

**Clinical trial results:****An Open-label, Ascending Multiple-dose Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Romosozumab in Children and Adolescents With Osteogenesis Imperfecta****Summary**

EudraCT number	2017-004972-74
Trial protocol	HU DE GR IT AT
Global end of trial date	30 March 2023

Results information

Result version number	v1 (current)
This version publication date	13 October 2023
First version publication date	13 October 2023

Trial information**Trial identification**

Sponsor protocol code	20160227
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04545554
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001075-PIP04-15
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 March 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	30 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the pharmacokinetic (PK) profile following multiple subcutaneous (SC) doses of romosozumab in children and adolescents with osteogenesis imperfecta.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 January 2021
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Turkey: 7
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Spain: 3
Worldwide total number of subjects	25
EEA total number of subjects	18

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	13
Adolescents (12-17 years)	12
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 15 study centers in Austria, Germany, Greece, Hungary, Italy, Spain, Turkey, and the United States, and participated from 21 January 2021 until 30 March 2023.

Pre-assignment

Screening details:

Ambulatory children (5 to < 12 years of age) and adolescents (12 to < 18 years of age) with osteogenesis imperfecta were enrolled to receive 1 of 3 SC dose levels of romosozumab. Specific doses are blinded due to the protection of propriety information.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
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Arm title	Cohort 1: Romosozumab Dose A (12 to < 18 Years of Age)
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Arm description:

Participants received multiple SC doses of romosozumab Dose A (low dose).

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

Dosage and administration details:

Romosozumab Dose A was administered SC.

Arm title	Cohort 2: Romosozumab Dose A (5 to < 12 Years of Age)
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Arm description:

Participants received multiple SC doses of romosozumab Dose A (low dose).

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

Dosage and administration details:

Romosozumab Dose A was administered SC.

Arm title	Cohort 3: Romosozumab Dose B (12 to < 18 Years of Age)
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Arm description:

Participants received multiple SC doses of romosozumab Dose B (medium dose).

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

Dosage and administration details:

Romosozumab Dose B was administered SC.

Arm title	Cohort 4: Romosozumab Dose B (5 to < 12 Years of Age)
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Arm description:

Participants received multiple SC doses of romosozumab Dose B (medium dose).

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

Dosage and administration details:

Romosozumab Dose B was administered SC.

Arm title	Cohort 5: Romosozumab Dose C (12 to < 18 Years of Age)
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Arm description:

Participants received multiple SC doses of romosozumab Dose C (high dose).

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

Dosage and administration details:

Romosozumab Dose C was administered SC.

Arm title	Cohort 6: Romosozumab Dose C (5 to < 12 Years of Age)
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Arm description:

Participants received multiple SC doses of romosozumab Dose C (high dose).

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

Dosage and administration details:

Romosozumab Dose C was administered SC.

Number of subjects in period 1	Cohort 1: Romosozumab Dose A (12 to < 18 Years of Age)	Cohort 2: Romosozumab Dose A (5 to < 12 Years of Age)	Cohort 3: Romosozumab Dose B (12 to < 18 Years of Age)
Started	4	4	4
Received at least 1 dose romosozumab	4	4	4
Received all doses of romosozumab	4	4	4

Completed	4	4	4
Not completed	0	0	0
Consent withdrawn by subject	-	-	-

Number of subjects in period 1	Cohort 4: Romosozumab Dose B (5 to < 12 Years of Age)	Cohort 5: Romosozumab Dose C (12 to < 18 Years of Age)	Cohort 6: Romosozumab Dose C (5 to < 12 Years of Age)
Started	5	4	4
Received at least 1 dose romosozumab	5	4	4
Received all doses of romosozumab	4	4	4
Completed	4	4	4
Not completed	1	0	0
Consent withdrawn by subject	1	-	-

Baseline characteristics

Reporting groups

Reporting group title	Cohort 1: Romosozumab Dose A (12 to < 18 Years of Age)
Reporting group description:	Participants received multiple SC doses of romosozumab Dose A (low dose).
Reporting group title	Cohort 2: Romosozumab Dose A (5 to < 12 Years of Age)
Reporting group description:	Participants received multiple SC doses of romosozumab Dose A (low dose).
Reporting group title	Cohort 3: Romosozumab Dose B (12 to < 18 Years of Age)
Reporting group description:	Participants received multiple SC doses of romosozumab Dose B (medium dose).
Reporting group title	Cohort 4: Romosozumab Dose B (5 to < 12 Years of Age)
Reporting group description:	Participants received multiple SC doses of romosozumab Dose B (medium dose).
Reporting group title	Cohort 5: Romosozumab Dose C (12 to < 18 Years of Age)
Reporting group description:	Participants received multiple SC doses of romosozumab Dose C (high dose).
Reporting group title	Cohort 6: Romosozumab Dose C (5 to < 12 Years of Age)
Reporting group description:	Participants received multiple SC doses of romosozumab Dose C (high dose).

Reporting group values	Cohort 1: Romosozumab Dose A (12 to < 18 Years of Age)	Cohort 2: Romosozumab Dose A (5 to < 12 Years of Age)	Cohort 3: Romosozumab Dose B (12 to < 18 Years of Age)
Number of subjects	4	4	4
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	4	0
Adolescents (12-17 years)	4	0	4
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	14.3	6.0	14.3
standard deviation	± 1.9	± 1.4	± 0.5
Sex: Female, Male Units: participants			
Female	1	0	1
Male	3	4	3

Race/Ethnicity, Customized Units: Subjects			
Asian	0	0	0
White	4	4	4
Other	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	4	4	4
Unknown or Not Reported	0	0	0

Reporting group values	Cohort 4: Romosozumab Dose B (5 to < 12 Years of Age)	Cohort 5: Romosozumab Dose C (12 to < 18 Years of Age)	Cohort 6: Romosozumab Dose C (5 to < 12 Years of Age)
Number of subjects	5	4	4
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	5	0	4
Adolescents (12-17 years)	0	4	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	8.4	14.0	6.5
standard deviation	± 2.4	± 1.8	± 0.6
Sex: Female, Male Units: participants			
Female	4	2	1
Male	1	2	3
Race/Ethnicity, Customized Units: Subjects			
Asian	0	0	1
White	4	4	2
Other	1	0	1
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	1	0
Not Hispanic or Latino	3	3	4
Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	25		
Age categorical Units: Subjects			
In utero	0		

Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	13		
Adolescents (12-17 years)	12		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age Continuous Units: years arithmetic mean standard deviation	-		
Sex: Female, Male Units: participants			
Female	9		
Male	16		
Race/Ethnicity, Customized Units: Subjects			
Asian	1		
White	22		
Other	2		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	3		
Not Hispanic or Latino	22		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	Cohort 1: Romosozumab Dose A (12 to < 18 Years of Age)
Reporting group description:	Participants received multiple SC doses of romosozumab Dose A (low dose).
Reporting group title	Cohort 2: Romosozumab Dose A (5 to < 12 Years of Age)
Reporting group description:	Participants received multiple SC doses of romosozumab Dose A (low dose).
Reporting group title	Cohort 3: Romosozumab Dose B (12 to < 18 Years of Age)
Reporting group description:	Participants received multiple SC doses of romosozumab Dose B (medium dose).
Reporting group title	Cohort 4: Romosozumab Dose B (5 to < 12 Years of Age)
Reporting group description:	Participants received multiple SC doses of romosozumab Dose B (medium dose).
Reporting group title	Cohort 5: Romosozumab Dose C (12 to < 18 Years of Age)
Reporting group description:	Participants received multiple SC doses of romosozumab Dose C (high dose).
Reporting group title	Cohort 6: Romosozumab Dose C (5 to < 12 Years of Age)
Reporting group description:	Participants received multiple SC doses of romosozumab Dose C (high dose).

Primary: Maximum Observed Serum Concentration (Cmax) of Romosozumab

End point title	Maximum Observed Serum Concentration (Cmax) of Romosozumab ^[1]
End point description:	Mean Cmax values following single and multiple SC administrations of romosozumab are presented. Pharmacokinetic (PK) Analysis Set: all participants for whom at least 1 PK parameter or endpoint could be adequately tested.
End point type	Primary
End point timeframe:	Day 1 to Day 169

Notes:

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

Justification: No comparative statistical analysis was planned for this endpoint; summary statistics were provided for the primary endpoint.

End point values	Cohort 1: Romosozumab Dose A (12 to < 18 Years of Age)	Cohort 2: Romosozumab Dose A (5 to < 12 Years of Age)	Cohort 3: Romosozumab Dose B (12 to < 18 Years of Age)	Cohort 4: Romosozumab Dose B (5 to < 12 Years of Age)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	4
Units: µg/mL				
arithmetic mean (standard deviation)				
Single Dose	2.64 (± 1.06)	1.74 (± 0.825)	13.8 (± 6.32)	10.3 (± 1.70)
Multiple Doses	2.43 (± 1.36)	5.55 (± 2.11)	12.8 (± 6.31)	9.14 (± 7.50)

End point values	Cohort 5: Romozosumab Dose C (12 to < 18 Years of Age)	Cohort 6: Romozosumab Dose C (5 to < 12 Years of Age)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: µg/mL				
arithmetic mean (standard deviation)				
Single Dose	25.7 (± 3.02)	21.3 (± 6.45)		
Multiple Doses	22.8 (± 10.5)	19.4 (± 2.14)		

Statistical analyses

No statistical analyses for this end point

Primary: Time to Cmax (tmax) of Romozosumab

End point title	Time to Cmax (tmax) of Romozosumab ^[2]
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End point description:

Median tmax values following single and multiple SC administrations of romozosumab are presented. PK Analysis Set: all participants for whom at least 1 PK parameter or endpoint could be adequately tested.

End point type	Primary
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End point timeframe:

Day 1 to Day 169

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No comparative statistical analysis was planned for this endpoint; summary statistics were provided for the primary endpoint.

End point values	Cohort 1: Romozosumab Dose A (12 to < 18 Years of Age)	Cohort 2: Romozosumab Dose A (5 to < 12 Years of Age)	Cohort 3: Romozosumab Dose B (12 to < 18 Years of Age)	Cohort 4: Romozosumab Dose B (5 to < 12 Years of Age)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	4
Units: day				
median (full range (min-max))				
Single Dose	6.5 (5.9 to 7.9)	7.9 (7.9 to 15)	6.9 (6.9 to 7.0)	6.9 (4.9 to 7.1)
Multiple Doses	7.0 (7.0 to 12)	7.0 (6.9 to 7.0)	7.0 (6.0 to 7.9)	8.0 (6.0 to 11)

End point values	Cohort 5: Romozosumab Dose C (12 to < 18 Years of Age)	Cohort 6: Romozosumab Dose C (5 to < 12 Years of Age)		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: day				
median (full range (min-max))				
Single Dose	7.0 (4.9 to 8.0)	7.5 (6.9 to 8.9)		
Multiple Doses	7.0 (4.0 to 12)	7.5 (6.0 to 8.8)		

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Serum Concentration Time Curve (AUC) During the Dosing Interval (AUCtau) of Romosozumab

End point title	Area Under the Serum Concentration Time Curve (AUC) During the Dosing Interval (AUCtau) of Romosozumab ^[3]
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End point description:

Mean AUCtau values following single and multiple SC administrations of romosozumab are presented. PK Analysis Set: all participants for whom at least 1 PK parameter or endpoint could be adequately tested.

End point type	Primary
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End point timeframe:

Day 1 to Day 85

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: No comparative statistical analysis was planned for this endpoint; summary statistics were provided for the primary endpoint.

End point values	Cohort 1: Romosozumab Dose A (12 to < 18 Years of Age)	Cohort 2: Romosozumab Dose A (5 to < 12 Years of Age)	Cohort 3: Romosozumab Dose B (12 to < 18 Years of Age)	Cohort 4: Romosozumab Dose B (5 to < 12 Years of Age)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	4
Units: day*µg/mL				
arithmetic mean (standard deviation)				
Single Dose	30.9 (± 13.5)	16.9 (± 5.78)	163 (± 89.1)	113 (± 50.3)
Multiple Doses	27.4 (± 15.1)	50.5 (± 20.7)	153 (± 86.7)	95.1 (± 76.1)

End point values	Cohort 5: Romosozumab Dose C (12 to < 18 Years of Age)	Cohort 6: Romosozumab Dose C (5 to < 12 Years of Age)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: day*µg/mL				
arithmetic mean (standard deviation)				
Single Dose	344 (± 106)	234 (± 93.7)		
Multiple Doses	293 (± 134)	203 (± 40.7)		

Statistical analyses

No statistical analyses for this end point

Primary: Accumulation Ratio of Romosozumab

End point title Accumulation Ratio of Romosozumab^[4]

End point description:

The accumulation ratio was calculated as AUCtau after multiple doses/AUCtau Dose 1.
PK Analysis Set: all participants for whom at least 1 PK parameter or endpoint could be adequately tested.

End point type Primary

End point timeframe:

Day 1 to Day 85

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No comparative statistical analysis was planned for this endpoint; summary statistics were provided for the primary endpoint.

End point values	Cohort 1: Romosozumab Dose A (12 to < 18 Years of Age)	Cohort 2: Romosozumab Dose A (5 to < 12 Years of Age)	Cohort 3: Romosozumab Dose B (12 to < 18 Years of Age)	Cohort 4: Romosozumab Dose B (5 to < 12 Years of Age)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	4
Units: ratio				
arithmetic mean (standard deviation)	0.885 (± 0.487)	3.6 (± 2.56)	0.922 (± 0.0673)	0.724 (± 0.392)

End point values	Cohort 5: Romosozumab Dose C (12 to < 18 Years of Age)	Cohort 6: Romosozumab Dose C (5 to < 12 Years of Age)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: ratio				
arithmetic mean (standard deviation)	0.843 (± 0.260)	0.935 (± 0.283)		

Statistical analyses

No statistical analyses for this end point

Primary: Terminal Half-life of Romosozumab

End point title	Terminal Half-life of Romosozumab ^[5]
End point description:	Median terminal half-life values following multiple SC administrations of romosozumab are presented. PK Analysis Set: all participants for whom at least 1 PK parameter or endpoint could be adequately tested. Data is presented for participants with evaluable data. 99999 = data is not available.
End point type	Primary
End point timeframe:	Day 1 to Day 169

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: No comparative statistical analysis was planned for this endpoint; summary statistics were provided for the primary endpoint.

End point values	Cohort 1: Romosozumab Dose A (12 to < 18 Years of Age)	Cohort 2: Romosozumab Dose A (5 to < 12 Years of Age)	Cohort 3: Romosozumab Dose B (12 to < 18 Years of Age)	Cohort 4: Romosozumab Dose B (5 to < 12 Years of Age)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[6]	2	0 ^[7]	1
Units: day				
median (full range (min-max))	(to)	9.41 (7.62 to 11.2)	(to)	7.01 (7.01 to 7.01)

Notes:

[6] - No participants were evaluated in Cohort 1 for this endpoint.

[7] - No participants were evaluated in Cohort 3 for this endpoint.

End point values	Cohort 5: Romosozumab Dose C (12 to < 18 Years of Age)	Cohort 6: Romosozumab Dose C (5 to < 12 Years of Age)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	0 ^[8]		
Units: day				
median (full range (min-max))	6.11 (5.58 to 6.56)	(to)		

Notes:

[8] - No participants were evaluated in Cohort 6 for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Changes from Baseline in Cranial Nerve VII Examination Findings at Day 57, Day 85, and Day 169

End point title	Number of Participants with Changes from Baseline in Cranial Nerve VII Examination Findings at Day 57, Day 85, and Day 169
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End point description:

Facial nerve (cranial nerve VII) function was assessed clinically by facial symmetry inspection at rest, followed by assessment of the symmetry of specific facial movements: raising eyebrows, closing the eyes, blowing out the cheeks, smiling, pursing and closing the lips. Results of the cranial nerve examination were classed as 0 = Normal; 1 = Abnormal not clinically significant; and 2 = Abnormal clinically significant. An increase from baseline indicates an increase in abnormal clinical findings on the

cranial nerve VII examination.

Safety Analysis Set: all participants enrolled in the study who received at least 1 dose of investigational product. Participants with data available at each time point are presented.

End point type	Secondary
End point timeframe:	
Baseline (Day 1), Day 57, Day 85, and Day 169	

End point values	Cohort 1: Romosozumab Dose A (12 to < 18 Years of Age)	Cohort 2: Romosozumab Dose A (5 to < 12 Years of Age)	Cohort 3: Romosozumab Dose B (12 to < 18 Years of Age)	Cohort 4: Romosozumab Dose B (5 to < 12 Years of Age)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	5
Units: participants				
Day 57: Blowing out of cheeks - No change (0)	4	4	4	3
Day 57: Blowing out of cheeks - Undetermined	0	0	0	2
Day 57: Closing eyes - No change (0)	4	4	4	3
Day 57: Closing eyes - Undetermined	0	0	0	2
Day 57: Closing of lips - No change (0)	4	4	4	3
Day 57: Closing of lips - Undetermined	0	0	0	2
Day 57: Pursing of lips - No change (0)	4	4	4	3
Day 57: Pursing of lips - Undetermined	0	0	0	2
Day 57: Raising eyebrows - No change (0)	4	4	4	3
Day 57: Raising eyebrows - Undetermined	0	0	0	2
Day 57: Smiling - No change (0)	4	4	4	3
Day 57: Smiling - Undetermined	0	0	0	2
Day 85: Blowing out of cheeks - No change (0)	4	4	4	4
Day 85: Blowing out of cheeks - Undetermined	0	0	0	1
Day 85: Closing eyes - No change (0)	4	4	4	4
Day 85: Closing eyes - Undetermined	0	0	0	1
Day 85: Closing of lips - No change (0)	4	3	4	4
Day 85: Closing of lips - Increase (to 1)	0	1	0	0
Day 85: Closing of lips - Undetermined	0	0	0	1
Day 85: Pursing of lips - No change (0)	4	4	4	4
Day 85: Pursing of lips - Undetermined	0	0	0	1
Day 85: Raising eyebrows - No change (0)	4	4	4	4
Day 85: Raising eyebrows - Undetermined	0	0	0	1
Day 85: Smiling - No change (0)	4	4	4	4
Day 85: Smiling - Undetermined	0	0	0	1
Day 169: Blowing out of cheeks - No change (0)	4	4	4	4
Day 169: Blowing out of cheeks - Undetermined	0	0	0	1
Day 169: Closing eyes - No change (0)	4	4	4	4
Day 169: Closing eyes - Undetermined	0	0	0	1

Day 169: Closing of lips - No change (0)	4	4	4	4
Day 169: Closing of lips - Undetermined	0	0	0	1
Day 169: Pursing of lips - No change (0)	4	4	4	4
Day 169: Pursing of lips - Undetermined	0	0	0	1
Day 169: Raising eyebrows - No change (0)	4	4	4	4
Day 169: Raising eyebrows - Undetermined	0	0	0	1
Day 169: Smiling - No change (0)	4	4	4	4
Day 169: Smiling - Undetermined	0	0	0	1

End point values	Cohort 5: Romosozumab Dose C (12 to < 18 Years of Age)	Cohort 6: Romosozumab Dose C (5 to < 12 Years of Age)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: participants				
Day 57: Blowing out of cheeks - No change (0)	4	4		
Day 57: Blowing out of cheeks - Undetermined	0	0		
Day 57: Closing eyes - No change (0)	4	4		
Day 57: Closing eyes - Undetermined	0	0		
Day 57: Closing of lips - No change (0)	4	4		
Day 57: Closing of lips - Undetermined	0	0		
Day 57: Pursing of lips - No change (0)	4	4		
Day 57: Pursing of lips - Undetermined	0	0		
Day 57: Raising eyebrows - No change (0)	4	4		
Day 57: Raising eyebrows - Undetermined	0	0		
Day 57: Smiling - No change (0)	4	4		
Day 57: Smiling - Undetermined	0	0		
Day 85: Blowing out of cheeks - No change (0)	4	4		
Day 85: Blowing out of cheeks - Undetermined	0	0		
Day 85: Closing eyes - No change (0)	4	4		
Day 85: Closing eyes - Undetermined	0	0		
Day 85: Closing of lips - No change (0)	4	4		
Day 85: Closing of lips - Increase (to 1)	0	0		
Day 85: Closing of lips - Undetermined	0	0		
Day 85: Pursing of lips - No change (0)	4	4		
Day 85: Pursing of lips - Undetermined	0	0		
Day 85: Raising eyebrows - No change (0)	4	4		
Day 85: Raising eyebrows - Undetermined	0	0		
Day 85: Smiling - No change (0)	4	4		
Day 85: Smiling - Undetermined	0	0		
Day 169: Blowing out of cheeks - No change (0)	4	4		

Day 169: Blowing out of cheeks - Undetermined	0	0		
Day 169: Closing eyes - No change (0)	4	4		
Day 169: Closing eyes - Undetermined	0	0		
Day 169: Closing of lips - No change (0)	4	4		
Day 169: Closing of lips - Undetermined	0	0		
Day 169: Pursing of lips - No change (0)	4	4		
Day 169: Pursing of lips - Undetermined	0	0		
Day 169: Raising eyebrows - No change (0)	4	4		
Day 169: Raising eyebrows - Undetermined	0	0		
Day 169: Smiling - No change (0)	4	4		
Day 169: Smiling - Undetermined	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Participants with Treatment-Emergent Adverse Events (TEAEs)
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End point description:

TEAEs were adverse events (AEs) that started on or after first dose of investigational product up to the end of study (up to Day 169). Any clinically significant changes in vital signs, electrocardiogram parameters, physical exam findings, and clinical laboratory parameters were reported as TEAEs.

Injection site reactions were events of interest (EOI) for this study.

Safety Analysis Set: all participants enrolled in the study who received at least 1 dose of investigational product.

End point type	Secondary
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End point timeframe:

Day 1 to end of study (up to Day 169); median duration on study was 5.55 months

End point values	Cohort 1: Romosozumab Dose A (12 to < 18 Years of Age)	Cohort 2: Romosozumab Dose A (5 to < 12 Years of Age)	Cohort 3: Romosozumab Dose B (12 to < 18 Years of Age)	Cohort 4: Romosozumab Dose B (5 to < 12 Years of Age)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	5
Units: participants				
Any TEAE	1	1	2	4
Any Treatment-emergent EOI	0	0	0	0

End point values	Cohort 5: Romosozumab Dose C (12 to < 18 Years of	Cohort 6: Romosozumab Dose C (5 to < 12 Years of		

	Age)	Age)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: participants				
Any TEAE	1	3		
Any Treatment-emergent EOI	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Anti-romosozumab Antibodies

End point title	Number of Participants with Anti-romosozumab Antibodies
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End point description:

Treatment-boosted anti-romosozumab antibody was defined as binding antibody positive at baseline with a >4 x increase in magnitude post-baseline. Transient results were defined as negative results at the participant's last time point tested within the study period.

Safety Analysis Set: all participants enrolled in the study who received at least 1 dose of investigational product.

Ab - antibody; NAb = neutralizing antibody; +ve = positive; -ve = negative; BL = baseline; tran = transient

End point type	Secondary
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End point timeframe:

Blood samples for anti-romosozumab antibodies were taken Day 1 (baseline), Day 15, Day 29, Day 85, and Day 169

End point values	Cohort 1: Romosozumab Dose A (12 to < 18 Years of Age)	Cohort 2: Romosozumab Dose A (5 to < 12 Years of Age)	Cohort 3: Romosozumab Dose B (12 to < 18 Years of Age)	Cohort 4: Romosozumab Dose B (5 to < 12 Years of Age)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	5
Units: participants				
Binding Ab +ve anytime	0	1	2	0
NAb +ve anytime	0	0	2	0
Binding Ab +ve at/before BL	0	0	0	0
NAb +ve at/before baseline	0	0	0	0
Treatment boosted Ab +ve	0	0	0	0
Binding Ab +ve post-BL with -ve/no results at BL	0	1	2	0
Tran binding Ab +ve post-BL with - ve/no results BL	0	0	0	0
NAb +ve post-BL with -ve/no result at BL	0	0	2	0
Tran NAb +ve post-BL with -ve/no result BL	0	0	0	0

End point values	Cohort 5: Romosozumab Dose C (12 to < 18 Years of Age)	Cohort 6: Romosozumab Dose C (5 to < 12 Years of Age)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: participants				
Binding Ab +ve anytime	1	1		
NAb +ve anytime	1	0		
Binding Ab +ve at/before BL	0	0		
NAb +ve at/before baseline	0	0		
Treatment boosted Ab +ve	0	0		
Binding Ab +ve post-BL with -ve/no results at BL	1	1		
Tran binding Ab +ve post-BL with - ve/no results BL	0	0		
NAb +ve post-BL with -ve/no result at BL	1	0		
Tran NAb +ve post-BL with -ve/no result BL	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline in Serum Concentrations of Serum Type 1 Collagen C-Telopeptide (CTX)

End point title	Percentage Change from Baseline in Serum Concentrations of Serum Type 1 Collagen C-Telopeptide (CTX)
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End point description:

Serum concentrations of the bone turnover marker CTX were determined at pre-specified time points. PD Analysis Set: all participants for whom at least 1 PD parameter or endpoint could be adequately estimated. Participants with data available at each time point are presented.

End point type	Secondary
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End point timeframe:

Blood samples were taken Day 1 (baseline), Day 8, Day 15, Day 29, Day 57, Days 64, 71, 85, 113, and 169

End point values	Cohort 1: Romosozumab Dose A (12 to < 18 Years of Age)	Cohort 2: Romosozumab Dose A (5 to < 12 Years of Age)	Cohort 3: Romosozumab Dose B (12 to < 18 Years of Age)	Cohort 4: Romosozumab Dose B (5 to < 12 Years of Age)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	5
Units: percentage change				
arithmetic mean (standard deviation)				
Day 8 (N=4,3,4,5,4,4)	2.65 (± 27.91)	-19.93 (± 33.97)	8.79 (± 19.21)	-19.38 (± 20.01)
Day 15 (N=3,4,4,4,4,3)	12.26 (± 28.20)	-3.24 (± 41.30)	-2.14 (± 52.91)	-20.24 (± 21.12)

Day 29 (N=4,4,4,4,4)	-4.67 (± 21.35)	-6.67 (± 39.99)	26.00 (± 15.11)	-7.43 (± 18.63)
Day 57 (N=4,4,4,4,4)	1.03 (± 34.14)	-7.34 (± 25.32)	-0.32 (± 32.21)	-7.66 (± 13.16)
Day 64 (N=3,4,4,3,3,2)	-13.37 (± 36.33)	-18.26 (± 49.19)	19.91 (± 43.95)	-10.60 (± 36.12)
Day 71 (N=4,4,4,3,4,4)	18.20 (± 53.85)	-25.30 (± 50.43)	35.26 (± 68.16)	-3.37 (± 8.25)
Day 85 (N=4,4,4,4,4,4)	-10.56 (± 22.18)	-37.50 (± 14.12)	9.95 (± 30.71)	5.08 (± 24.34)
Day 113 (N=4,4,4,4,4,4)	-3.83 (± 22.30)	-30.38 (± 19.59)	25.94 (± 39.76)	6.98 (± 37.98)
Day 169 (N=4,4,4,4,4,4)	-6.15 (± 54.87)	-29.78 (± 31.60)	-1.72 (± 40.42)	11.08 (± 16.19)

End point values	Cohort 5: Romosozumab Dose C (12 to < 18 Years of Age)	Cohort 6: Romosozumab Dose C (5 to < 12 Years of Age)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: percentage change				
arithmetic mean (standard deviation)				
Day 8 (N=4,3,4,5,4,4)	-12.33 (± 12.93)	7.14 (± 29.89)		
Day 15 (N=3,4,4,4,4,3)	-17.22 (± 17.39)	42.62 (± 54.95)		
Day 29 (N=4,4,4,4,4,4)	-16.09 (± 27.05)	3.76 (± 24.72)		
Day 57 (N=4,4,4,4,4,4)	-1.40 (± 38.10)	44.17 (± 95.30)		
Day 64 (N=3,4,4,3,3,2)	10.95 (± 23.38)	-28.14 (± 11.51)		
Day 71 (N=4,4,4,3,4,4)	15.14 (± 51.39)	60.12 (± 106.28)		
Day 85 (N=4,4,4,4,4,4)	0.71 (± 44.55)	15.77 (± 58.40)		
Day 113 (N=4,4,4,4,4,4)	7.03 (± 40.23)	-19.58 (± 10.98)		
Day 169 (N=4,4,4,4,4,4)	-8.07 (± 16.73)	8.08 (± 49.45)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline in Serum Concentrations of Procollagen Type 1 N-terminal Propeptide (P1NP)

End point title	Percentage Change from Baseline in Serum Concentrations of Procollagen Type 1 N-terminal Propeptide (P1NP)
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End point description:

Serum concentrations of the bone turnover marker P1NP were determined at pre-specified time points. PD Analysis Set: all participants for whom at least 1 PD parameter or endpoint could be adequately

estimated. Participants with data available at each time point are presented.

End point type	Secondary
End point timeframe:	
Blood samples were taken Day 1 (baseline), Day 8, Day 15, Day 29, Day 57, Days 64, 71, 85, 113, and 169	

End point values	Cohort 1: Romosozumab Dose A (12 to < 18 Years of Age)	Cohort 2: Romosozumab Dose A (5 to < 12 Years of Age)	Cohort 3: Romosozumab Dose B (12 to < 18 Years of Age)	Cohort 4: Romosozumab Dose B (5 to < 12 Years of Age)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	5
Units: percentage change				
arithmetic mean (standard deviation)				
Day 8 (N=4,3,4,5,4,4)	19.81 (± 20.96)	12.75 (± 13.03)	65.12 (± 17.75)	31.77 (± 11.69)
Day 15 (N=3,4,4,4,4,3)	11.03 (± 13.94)	12.43 (± 13.07)	52.25 (± 29.71)	10.52 (± 14.72)
Day 29 (N=4,4,4,4,4,4)	5.24 (± 12.87)	6.18 (± 18.64)	21.52 (± 25.01)	1.96 (± 9.22)
Day 57 (N=4,4,4,4,4,4)	-2.11 (± 20.26)	-22.37 (± 19.82)	14.57 (± 36.09)	-6.36 (± 17.51)
Day 64 (N=3,4,4,3,3,4)	14.82 (± 28.86)	19.12 (± 40.48)	39.63 (± 31.92)	25.42 (± 16.73)
Day 71 (N=4,4,4,3,4,4)	12.19 (± 21.37)	-5.72 (± 28.50)	49.37 (± 37.99)	16.79 (± 12.29)
Day 85 (N=4,4,4,4,4,4)	-7.34 (± 22.50)	-23.50 (± 13.42)	26.12 (± 48.97)	-0.72 (± 21.29)
Day 113 (N=4,4,4,4,4,4)	-1.13 (± 13.42)	-13.75 (± 19.11)	21.10 (± 40.61)	2.53 (± 42.46)
Day 169 (N=4,4,4,4,4,4)	-6.62 (± 30.96)	-3.13 (± 10.54)	18.10 (± 57.53)	-2.24 (± 23.99)

End point values	Cohort 5: Romosozumab Dose C (12 to < 18 Years of Age)	Cohort 6: Romosozumab Dose C (5 to < 12 Years of Age)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: percentage change				
arithmetic mean (standard deviation)				
Day 8 (N=4,3,4,5,4,4)	35.91 (± 21.89)	35.35 (± 47.08)		
Day 15 (N=3,4,4,4,4,3)	58.58 (± 54.61)	28.35 (± 55.00)		
Day 29 (N=4,4,4,4,4,4)	32.13 (± 59.10)	-11.54 (± 11.35)		
Day 57 (N=4,4,4,4,4,4)	19.07 (± 56.24)	-14.26 (± 12.93)		
Day 64 (N=3,4,4,3,3,4)	77.17 (± 109.07)	17.51 (± 35.74)		

Day 71 (N=4,4,4,3,4,4)	42.16 (± 59.39)	5.12 (± 29.54)		
Day 85 (N=4,4,4,4,4,4)	5.79 (± 23.45)	-11.78 (± 30.09)		
Day 113 (N=4,4,4,4,4,4)	-5.02 (± 21.00)	-26.95 (± 10.23)		
Day 169 (N=4,4,4,4,4,4)	-14.30 (± 19.41)	-21.85 (± 16.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline in Bone Mineral Density (BMD) of the Lumbar Spine

End point title	Percentage Change from Baseline in Bone Mineral Density (BMD) of the Lumbar Spine
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End point description:

BMD was assessed by dual energy X-ray absorptiometry (DXA) scans of the anteroposterior lumbar spine (L1 through L4) and analyzed by a central imaging laboratory. At least 2 lumbar vertebrae from L1 - L4 must be evaluable by DXA.

The BMD Analysis Set: all participants who have a baseline lumbar spine DXA BMD measurement and at least 1 post-baseline lumbar spine DXA BMD measurement. Participants with data available at each time point are presented.

End point type	Secondary
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End point timeframe:

DXA scans were during screening (baseline) and at Day 85 and Day 169

End point values	Cohort 1: Romosozumab Dose A (12 to < 18 Years of Age)	Cohort 2: Romosozumab Dose A (5 to < 12 Years of Age)	Cohort 3: Romosozumab Dose B (12 to < 18 Years of Age)	Cohort 4: Romosozumab Dose B (5 to < 12 Years of Age)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	5
Units: percentage change				
arithmetic mean (standard deviation)				
Day 85 (N=4,4,4,4,4,4)	4.84 (± 3.29)	7.94 (± 5.32)	12.91 (± 2.60)	7.78 (± 9.16)
Day 169 (N=4,4,4,4,4,4)	7.80 (± 2.23)	9.24 (± 7.98)	15.04 (± 4.32)	7.09 (± 7.03)

End point values	Cohort 5: Romosozumab Dose C (12 to < 18 Years of Age)	Cohort 6: Romosozumab Dose C (5 to < 12 Years of Age)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: percentage change				
arithmetic mean (standard deviation)				

Day 85 (N=4,4,4,4,4)	7.88 (± 1.99)	13.07 (± 13.45)		
Day 169 (N=4,4,4,4,4)	7.10 (± 6.58)	12.70 (± 12.86)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline in Bone Mineral Content (BMC) of the Lumbar Spine

End point title	Percentage Change from Baseline in Bone Mineral Content (BMC) of the Lumbar Spine
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End point description:

BMC was assessed by DXA scans of the anteroposterior lumbar spine (L1 through L4) and analyzed by a central imaging laboratory. At least 2 lumbar vertebrae from L1 - L4 must be evaluable by DXA. The BMD Analysis Set: all participants who have a baseline lumbar spine DXA BMD measurement and at least 1 post-baseline lumbar spine DXA BMD measurement. Participants with data available at each time point are presented.

End point type	Secondary
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End point timeframe:

DXA scans were during screening (baseline) and at Day 85 and Day 169

End point values	Cohort 1: Romosozumab Dose A (12 to < 18 Years of Age)	Cohort 2: Romosozumab Dose A (5 to < 12 Years of Age)	Cohort 3: Romosozumab Dose B (12 to < 18 Years of Age)	Cohort 4: Romosozumab Dose B (5 to < 12 Years of Age)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	5
Units: percentage change				
arithmetic mean (standard deviation)				
Day 85 (N=4,4,4,4,4)	7.68 (± 8.10)	10.13 (± 6.05)	18.16 (± 7.86)	8.41 (± 6.90)
Day 169 (N=4,4,4,4,4)	12.64 (± 4.07)	11.40 (± 7.82)	21.29 (± 11.31)	7.98 (± 7.77)

End point values	Cohort 5: Romosozumab Dose C (12 to < 18 Years of Age)	Cohort 6: Romosozumab Dose C (5 to < 12 Years of Age)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: percentage change				
arithmetic mean (standard deviation)				
Day 85 (N=4,4,4,4,4)	14.62 (± 3.39)	16.03 (± 8.32)		
Day 169 (N=4,4,4,4,4)	14.27 (± 5.52)	12.42 (± 10.72)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline in Lumbar Spine Bone Area

End point title	Percentage Change from Baseline in Lumbar Spine Bone Area
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End point description:

Bone area was assessed by DXA scans of the anteroposterior lumbar spine (L1 through L4) and analyzed by a central imaging laboratory. At least 2 lumbar vertebrae from L1 - L4 must be evaluable by DXA. The BMD Analysis Set: all participants who have a baseline lumbar spine DXA BMD measurement and at least 1 post-baseline lumbar spine DXA BMD measurement. Participants with data available at each time point are presented.

End point type	Secondary
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End point timeframe:

DXA scans were during screening (baseline) and at Day 85 and Day 169

End point values	Cohort 1: Romosozumab Dose A (12 to < 18 Years of Age)	Cohort 2: Romosozumab Dose A (5 to < 12 Years of Age)	Cohort 3: Romosozumab Dose B (12 to < 18 Years of Age)	Cohort 4: Romosozumab Dose B (5 to < 12 Years of Age)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	5
Units: percentage change				
arithmetic mean (standard deviation)				
Day 85 (N=4,4,4,4,4,4)	2.72 (± 6.99)	2.03 (± 1.62)	4.60 (± 5.00)	0.80 (± 4.62)
Day 169 (N=4,4,4,4,4,4)	4.53 (± 4.92)	1.92 (± 0.66)	5.30 (± 6.06)	0.82 (± 1.95)

End point values	Cohort 5: Romosozumab Dose C (12 to < 18 Years of Age)	Cohort 6: Romosozumab Dose C (5 to < 12 Years of Age)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: percentage change				
arithmetic mean (standard deviation)				
Day 85 (N=4,4,4,4,4,4)	6.23 (± 2.15)	3.44 (± 11.05)		
Day 169 (N=4,4,4,4,4,4)	6.87 (± 5.14)	-0.09 (± 4.27)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Lumbar Spine BMD Z-Score

End point title | Mean Change from Baseline in Lumbar Spine BMD Z-Score

End point description:

Lumbar spine BMD was assessed by DXA scans. The results were then converted to Z-scores. The Z-score indicated the number of standard deviations away from the reference population and a score of 0 is equal to the mean. Positive changes from baseline indicated an improvement in lumbar spine BMD. The BMD Analysis Set: all participants who have a baseline lumbar spine DXA BMD measurement and at least 1 post-baseline lumbar spine DXA BMD measurement. Participants with data available at each time point are presented.

End point type | Secondary

End point timeframe:

DXA scans were during screening (baseline) and at Day 85 and Day 169

End point values	Cohort 1: Romosozumab Dose A (12 to < 18 Years of Age)	Cohort 2: Romosozumab Dose A (5 to < 12 Years of Age)	Cohort 3: Romosozumab Dose B (12 to < 18 Years of Age)	Cohort 4: Romosozumab Dose B (5 to < 12 Years of Age)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	5
Units: Z-score				
arithmetic mean (standard deviation)				
Day 85 (N=4,3,4,4,4,4)	0.20 (± 0.39)	0.45 (± 0.37)	0.50 (± 0.12)	0.33 (± 0.53)
Day 169 (N=4,4,4,4,4,4)	0.33 (± 0.46)	0.48 (± 0.51)	0.48 (± 0.21)	0.25 (± 0.39)

End point values	Cohort 5: Romosozumab Dose C (12 to < 18 Years of Age)	Cohort 6: Romosozumab Dose C (5 to < 12 Years of Age)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: Z-score				
arithmetic mean (standard deviation)				
Day 85 (N=4,3,4,4,4,4)	0.33 (± 0.26)	0.53 (± 0.79)		
Day 169 (N=4,4,4,4,4,4)	0.23 (± 0.56)	0.50 (± 0.62)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study drug to the end of study visit (up to Day 169); median duration of treatment was 5.55 months.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Cohort 1: Romosozumab Dose A (12 to < 18 Years of Age)
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Reporting group description:

Participants received multiple SC doses of romosozumab Dose A (low dose).

Reporting group title	Cohort 2: Romosozumab Dose A (5 to < 12 Years of Age)
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Reporting group description:

Participants received multiple SC doses of romosozumab Dose A (low dose).

Reporting group title	Cohort 3: Romosozumab Dose B (12 to < 18 Years of Age)
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Reporting group description:

Participants received multiple SC doses of romosozumab Dose B (medium dose).

Reporting group title	Cohort 4: Romosozumab Dose B (5 to < 12 Years of Age)
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Reporting group description:

Participants received multiple SC doses of romosozumab Dose B (medium dose).

Reporting group title	Cohort 5: Romosozumab Dose C (12 to < 18 Years of Age)
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Reporting group description:

Participants received multiple SC doses of romosozumab Dose C (high dose).

Reporting group title	Cohort 6: Romosozumab Dose C (5 to < 12 Years of Age)
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Reporting group description:

Participants received multiple SC doses of romosozumab Dose C (high dose).

Serious adverse events	Cohort 1: Romosozumab Dose A (12 to < 18 Years of Age)	Cohort 2: Romosozumab Dose A (5 to < 12 Years of Age)	Cohort 3: Romosozumab Dose B (12 to < 18 Years of Age)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (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
Femur fracture			

subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (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	Cohort 4: Romosozumab Dose B (5 to < 12 Years of Age)	Cohort 5: Romosozumab Dose C (12 to < 18 Years of Age)	Cohort 6: Romosozumab Dose C (5 to < 12 Years of Age)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Femur fracture			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 4 (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

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

Non-serious adverse events	Cohort 1: Romosozumab Dose A (12 to < 18 Years of Age)	Cohort 2: Romosozumab Dose A (5 to < 12 Years of Age)	Cohort 3: Romosozumab Dose B (12 to < 18 Years of Age)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	2 / 4 (50.00%)
Investigations			
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Ankle fracture			

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Femur fracture subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Tooth fracture subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Neck injury subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
General disorders and administration site conditions Injection site swelling subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Injection site erythema subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Injection site pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Eye disorders Ocular hyperaemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0

Constipation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Abnormal faeces			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Haematochezia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Catarrh			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Increased upper airway secretion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Muscle contracture			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Muscle swelling			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
COVID-19			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 4: Romosozumab Dose B (5 to < 12 Years of Age)	Cohort 5: Romosozumab Dose C (12 to < 18 Years of Age)	Cohort 6: Romosozumab Dose C (5 to < 12 Years of Age)
Total subjects affected by non-serious			

adverse events			
subjects affected / exposed	4 / 5 (80.00%)	1 / 4 (25.00%)	3 / 4 (75.00%)
Investigations			
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Ankle fracture			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Femur fracture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Tooth fracture			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Neck injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	3
General disorders and administration site conditions			
Injection site swelling			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Injection site erythema			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	2
Injection site pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Pyrexia			

subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1
Eye disorders Ocular hyperaemia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Constipation subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Abnormal faeces subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Toothache subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0
Haematochezia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 2	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Abdominal pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1
Respiratory, thoracic and mediastinal disorders Catarrh subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 3	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Increased upper airway secretion subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Cough subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 4 (0.00%) 0	2 / 4 (50.00%) 4
Skin and subcutaneous tissue disorders			

Pruritus subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1
Rash maculo-papular subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 3	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1
Back pain subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Muscle contracture subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Muscle swelling subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	0 / 4 (0.00%) 0	2 / 4 (50.00%) 3
Infections and infestations Upper respiratory tract infection			

subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	2
Nasopharyngitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	3
COVID-19			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 April 2020	<ul style="list-style-type: none">- The placebo group was removed from the study.- Increased number of participants with active treatment from 3 to 4 for better understanding of PK variability at each dose level.- Hip DXA was removed.- BMD, BMC, and bone area were added as DXA parameters in the secondary endpoints.- ECG assessment was added on Day 29.- Serum PK collection was added to Day 169 and removed from Day 61. Anti-drug antibody collection was added to Day 15.- Pregnancy testing at screening was to be done using serum samples, but all other pregnancy assessments remained unchanged using urine samples.- Exclusion criteria were updated to exclude participants with body weight < 10 kg and > 90 kg; to add conditions associated with increased risk of cardiovascular disease; to clarify that removal of baby teeth was not considered an invasive dental procedure; to exclude participants within 12 months of prior denosumab used.- Common Terminology Criteria for Adverse Events grading scale was replaced with the Amgen Standard Grading Scale as it was more appropriate for the study design and population.- Tanner staging was removed. A history of menarche was to be solely used to determine whether female participants would undergo pregnancy testing.- Adjudication of atypical femoral fractures and potential cardiovascular events was removed.- Disease-related events were removed from the protocol to align with Amgen's current processes for reporting adverse events. The anticipated serious adverse event definition was removed because all serious adverse events were to be reported to health authorities in an expedited manner.
26 May 2020	<ul style="list-style-type: none">- Updated participant screening number assignment to using interactive response technology.
19 February 2021	<ul style="list-style-type: none">- Updated Schedule of Assessments table and protocol to include visits 2 hours post-dose and removed Day 61 visit; updated to include information about home care services and assessments that could be performed at home; and updated alcohol and drug testing and ECG, telephonic safety assessments at screening visits.- Updated study design to include the participant monitoring details for 2 hours after the first and subsequent dosing of romosozumab.- Pediatric risk assessment language was updated to include risk of valvular heart disease and safety monitoring to include neurological assessments; and to add details of potential COVID-19 risks.- Study rationale was updated to include details of romosozumab PK model for children.- Exclusion criteria were updated to include clinically significant valvular heart disease.- Added details regarding drug substances of abuse along with alcohol and tobacco restrictions.- Updated the contraceptive requirements to include progesterone-only hormonal contraception language and removed two-barrier methods.- Updated the text to include adverse event reporting after signing the informed consent form through to end of study.- Removed language for the worldwide reporting regulations for all adverse events unblinding from reporting procedures for serious adverse events.- Included the BMD analysis set.- Remove 'by treatment group' for statistical considerations.

28 February 2023

- Corrected text regarding laboratory assessments to be completed by the central laboratory as the Schedule of Assessments erroneously listed them to be completed by the local laboratory.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported