Osteogenesis Imperfecta Specific Quality of Life Questionnaire for Adults (OIQoL-A) Total Score at Months 6 and 12[27]

End point description:

The OIQoL-A measures 5 areas of quality of life related to OI (Physical Function, Pain, Hearing Loss, Taking Care/Concerns, Social and Family Life and Activities). The total score is calculated on a 0-100 scale, where higher scores indicate a greater (negative) impact on quality of life.

Full Analysis Set: all participants who are randomized to one of the blinded treatment arms and took at least 1 dose of study treatment. n=participants with an assessment at given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Months 6, 12 (EOT)

Notes:

[27] - 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: Per protocol almost all efficacy endpoints were to be analyzed only in the blinded treatment arms.

End point values	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	29	30	
Units: score on a scale				
least squares mean (confidence interval 95%)				

Month 6; n=27, 25, 26	-3.584 (-8.491 to 1.324)	-1.848 (-6.899 to 3.203)	-0.649 (-5.751 to 4.452)	
Month 12; n=25, 24, 25	-1.668 (-7.395 to 4.059)	-0.587 (-6.310 to 5.137)	-3.846 (-9.592 to 1.901)	

Attachments (see zip file)	Endpoint 24 Stat Analyses.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in OIQoL-A Pain Subscale Score at Months 6 and 12

End point title	Change From Baseline in OIQoL-A Pain Subscale Score at Months 6 and 12[28]

End point description:

The OIQoL-A measures 5 areas of quality of life related to OI (Physical Function, Pain, Hearing Loss, Taking Care/Concerns, Social and Family Life and Activities). The Pain subscale ranges from 0 to 10, with higher value representing worse pain.

Full Analysis Set: all participants who are randomized to one of the blinded treatment arms and took at least 1 dose of study treatment. n=participants with an assessment at given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Months 6, 12 (EOT)

Notes:

[28] - 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: Per protocol almost all efficacy endpoints were to be analyzed only in the blinded treatment arms.

End point values	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	29	30	
Units: score on a scale				
least squares mean (confidence interval 95%)				
Month 6; n=27, 26, 26	-3.990 (-11.267 to 3.287)	-3.906 (-11.239 to 3.426)	-6.003 (-13.495 to 1.489)	
Month 12; n=26, 26, 25	-3.655 (-11.505 to 4.195)	-4.968 (-12.709 to 2.772)	-7.178 (-15.183 to 0.827)	

Attachments (see zip file)	Endpoint 25 Stat Analyses.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in OIQoL-A Activity Subscale Score at Months 6 and 12

End point title	Change From Baseline in OIQoL-A Activity Subscale Score at Months 6 and 12[29]

End point description:

The OIQoL-A measures 5 areas of quality of life related to OI (Physical Function, Pain, Hearing Loss, Taking Care/Concerns, Social and Family Life and Activities). The Activities subscale ranges from 0 to 100, with higher value representing increased difficulty.

Full Analysis Set: all participants who are randomized to one of the blinded treatment arms and took at least 1 dose of study treatment. n=participants with an assessment at given timepoint.

End point type	Secondary

End point timeframe:

Baseline, Months 6, 12 (EOT)

Notes:

[29] - 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: Per protocol almost all efficacy endpoints were to be analyzed only in the blinded treatment arms.

End point values	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	29	30	
Units: score on a scale				
least squares mean (confidence interval 95%)				
Month 6; n=27, 26, 26	-5.980 (-11.597 to -0.363)	-2.722 (-8.397 to 2.953)	1.907 (-3.906 to 7.719)	
Month 12; n=26, 25, 25	-0.964 (-8.006 to 6.079)	4.489 (-2.620 to 11.598)	-1.630 (-8.869 to 5.609)	

Attachments (see zip file)	Endpoint 26 Stat Analyses.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Were Positive for Anti-Setrusumab Antibodies at Any Time During the Study up to Month 14

End point title	Percentage of Participants Who Were Positive for Anti-Setrusumab Antibodies at Any Time During the Study up to Month 14

End point description:

Serum samples were screened for antibodies binding to setrusumab using a validated assay method by or under the supervision of the sponsor.

Safety Population: all participants who received at least 1 dose of study drug. The 19 participants who transitioned from the Placebo arm to the Setrusumab 20 mg/kg Open-Label arm are reflected in both arms for this analysis.

End point type	Secondary

End point timeframe:

up to Month 14

End point values	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)	Setrusumab 20 mg/kg (Open-Label)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	29	30	21
Units: percentage of participants				
number (not applicable)				
Binding Antibodies	16.1	17.2	16.7	9.5
Neutralizing Antibodies	16.1	17.2	16.7	0
Both Binding and Neutralizing Antibodies	16.1	17.2	16.7	0

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: percentage of participants				
number (not applicable)				
Binding Antibodies	15.0			
Neutralizing Antibodies	0			
Both Binding and Neutralizing Antibodies	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Adverse Events (AEs), Treatment-Emergent AEs (TEAEs), Serious TEAEs, and TEAEs Leading to Discontinuation or Death

End point title	Percentage of Participants With Adverse Events (AEs), Treatment-Emergent AEs (TEAEs), Serious TEAEs, and TEAEs Leading to Discontinuation or Death

End point description:

An AE is any untoward medical occurrence, which does not necessarily have a causal relationship with treatment. A SAE is defined as any untoward medical occurrence that, at any dose: results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent disability/incapacity; is a congenital anomaly/birth defect; is another important medical event. The intensity for each AE was graded as mild, moderate or severe, according to the investigator's judgement. An event was considered related to study drug if there were a "reasonable possibility" of a relationship, according to the investigator's clinical judgment. A TEAE was defined as an event occurring or worsening on or after the first dose of study medication.

Safety Population: all participants who received at least 1 dose of study drug. The 19 participants who transitioned from the Placebo arm to the Setrusumab 20 mg/kg Open-Label arm are reflected in both arms

End point type	Secondary

End point timeframe:

Non-serious AEs: up to Month 14; Serious AEs: up to Month 24. (Average duration of exposure to placebo was 5 months and for setrusumab was 11 month plus follow-up to 24 months.)

End point values	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)	Setrusumab 20 mg/kg (Open-Label)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	29	30	21
Units: percentage of participants				
number (not applicable)				
All AEs	100.0	96.6	90.0	100.0
TEAEs	100.0	96.6	90.0	95.2
Treatment-Related TEAEs	71.0	41.4	36.7	42.9
Serious TEAEs	12.9	24.1	23.3	23.8
Treatment-Related Serious TEAEs	6.5	0	0	9.5
TEAEs Leading to Death	0	0	0	0
TEAEs Leading to Permanent Study Treatment Discon.	6.5	0	0	9.5

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: percentage of participants				
number (not applicable)				
All AEs	90.0			
TEAEs	80.0			
Treatment-Related TEAEs	25.0			
Serious TEAEs	10.0			
Treatment-Related Serious TEAEs	0			
TEAEs Leading to Death	0			
TEAEs Leading to Permanent Study Treatment Discon.	5.0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Non-serious AEs: up to Month 14; Serious AEs: up to Month 24. (Average duration of exposure to placebo was 5 months and for setrusumab was 11 month plus follow-up to 24 months.)

Adverse event reporting additional description:

Safety Population: all participants who received at least 1 dose of study drug. The 19 participants who transitioned from the Placebo arm to the Setrusumab 20 mg/kg Open-Label arm are reflected in both arms for this analysis.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Setrusumab 20 mg/kg (Blinded)

Reporting group description:

Setrusumab 20 mg/kg intravenous (IV) infusion once a month for 12 months plus 500 mg calcium oral tablets and 800 IU vitamin D capsules.

Reporting group title	Setrusumab 8 mg/kg (Blinded)

Reporting group description:

Setrusumab 8 mg/kg IV infusion once a month for 12 months plus 500 mg calcium oral tablets and 800 IU vitamin D capsules.

Reporting group title	Setrusumab 2 mg/kg (Blinded)

Reporting group description:

Setrusumab 2 mg/kg IV infusion once a month for 12 months plus 500 mg calcium oral tablets and 800 IU vitamin D capsules.

Reporting group title	Setrusumab 20 mg/kg (Open-Label)

Reporting group description:

Setrusumab 20 mg/kg IV infusion once a month for 12 months plus 500 mg calcium oral tablets and 800 IU vitamin D capsules.

Reporting group title	Placebo

Reporting group description:

Placebo IV infusion once a month for 12 months plus 500 mg calcium oral tablets and 800 IU vitamin D capsules. Due to a protocol amendment, placebo was actually received for an average of 5 months.

Serious adverse events	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 31 (12.90%)	7 / 29 (24.14%)	7 / 30 (23.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 30 (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

Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	0 / 30 (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
Ankle fracture			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 30 (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
Fracture of penis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ilium fracture			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	0 / 30 (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

Lumbar vertebral fracture			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 30 (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
Radius fracture			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	0 / 30 (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
Subcutaneous haematoma			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	0 / 30 (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
Scapula fracture			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 30 (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
Congenital, familial and genetic disorders			
Platybasia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 30 (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
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	0 / 30 (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

Hydrocephalus			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	0 / 30 (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
Neuritis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 30 (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
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	0 / 30 (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
Eye disorders			
Blindness unilateral			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual impairment			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 30 (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
Gastrointestinal disorders			
Noninfective sialoadenitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			

subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	0 / 30 (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
Pneumonia aspiration			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	0 / 30 (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
Pneumothorax			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	0 / 30 (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
Pulmonary hypertension			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 30 (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
Respiratory failure			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	0 / 30 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	0 / 30 (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
Bone pain			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	0 / 30 (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
Fracture nonunion			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	0 / 30 (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
Device related infection			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 30 (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
Joint abscess			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 30 (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
Pneumonia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	0 / 30 (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
Wound infection			

subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	0 / 30 (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
Pyelonephritis acute			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 30 (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

Serious adverse events	Setrusumab 20 mg/kg (Open-Label)	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 21 (23.81%)	2 / 20 (10.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (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			
Femur fracture			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			

subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture of penis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ilium fracture			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (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	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous haematoma			

subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scapula fracture			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Platybasia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (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			
Headache			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuritis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chills			

subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness unilateral			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual impairment			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Noninfective sialoadenitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			

subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture nonunion			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint abscess			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Setrusumab 20 mg/kg (Blinded)	Setrusumab 8 mg/kg (Blinded)	Setrusumab 2 mg/kg (Blinded)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 31 (93.55%)	28 / 29 (96.55%)	27 / 30 (90.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	2 / 30 (6.67%)
occurrences (all)	1	0	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	3 / 31 (9.68%)	2 / 29 (6.90%)	7 / 30 (23.33%)
occurrences (all)	4	2	7
Influenza like illness			
subjects affected / exposed	1 / 31 (3.23%)	2 / 29 (6.90%)	0 / 30 (0.00%)
occurrences (all)	1	2	0
Injection site extravasation			
subjects affected / exposed	1 / 31 (3.23%)	1 / 29 (3.45%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
Malaise			
subjects affected / exposed	0 / 31 (0.00%)	2 / 29 (6.90%)	0 / 30 (0.00%)
occurrences (all)	0	16	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 31 (0.00%)	2 / 29 (6.90%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Pain			
subjects affected / exposed	2 / 31 (6.45%)	0 / 29 (0.00%)	2 / 30 (6.67%)
occurrences (all)	2	0	2
Peripheral swelling			
subjects affected / exposed	0 / 31 (0.00%)	2 / 29 (6.90%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Pyrexia			

subjects affected / exposed	1 / 31 (3.23%)	2 / 29 (6.90%)	2 / 30 (6.67%)
occurrences (all)	5	3	2
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Menorrhagia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 31 (6.45%)	2 / 29 (6.90%)	2 / 30 (6.67%)
occurrences (all)	2	2	2
Dyspnoea			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	2 / 30 (6.67%)
occurrences (all)	0	1	2
Investigations			
Alanine aminotransferase abnormal			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase increased			
subjects affected / exposed	2 / 31 (6.45%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences (all)	2	0	1
Aspartate aminotransferase abnormal			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 31 (6.45%)	1 / 29 (3.45%)	1 / 30 (3.33%)
occurrences (all)	2	1	1
Blood alkaline phosphatase increased			

subjects affected / exposed	2 / 31 (6.45%)	0 / 29 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
International normalised ratio increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	3 / 30 (10.00%)
occurrences (all)	0	1	3
Lipase increased			
subjects affected / exposed	1 / 31 (3.23%)	1 / 29 (3.45%)	0 / 30 (0.00%)
occurrences (all)	1	2	0
Prothrombin time prolonged			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	3 / 30 (10.00%)
occurrences (all)	0	1	3
Vitamin D decreased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	2 / 30 (6.67%)
occurrences (all)	0	1	3
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 31 (3.23%)	2 / 29 (6.90%)	1 / 30 (3.33%)
occurrences (all)	1	3	1
Fall			
subjects affected / exposed	6 / 31 (19.35%)	4 / 29 (13.79%)	3 / 30 (10.00%)
occurrences (all)	8	4	5
Foot fracture			
subjects affected / exposed	3 / 31 (9.68%)	4 / 29 (13.79%)	3 / 30 (10.00%)
occurrences (all)	3	5	3
Hand fracture			
subjects affected / exposed	1 / 31 (3.23%)	3 / 29 (10.34%)	2 / 30 (6.67%)
occurrences (all)	1	3	2
Infusion related reaction			
subjects affected / exposed	4 / 31 (12.90%)	3 / 29 (10.34%)	1 / 30 (3.33%)
occurrences (all)	12	9	1
Joint dislocation			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	2
Joint injury			

subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			
subjects affected / exposed	3 / 31 (9.68%)	1 / 29 (3.45%)	2 / 30 (6.67%)
occurrences (all)	3	1	2
Limb injury			
subjects affected / exposed	0 / 31 (0.00%)	3 / 29 (10.34%)	1 / 30 (3.33%)
occurrences (all)	0	4	1
Muscle strain			
subjects affected / exposed	1 / 31 (3.23%)	2 / 29 (6.90%)	0 / 30 (0.00%)
occurrences (all)	1	3	0
Procedural pain			
subjects affected / exposed	2 / 31 (6.45%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences (all)	2	0	1
Rib fracture			
subjects affected / exposed	2 / 31 (6.45%)	3 / 29 (10.34%)	3 / 30 (10.00%)
occurrences (all)	2	4	5
Tooth fracture			
subjects affected / exposed	3 / 31 (9.68%)	2 / 29 (6.90%)	6 / 30 (20.00%)
occurrences (all)	4	3	12
Wound			
subjects affected / exposed	0 / 31 (0.00%)	2 / 29 (6.90%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	3 / 30 (10.00%)
occurrences (all)	0	0	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 31 (6.45%)	0 / 29 (0.00%)	3 / 30 (10.00%)
occurrences (all)	2	0	3
Headache			
subjects affected / exposed	4 / 31 (12.90%)	5 / 29 (17.24%)	6 / 30 (20.00%)
occurrences (all)	4	13	8
Hypoaesthesia			

subjects affected / exposed	3 / 31 (9.68%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences (all)	3	0	1
Migraine			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	3 / 30 (10.00%)
occurrences (all)	1	0	3
Paraesthesia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Trigeminal neuralgia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	2 / 30 (6.67%)
occurrences (all)	1	0	3
Increased tendency to bruise			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 31 (0.00%)	2 / 29 (6.90%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Middle ear effusion			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Blepharospasm			
subjects affected / exposed	2 / 31 (6.45%)	0 / 29 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Dental caries			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	4 / 31 (12.90%)	3 / 29 (10.34%)	2 / 30 (6.67%)
occurrences (all)	4	4	2
Dyspepsia			

subjects affected / exposed	2 / 31 (6.45%)	0 / 29 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 31 (3.23%)	2 / 29 (6.90%)	1 / 30 (3.33%)
occurrences (all)	1	2	1
Nausea			
subjects affected / exposed	2 / 31 (6.45%)	3 / 29 (10.34%)	5 / 30 (16.67%)
occurrences (all)	2	4	10
Toothache			
subjects affected / exposed	2 / 31 (6.45%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences (all)	2	0	1
Vomiting			
subjects affected / exposed	3 / 31 (9.68%)	1 / 29 (3.45%)	1 / 30 (3.33%)
occurrences (all)	3	1	1
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	1 / 31 (3.23%)	1 / 29 (3.45%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
Renal colic			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	15 / 31 (48.39%)	8 / 29 (27.59%)	9 / 30 (30.00%)
occurrences (all)	29	17	24
Back pain			
subjects affected / exposed	6 / 31 (19.35%)	4 / 29 (13.79%)	8 / 30 (26.67%)
occurrences (all)	7	4	13
Bone pain			
subjects affected / exposed	4 / 31 (12.90%)	3 / 29 (10.34%)	4 / 30 (13.33%)
occurrences (all)	4	3	6
Muscle spasms			

subjects affected / exposed	2 / 31 (6.45%)	1 / 29 (3.45%)	2 / 30 (6.67%)
occurrences (all)	2	2	2
Musculoskeletal chest pain			
subjects affected / exposed	2 / 31 (6.45%)	1 / 29 (3.45%)	3 / 30 (10.00%)
occurrences (all)	2	1	4
Musculoskeletal discomfort			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	2 / 31 (6.45%)	1 / 29 (3.45%)	0 / 30 (0.00%)
occurrences (all)	3	2	0
Neck pain			
subjects affected / exposed	1 / 31 (3.23%)	1 / 29 (3.45%)	4 / 30 (13.33%)
occurrences (all)	1	1	10
Pain in extremity			
subjects affected / exposed	5 / 31 (16.13%)	5 / 29 (17.24%)	3 / 30 (10.00%)
occurrences (all)	5	8	3
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 31 (3.23%)	1 / 29 (3.45%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
Cystitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Ear infection			
subjects affected / exposed	3 / 31 (9.68%)	1 / 29 (3.45%)	0 / 30 (0.00%)
occurrences (all)	3	1	0
Gastroenteritis			
subjects affected / exposed	3 / 31 (9.68%)	2 / 29 (6.90%)	0 / 30 (0.00%)
occurrences (all)	3	3	0
Herpes zoster			
subjects affected / exposed	2 / 31 (6.45%)	1 / 29 (3.45%)	0 / 30 (0.00%)
occurrences (all)	2	1	0
Influenza			
subjects affected / exposed	2 / 31 (6.45%)	0 / 29 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0

Lower respiratory tract infection			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	5 / 31 (16.13%)	3 / 29 (10.34%)	4 / 30 (13.33%)
occurrences (all)	5	4	4
Sinusitis			
subjects affected / exposed	2 / 31 (6.45%)	3 / 29 (10.34%)	4 / 30 (13.33%)
occurrences (all)	2	3	6
Tooth abscess			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	4
Upper respiratory tract infection			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1
Urinary tract infection			
subjects affected / exposed	3 / 31 (9.68%)	3 / 29 (10.34%)	2 / 30 (6.67%)
occurrences (all)	4	4	3
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 29 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 31 (0.00%)	2 / 29 (6.90%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Vitamin D deficiency			
subjects affected / exposed	2 / 31 (6.45%)	0 / 29 (0.00%)	1 / 30 (3.33%)
occurrences (all)	2	0	1

Non-serious adverse events	Setrusumab 20 mg/kg (Open-Label)	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 21 (90.48%)	16 / 20 (80.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
General disorders and administration			

site conditions			
Asthenia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	2 / 21 (9.52%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Fatigue			
subjects affected / exposed	3 / 21 (14.29%)	0 / 20 (0.00%)	
occurrences (all)	4	0	
Influenza like illness			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Injection site extravasation			
subjects affected / exposed	1 / 21 (4.76%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Malaise			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Pain			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Peripheral swelling			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	2 / 21 (9.52%)	2 / 20 (10.00%)	
occurrences (all)	3	2	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			

Dysmenorrhoea			
subjects affected / exposed	1 / 21 (4.76%)	1 / 20 (5.00%)	
occurrences (all)	3	1	
Menorrhagia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 21 (14.29%)	0 / 20 (0.00%)	
occurrences (all)	4	0	
Dyspnoea			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Investigations			
Alanine aminotransferase abnormal			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Aspartate aminotransferase abnormal			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
International normalised ratio increased			
subjects affected / exposed	1 / 21 (4.76%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Lipase increased			

subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Prothrombin time prolonged			
subjects affected / exposed	1 / 21 (4.76%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Vitamin D decreased			
subjects affected / exposed	2 / 21 (9.52%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 21 (14.29%)	0 / 20 (0.00%)	
occurrences (all)	5	0	
Fall			
subjects affected / exposed	2 / 21 (9.52%)	2 / 20 (10.00%)	
occurrences (all)	3	3	
Foot fracture			
subjects affected / exposed	6 / 21 (28.57%)	1 / 20 (5.00%)	
occurrences (all)	8	2	
Hand fracture			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Infusion related reaction			
subjects affected / exposed	2 / 21 (9.52%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Joint dislocation			
subjects affected / exposed	3 / 21 (14.29%)	0 / 20 (0.00%)	
occurrences (all)	9	0	
Joint injury			
subjects affected / exposed	1 / 21 (4.76%)	1 / 20 (5.00%)	
occurrences (all)	3	1	
Ligament sprain			
subjects affected / exposed	1 / 21 (4.76%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Limb injury			

subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Muscle strain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Procedural pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Rib fracture			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Tooth fracture			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Wound			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	7 / 21 (33.33%)	2 / 20 (10.00%)	
occurrences (all)	11	4	
Hypoaesthesia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Migraine			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Paraesthesia			

subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Trigeminal neuralgia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 21 (9.52%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Increased tendency to bruise			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Middle ear effusion			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Eye disorders			
Blepharospasm			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Dental caries			
subjects affected / exposed	1 / 21 (4.76%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Diarrhoea			
subjects affected / exposed	1 / 21 (4.76%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Dyspepsia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Nausea			

subjects affected / exposed	2 / 21 (9.52%)	2 / 20 (10.00%)	
occurrences (all)	2	2	
Toothache			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	3 / 21 (14.29%)	1 / 20 (5.00%)	
occurrences (all)	3	1	
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Renal colic			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 21 (38.10%)	5 / 20 (25.00%)	
occurrences (all)	12	5	
Back pain			
subjects affected / exposed	4 / 21 (19.05%)	1 / 20 (5.00%)	
occurrences (all)	5	1	
Bone pain			
subjects affected / exposed	2 / 21 (9.52%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Muscle spasms			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 21 (9.52%)	0 / 20 (0.00%)	
occurrences (all)	4	0	
Musculoskeletal discomfort			

subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	1 / 21 (4.76%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Neck pain			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	4 / 21 (19.05%)	1 / 20 (5.00%)	
occurrences (all)	8	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 21 (4.76%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Cystitis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Ear infection			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Influenza			
subjects affected / exposed	4 / 21 (19.05%)	1 / 20 (5.00%)	
occurrences (all)	4	3	
Lower respiratory tract infection			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	5 / 21 (23.81%)	3 / 20 (15.00%)	
occurrences (all)	9	5	

Sinusitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Tooth abscess			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 21 (4.76%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Urinary tract infection			
subjects affected / exposed	3 / 21 (14.29%)	1 / 20 (5.00%)	
occurrences (all)	4	1	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	2 / 21 (9.52%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 21 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Vitamin D deficiency			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2017	• Change to OI-QoL-A endpoints
02 May 2017	• Added 60-day Follow-up Period per UK regulatory agency • Clarified the schedule of activities
18 January 2018	• Adjusted the primary analysis to 12 months • Removed DXA vertebral fracture assessment as study endpoint
18 May 2018	• Placebo arm was replaced by 20 mg/kg of setrusumab open-label treatment arm • Addition of 12-month Follow-up Period following the double-blind Treatment Period
12 December 2018	• Addition of optional zoledronic acid therapy during Follow-up Period
19 July 2019	• Clarified open-label data on Tr. vBMD (tibia & radius) on HRpQCT and bone strength on FEA would be assessed up to Month 12

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported