14 December 2023
EMA/39377/2024
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Evenity

Romosozumab

Procedure no: EMEA/H/C/004465/P46/007

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	16 Oct 2023	16 Oct 2023	☐
☐	CHMP Rapporteur Assessment Report	20 Nov 2023	16 Nov 2023	☐
☐	CHMP members comments	04 Dec 2023	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	07 Dec 2023	n/a	☐
☒	CHMP adoption of conclusions	14 Dec 2023	14 Dec 2023	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

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1. Introduction

On 27 September 2023, the MAH submitted a completed Clinical Study Report (CSR) for Evenity, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Briefly, this is a CSR for an Open-label, ascending multiple-dose study to evaluate safety, tolerability, pharmacokinetics, and pharmacodynamics of Romosozumab in children and adolescents with Osteogenesis Imperfecta as part of a clinical development program for new indication of Evenity in children (in addition to indication for the treatment of osteoporosis in postmenopausal women).

2. Scientific discussion

2.1. Information on the development program

Romosozumab is a humanized monoclonal antibody immunoglobulin 2 that binds and inhibits sclerostin and has a dual effect on bone of increasing bone formation and decreasing bone resorption. Romosozumab is indicated for the treatment of osteoporosis in postmenopausal women at high risk of fracture in the United States (US EVENITY® Prescribing Information), and for severe osteoporosis in postmenopausal women at high risk for fracture in the European Union (EU EVENITY Summary of Product Characteristics).

The medical management of pediatric OI includes the orthopedic prevention and treatment of fractures, bowing, and scoliosis.

There are no approved medicinal products for the treatment of OI in children except for neridronate and pamidronate, approved for the treatment of OI in Italy and Japan, respectively. Clinicians have been using bisphosphonates in children with moderate to severe OI to reduce osteoclast activity and increase bone mineral density (BMD) (even though abnormal collagen is usually present [Byers, 2000]) with the aim of reducing fractures (Ward et al, 2016; Rauch and Glorieux, 2004). Teriparatide, an osteoanabolic agent, has been shown to increase bone mass and strength in adults with OI, though its benefit in children is not known (Orwoll et al, 2014). Thus, an unmet need remains in children with OI.

The romosozumab pediatric OI program consists of Studies 20160227 and 20200105.

Study 20160227 was a phase 1b, multicenter, open label, ascending multiple-dose study to evaluate romosozumab in ambulatory children (5 to <12 years of age) and adolescents (12 to <18 years of age) with OI.

Study 20200105 is a phase 3, open label, multicenter, randomized study to evaluate the efficacy and safety of romosozumab in children (5 to <12 years of age) and adolescents (12 to <18 years of age) with OI and is scheduled to start enrolling in September 2023. A separate safety follow-up study is planned after the completion of Study 20200105. Subsequently, The MAH states in the application that "An Open-label, Ascending Multiple-dose Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Romosozumab in Children and Adolescents with Osteogenesis Imperfecta" with Study number 20160227 is part of a clinical development programme.

Subsequently, this present CSR evaluates PK, PD and Safety in the first phase 1b study 20160227.

2.2. Information on the pharmaceutical formulation used in the studies

The investigational product for this study was romosozumab. Romosozumab was provided in a 3 cc sterile vial filled with 1 mL deliverable volume of 90 mg/mL romosozumab. Doses for this study were

split into multiple syringes and capped at 1.5 mL per injection. Subjects received romosozumab via SC injection on days 1, 29, and 57.

The approved dose for the treatment of postmenopausal osteoporosis is 210 mg SC QM for 12 monthly doses. However, in Studies 20060220 and 20060221, subjects were administered higher doses or higher total exposures, supporting the exploration of the SC dose cohort if insufficient PK or PD responses were observed in the dose cohorts.

2.3. Clinical aspects

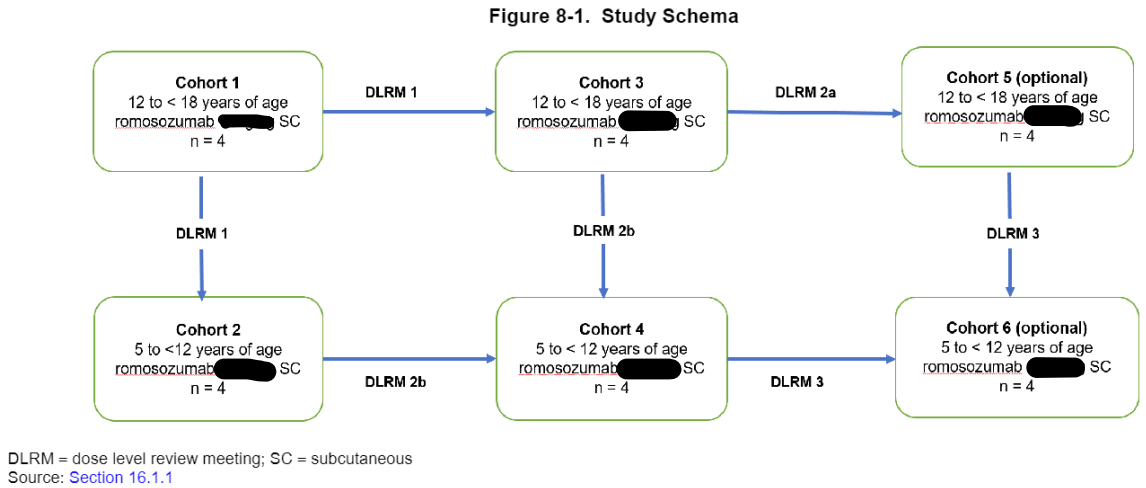
2.3.1. "Study 20160227 "An Open-label, Ascending Multiple-dose Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Romosozumab in Children and Adolescents with Osteogenesis Imperfecta Clinical study"

2.3.2. Description

Study 20160227 was a phase 1b, multicenter, open label, ascending multiple-dose study to evaluate romosozumab in ambulatory children (5 to <12 years of age) and adolescents (12 to <18 years of age) with OI.

The estimated study duration for each subject was approximately 7 months. This included a 35-day screening period before the first dose of investigational product and an on-study period of approximately 169 days. At the end of the initial 3-month treatment period, all subjects were followed and monitored for safety for an additional 3 months.

Fig. 1 Study design



DLRM = dose level review meeting; SC = subcutaneous
Source: Section 16.1.1

2.4. Methods

2.4.1. Study participants

Patients eligible for enrolment in the study were required to meet all the following criteria:

1) male or female children 5 to < 18 years of age
2) clinical diagnosis of OI defined as a clinical history consistent with type I to IV OI as determined by presence of expected phenotype (eg, facial shape, voice, blue sclera, dentinogenesis imperfecta, typical radiographic features, fracture pattern) and lack of additional features unrelated to type I to IV OI (eg, blindness, mental retardation, neuropathy, craniosynostosis, premature exfoliation of deciduous teeth) were enrolled.
3) Written informed consent from subject or legally acceptable representative (an individual or other body authorized under applicable law to consent on behalf of the subject)

Of 31 subjects screened, 25 subjects were enrolled in the study and received investigational product.

Of 25 subjects enrolled in the study, 24 (96.0%) completed treatment with investigational product. One subject (4.0%) discontinued treatment with investigational product because of withdrawal of consent and was also discontinued from the study.

The first subject was enrolled in the study on 21 January 2021 and last subject completed the study on 30 March 2023.

2.4.2. Treatments

Patients were categorized in two groups: ambulatory children (5 to < 12 years of age) and adolescents (12 to < 18 years of age) with OI. All subjects were to receive 3 SC doses of romosozumab QM.

Administered doses if romosozumab in cohorts are presented below:

Cohort 1, 3, 5 were 12 to <18 years of age:

- Cohort 1 romosozumab SC QM)
- Cohort 3 romosozumab SC QM
- Cohort 5: romosozumab SC QM)

Cohort 2, 4, 6 were 5 to <12 years of age:

- Cohort 2 romosozumab SC QM)
- Cohort 4 romosozumab SC QM
- Cohort 6 romosozumab SC QM

All subjects received daily supplementation with calcium and vitamin D. A dose level review meeting was held to review safety data for the purposes of making recommendations before escalation to the next higher dose or expansion to a younger age cohort. At the end of the initial 3-month treatment period, all subjects were followed and monitored for safety for an additional 3 months.

2.4.3. Objective(s)

The objective of this study was to evaluate pharmacokinetics (PK), pharmacodynamics (PD), and safety of romosozumab at, administered subcutaneously (SC) every 4 weeks (QM) to support the design of the planned phase 3 efficacy and safety study in pediatric subjects with osteogenesis imperfecta (OI).

2.4.4. Outcomes/endpoints

The primary endpoint in Study 20160227 was PK.

The secondary efficacy endpoints were:

- Bone turnover markers including procollagen type I N-terminal propeptide (P1NP) and serum type I collagen C-telopeptide (sCTX) measurements.
- Lumbar spine BMD, bone mineral content (BMC), bone area, and BMD Z-score as assessed by dual energy X-ray absorptiometry (DXA).

2.4.5. Sample size

This was a descriptive study. A descriptive approach was used and no formal hypothesis was planned for this study. Twenty-five subjects received investigational product. Twenty-four subjects completed investigational product. One subject discontinued investigational product because of withdrawn consent.

2.4.6. Randomisation and blinding (masking)

Not applicable in this open-label single arm study.

2.4.7. Statistical Methods

The PK parameters were estimated using non-compartmental methods. Actual dosing and sampling times were used for calculation of PK parameters. Summary statistics were generated for each PK parameter for each dose cohort. The PK analysis set was used for these analyses.

Actual value and percentage change from baseline in BMD, BMC, and bone area at the anteroposterior lumbar spine were descriptively summarized at each visit for each dose cohort. Graphs showing summary statistics (actual value and change from baseline) of BMD Z-score, and percentage change from baseline of BMD at lumbar spine over time by visit for age groups were provided. The BMD analysis set was used to for these analyses. BMD analysis set included subjects in the Full Analysis Set who had a baseline lumbar spine DXA BMD measurement and at least 1 postbaseline lumbar spine DXA BMD measurement.

The study statistical analysis plan provides detailed descriptions of the statistical methodology.

2.5. Results

2.5.1. Participant flow

Subject disposition with discontinuation reason is presented in Figure below.

Table 9-1. Subject Disposition With Discontinuation Reason (Full Analysis Set) (20160227 Final Analysis)

	Romosozumab [redacted] SC 12 - < 18 years of Age (N = 4) n (%)	Romosozumab [redacted] SC 5 - < 12 years of Age (N = 4) n (%)	Romosozumab [redacted] SC 12 - < 18 years of Age (N = 4) n (%)	Romosozumab [redacted] SC 5 - < 12 years of Age (N = 5) n (%)	Romosozumab [redacted] SC 12 - < 18 years of Age (N = 4) n (%)	Romosozumab [redacted] SC 5 - < 12 years of Age (N = 4) n (%)	Overall (N = 25) n (%)
Investigational product accounting							
Subjects who never received investigational product	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects who received investigational product	4 (100.0)	4 (100.0)	4 (100.0)	5 (100.0)	4 (100.0)	4 (100.0)	25 (100.0)
Subjects who completed investigational product	4 (100.0)	4 (100.0)	4 (100.0)	4 (80.0)	4 (100.0)	4 (100.0)	24 (96.0)
Subjects who discontinued investigational product	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (4.0)
Subject request	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (4.0)
Study completion accounting							
Subjects who completed study	4 (100.0)	4 (100.0)	4 (100.0)	4 (80.0)	4 (100.0)	4 (100.0)	24 (96.0)
Subjects who discontinued study	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (4.0)
Withdrawal of consent from study	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (4.0)

SC = subcutaneous
Number of subjects screened: 31.
First subject enrolled: 21 January 2021
Last subject completed study: 30 March 2023
Source: Modified from Table 14-1.1

2.5.2. Recruitment

The first subject was enrolled in the study on 21 January 2021 and last subject completed the study on 30 March 2023.

2.5.3. Baseline data

Baseline Demographics are presented in Table 2 below. The summary of baseline values of selected laboratory analytes and bone turnover markers is provided in Table 3.

Table 2. Baseline demographics in Study Sample.

	Romosozumab [redacted] SC 12 - < 18 years of Age (N = 4)	Romosozumab [redacted] SC 5 - < 12 years of Age (N = 4)	Romosozumab [redacted] SC 12 - < 18 years of Age (N = 4)	Romosozumab [redacted] SC 5 - < 12 years of Age (N = 5)	Romosozumab [redacted] SC 12 - < 18 years of Age (N = 4)	Romosozumab [redacted] SC 5 - < 12 years of Age (N = 4)	Overall (N = 25)
Sex–- n (%)							
Male	3 (75.0)	4 (100.0)	3 (75.0)	1 (20.0)	2 (50.0)	3 (75.0)	16 (64.0)
Female	1 (25.0)	0 (0.0)	1 (25.0)	4 (80.0)	2 (50.0)	1 (25.0)	9 (36.0)
Ethnicity–- n (%)							
Hispanic/Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic/Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race–- n (%)							
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (years)							
n	4	4	4	5	4	4	25
Mean	14.3	6.0	14.3	8.4	14.0	6.5	10.5
SD	1.9	1.4	0.5	2.4	1.8	0.6	4.0
Median	13.5	5.5	14.0	9.0	14.0	6.5	11.0
Q1, Q3	13.0, 15.5	5.0, 7.0	14.0, 14.5	7.0, 10.0	12.5, 15.5	6.0, 7.0	7.0, 14.0
Min, Max	13, 17	5, 8	14, 15	5, 11	12, 16	6, 7	5, 17
Geographic region–- n (%)							
Central and Eastern Europe	4 (100.0)	4 (100.0)	2 (50.0)	3 (60.0)	2 (50.0)	2 (50.0)	17 (68.0)
Western Europe	0 (0.0)	0 (0.0)	2 (50.0)	2 (40.0)	2 (50.0)	2 (50.0)	8 (32.0)
Height (cm)							
n	4	4	4	5	4	4	25
Mean	159.8	111.2	166.1	119.3	135.9	103.5	132.1
SD	13.7	9.9	12.1	24.6	24.6	13.1	28.6
Median	156.0	111.8	169.3	113.0	144.0	107.1	140.0
Q1, Q3	150.5, 169.1	103.8, 118.7	157.9, 174.3	98.0, 140.0	120.5, 151.3	94.5, 112.4	108.5, 153.0
Min, Max	148, 179	99, 122	149, 177	96, 150	100, 156	85, 115	85, 179
Weight (kg)							
n	4	4	4	5	4	4	25
Mean	55.9	19.5	66.0	26.7	43.6	16.9	37.6
SD	22.9	5.5	4.8	15.0	11.7	4.5	21.8
Median	48.8	18.8	68.0	18.8	45.6	17.2	38.0
Q1, Q3	39.8, 72.1	15.5, 23.4	63.0, 69.0	17.0, 42.7	34.1, 53.0	13.3, 20.4	18.8, 54.0
Min, Max	38, 88	14, 27	59, 69	12, 43	29, 54	11, 22	11, 88
Body mass index (kg/m^2)							
n	4	4	4	5	4	4	25
Mean	21.2	15.6	24.1	17.4	23.8	15.5	19.5
SD	4.8	3.1	2.0	4.0	3.9	1.0	4.7
Median	20.5	14.3	23.8	19.0	23.2	15.8	19.6
Q1, Q3	17.6, 24.8	13.6, 17.5	22.4, 25.7	13.3, 19.6	21.0, 26.5	14.9, 16.1	15.8, 22.3
Min, Max	16, 27	13, 20	22, 27	13, 22	20, 29	14, 16	13, 29

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SC = subcutaneous
Percentages based on number of subjects in full analysis set.
Source: Modified from Table 14-2.1

Table 3. Summary of baseline values of selected laboratory analytes and bone turnover markers in study sample.

	Romosozumab [redacted] SC 12 - < 18 years of Age (N = 4)	Romosozumab [redacted] SC 5 - < 12 years of Age (N = 4)	Romosozumab [redacted] SC 12 - < 18 years of Age (N = 4)	Romosozumab [redacted] SC 5 - < 12 years of Age (N = 5)	Romosozumab [redacted] SC 12 - < 18 years of Age (N = 4)	Romosozumab [redacted] SC 5 - < 12 years of Age (N = 4)	Overall (N = 25)
Type of OI n (%)							
I	3 (75.0)	3 (75.0)	3 (75.0)	1 (20.0)	2 (50.0)	2 (50.0)	14 (56.0)
II	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
III	0 (0.0)	1 (25.0)	1 (25.0)	4 (80.0)	2 (50.0)	2 (50.0)	10 (40.0)
IV	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.0)
Fracture history[a] n (%)							
Yes	4 (100.0)	4 (100.0)	4 (100.0)	5 (100.0)	4 (100.0)	4 (100.0)	25 (100.0)
Nonvertebral	2 (50.0)	4 (100.0)	4 (100.0)	5 (100.0)	4 (100.0)	3 (75.0)	22 (88.0)
No	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Prior osteoporosis medication use n (%)							
Yes	3 (75.0)	0 (0.0)	1 (25.0)	4 (80.0)	2 (50.0)	2 (50.0)	12 (48.0)
No	1 (25.0)	4 (100.0)	3 (75.0)	1 (20.0)	2 (50.0)	2 (50.0)	13 (52.0)
Lumbar spine BMD (g/cm^2)							
n	4	4	4	5	4	4	25
Mean	0.69	0.35	0.60	0.49	0.74	0.35	0.54
SD	0.24	0.04	0.09	0.07	0.28	0.10	0.21
Median	0.65	0.34	0.59	0.51	0.68	0.37	0.51
Q1, Q3	0.51, 0.87	0.33, 0.38	0.54, 0.67	0.48, 0.53	0.57, 0.91	0.28, 0.43	0.41, 0.61
Min, Max	0.5, 1.0	0.3, 0.4	0.5, 0.7	0.4, 0.6	0.5, 1.1	0.2, 0.4	0.2, 1.1
Lumbar spine BMC (g)							
n	4	4	4	5	4	4	25
Mean	31.46	10.92	25.97	14.80	28.73	8.71	19.89
SD	14.98	1.66	4.30	7.22	13.94	1.71	12.05
Median	31.21	10.75	25.14	14.32	26.05	8.71	15.97
Q1, Q3	18.88, 44.05	9.83, 12.02	22.88, 29.07	8.23, 17.87	20.14, 37.32	7.64, 9.77	10.57, 25.51
Min, Max	16.0, 47.5	9.1, 13.1	21.8, 31.8	8.2, 25.4	14.8, 48.1	6.6, 10.8	6.6, 48.1
Lumbar spine area (cm^2)							
n	4	4	4	5	4	4	25
Mean	44.59	30.85	43.07	29.36	37.69	25.72	34.98
SD	10.96	2.97	0.65	11.88	4.64	6.46	9.94
Median	47.48	32.13	43.20	28.22	38.57	24.87	32.71
Q1, Q3	38.20, 50.98	29.08, 32.62	42.60, 43.53	21.46, 31.91	34.90, 40.49	20.36, 31.08	28.85, 43.02
Min, Max	28.9, 54.5	26.4, 32.7	42.2, 43.7	17.2, 48.0	31.3, 42.4	19.8, 33.3	17.2, 54.5
Lumbar spine BMD Z-score							
n	4	4	4	5	4	4	25
Mean	-2.43	-3.08	-2.95	-1.90	-1.65	-3.60	-2.57
SD	2.89	0.99	0.83	0.93	1.03	1.78	1.55
Median	-1.60	-3.35	-3.10	-1.80	-1.65	-3.35	-2.70
Q1, Q3	-4.55, -0.30	-3.80, -2.35	-3.45, -2.45	-2.00, -1.30	-2.35, -0.95	-4.75, -2.45	-3.40, -1.70
Min, Max	-6.4, -0.1	-3.9, -1.7	-3.8, -1.8	-3.4, -1.0	-2.9, -0.4	-6.0, -1.7	-6.4, -0.1

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BMC = bone mineral content; BMD = bone mineral density; OI = osteogenesis imperfecta; SC = subcutaneous
Percentages based on number of subjects in full analysis set.
[a]Included all fractures reported on the electronic case report form.
Source: Modified from Table 14-2.2

CHMP comment:

Most of the subjects had type I OI (14 subjects; 56.0%) or type III OI (10 subjects; 40.0%). All 25 subjects enrolled in the study had history of fractures of whom 22 (88.0%) had nonvertebral fractures. Twelve of 25 subjects (48.0%) had received prior osteoporosis medications. The mean (SD) lumbar spine BMD was 0.54 (0.21) g/cm^2. The mean (SD) lumbar spine BMC was 19.89 (12.05) g and lumbar spine area was 34.98 (9.94) cm^2. The mean (SD) lumbar spine BMD Z-score was - 2.57 (1.55).

2.5.4. Number analysed.

Twenty-five subjects were enrolled in the study. Of these, 25 were included in safety population (defined as all patients who received at least one dose of the investigational product).

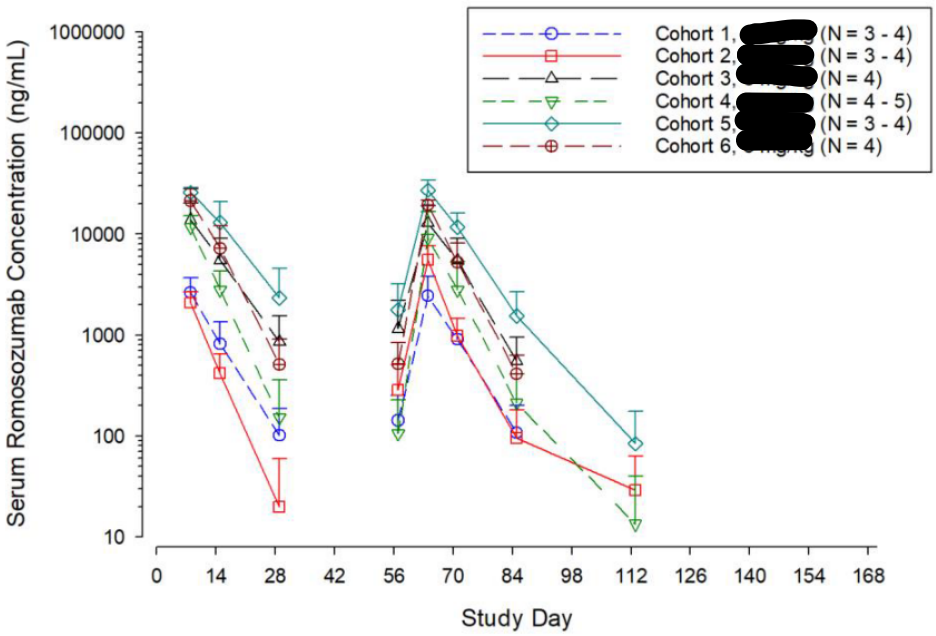
3. Clinical pharmacology results

3.1. Pharmacokinetics

Study 20160227 evaluated the PK of romosozumab. The PK analysis dataset was composed of 239 serum romosozumab samples from 25 subjects across 6 cohorts.

Observed mean serum concentration-time profiles per cohort are displayed in the figure below.

Figure 11-1. Mean (+SD) Serum Concentration-time Profiles After Multiple Subcutaneous Administrations of [redacted]Romosozumab to Children and Adolescents With Osteogenesis Imperfecta



In subjects 12 to <18 years of age, median time to maximum observed concentration (tmax) ranged from 6.5 to 7.0 days after the first dose and was 7.0 days after the third dose, across all dose groups. Mean maximum observed concentration (Cmax) increased with increasing dose, with a 5.2-fold change from (3-fold change in dose) and a 1.9-fold change from (1.6-fold change in dose) after the first dose.

Mean Cmax for the third dose increased with a 5.3-fold change from and a 1.8-fold change from. Mean area under the curve during the dosing interval, 0 to about 28 days (AUCtau) similarly increased with increasing dose, with a 5.3-fold change from and a 2.1-fold change from after the first dose. Mean AUCtau for the third dose increased with a 5.6-fold change from and a 1.9-fold change from. In cohorts 1, 3, and 5, mean AUCtau were calculated to 27.4, 153, and 293 day*µg/mL, respectively.

In subjects 5 to < 12 years of age, median tmax ranged from 6.9 to 7.9 days after the first dose and 6.0 to 8.0 days after the third dose, across all dose groups. Mean Cmax increased with increasing dose, with a 5.9-fold change from and a 2.1-fold change from after the first dose. Mean Cmax for the third dose increased with a 1.6-fold change from and a 2.1-fold change from. Mean AUCtau increased with increasing dose, with a 6.7-fold change from 1 to and a 2.1-fold change from after the first dose, respectively. Mean AUCtau for the third dose increased with a 1.9-fold change from and a 2.1-fold change from after the third dose. In cohorts 2, 4, and 6, mean AUCtau were calculated to 50.5, 95.1 and 203 day*µg/mL, respectively.

CHMP comment:

Descriptive statistics for PK parameters per cohort (age and dose dependent) have been provided. Due to the limited sample size per cohort, dose or age differences should be interpreted with caution. Nonetheless, there seem to be a slight trend that the AUCtau, per dose group, are lower in patients 5 to < 12 years compared to patients 12 to <18 years of age. For reference, none of the reported mean AUCtau exceed the reported adult AUC of 633 day*µg/mL [https://www.ema.europa.eu/en/documents/assessment-report/evenity-epar-public-assessment-report_en.pdf].

3.2. Immunogenicity

In Study 20160227, all 25 subjects were tested for the presence of antiromosozumab antibodies during the study. Of the 25 subjects with baseline results, no subjects had pre-existing antiromosozumab antibodies at baseline. Of the 25 subjects with postbaseline results, 5 subjects developed antibodies after administration of romosozumab, 3 of which were characterized as neutralizing. One of these subjects reported injection site erythema and injection site pain however, these adverse events occurred prior to the occurrence of antiromosozumab antibodies. No adverse events related to lack of efficacy or hypersensitivity were reported in any of these subjects.

CHMP comment:

The development of antibodies in 5 out of 25 patients (20%) is similar to the reported antibody incidence in adults (19.1% after multiple dosing) [https://www.ema.europa.eu/en/documents/assessment-report/evenity-epar-public-assessment-report_en.pdf].

4. Efficacy results

4.1. Primary endpoints

This study did not include primary clinical efficacy endpoints.

4.2. Secondary Efficacy Endpoints

. Markers of mechanistic effect were evaluated;

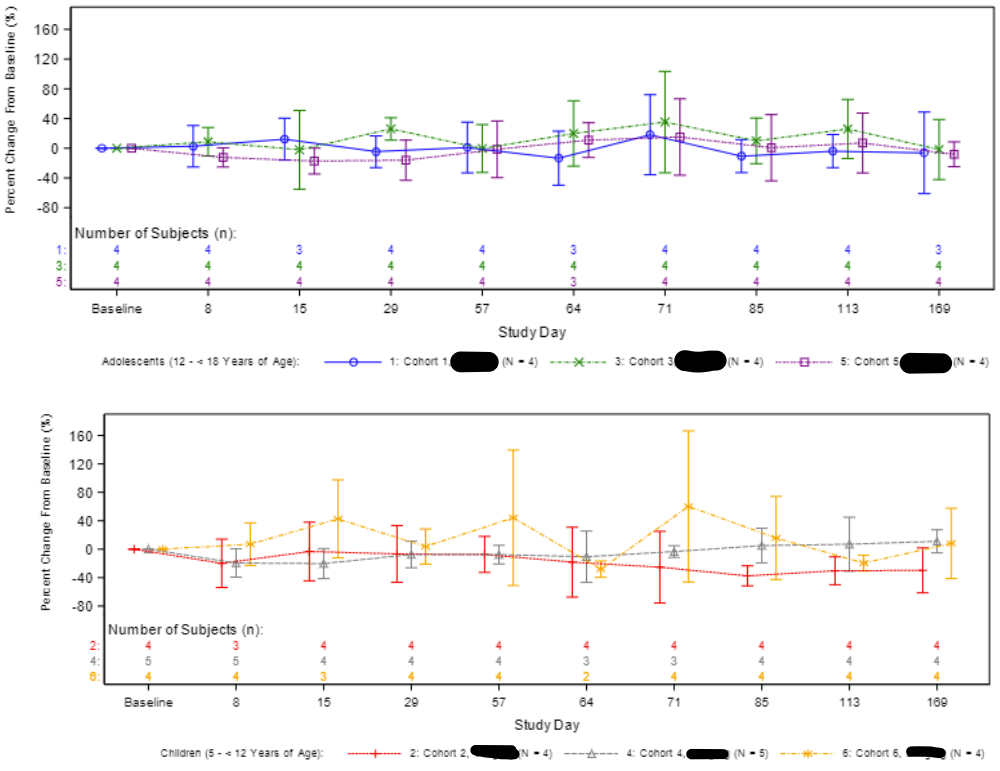
1) Bone Turnover Markers; Serum Type 1 Collagen C-telopeptide (sCTX), Procollagen Type I N-terminal Propeptide (P1NP),
2) Lumbar Spine Bone Mineral Density (BMD),
3) Lumbar Spine Bone Mineral Content (Lumbar Spine BMC),
4) Lumbar Spine Bone Area

4.3. Bone Turnover Markers

4.4. Serum Type 1 Collagen C-telopeptide

No clear dose response in sCTX levels was observed in adolescents and children. Due to the small sample size and variability between subjects, no firm conclusions could be drawn.

Figure 10-1. Mean (±SD) Serum CTX Percent Change From Baseline by Visit (PD Analysis Set, Observed Data) (20160227 Final Analysis))



CTX= serum type 1 collagen C-telopeptide; N = number of subjects with values at baseline and ≥ 1 postbaseline CTX values; n = number of subjects with evaluable data at the time point of interest
Vertical lines represent the standard deviation.
Source: Figure 14-4.2.2.

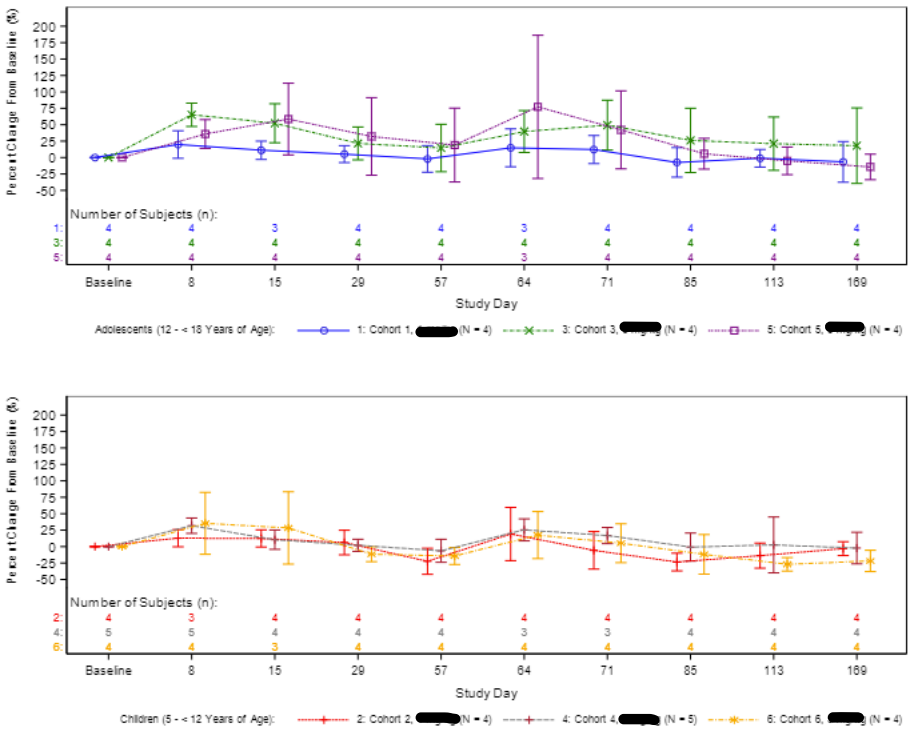
CHMP comment:

The Assessor agrees that no clear dose response in s CTX levels were observed in adolescents and children and that conclusions cannot be drawn due to sample size and variability between subjects.

4.5. Procollagen Type I N-terminal Propeptide

There appeared to be a dose response in elevation of the P1NP levels in both adolescents and children. P1NP levels increased when measured after dosing (on days 8 to 15). The mean percentage change in P1NP levels from baseline ranged from 11.03% to 58.58% at day 15 for the adolescents and from 10.52% to 28.35% at day 15 for the children. P1NP levels returned towards the baseline until next dosing. P1NP levels returned close to baseline by day 113 in both adolescents and children. Due to small the sample size and variability between subjects, no firm conclusions could be drawn.

Figure 10-2. Mean (±SD) Serum P1NP Percent Change From Baseline by Visit (PD Analysis Set, Observed Data) (20160227 Final Analysis)



P1NP = procollagen type 1 N-terminal peptide; N = number of subjects with values at baseline and ≥ 1 postbaseline P1NP values; n = number of subjects with evaluable data at the time point of interest
Vertical lines represent the standard deviation.
Source: Figure 14-4.3.2.

CHMP comment:

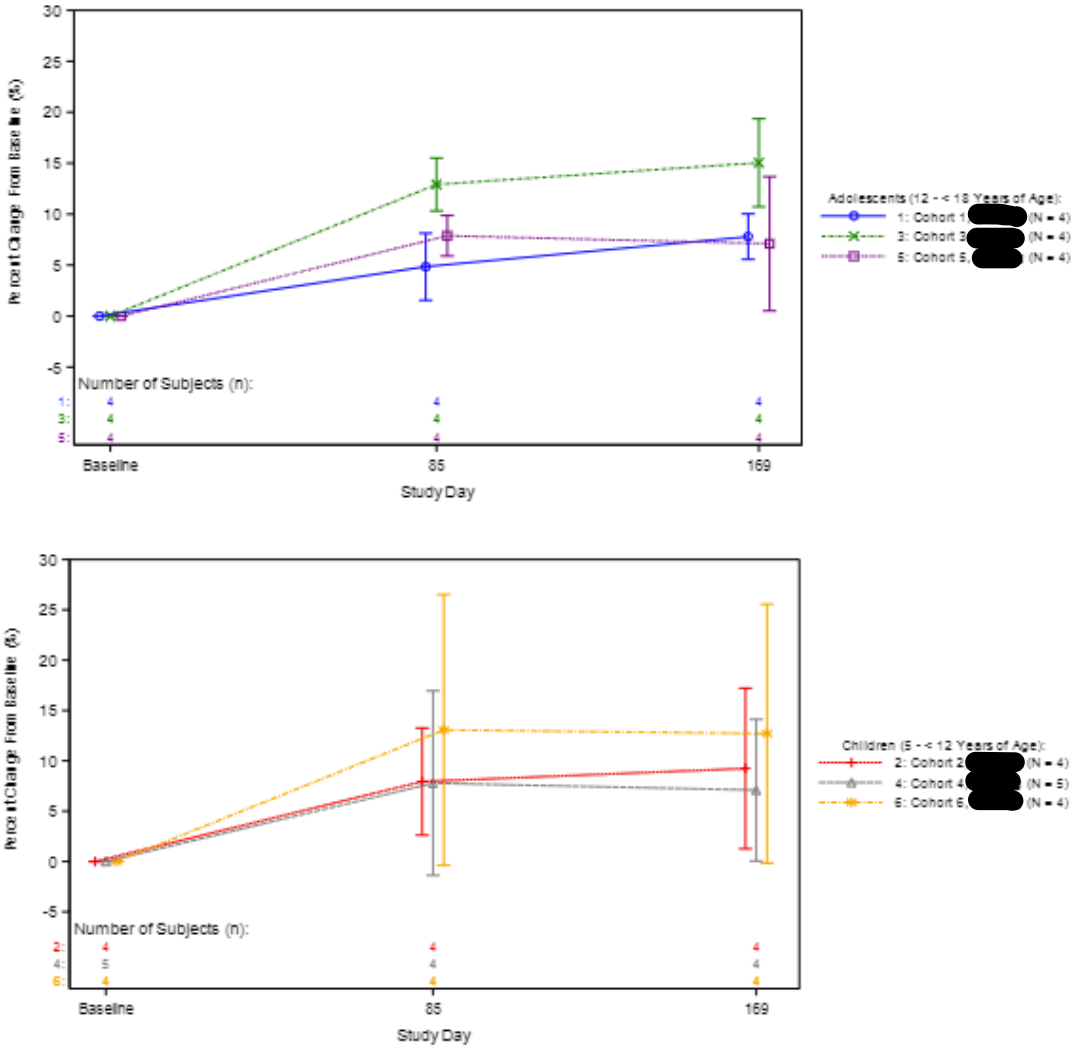
The Assessor agrees that conclusions cannot be drawn due to sample size and variability between subjects.

4.6. Lumbar Spine Bone Mineral Density

Most subjects, both adolescents and children, had increased lumbar spine BMD after 3 monthly doses of romosozumab. There was a trend of dose-related changes in lumbar spine BMD with increase in mean percentage change from baseline ranging from 4.84% to 12.91% at day 85 and from 7.10% to

15.04% at day 169 for the adolescents, and from 7.78% to 13.07% at day 85 and from 7.09% to 12.70% at day 169 for the children.

Figure 10-3. Mean (±SD) Lumbar Spine Bone Mineral Density Percent Change From Baseline by Visit (BMD Analysis Set, Observed Data) (20160227 Final Analysis)



BMD = bone mineral density; DXA = dual energy X ray absorptiometry; N = number of subjects with values at baseline and ≥ 1 postbaseline lumbar spine DXA BMD measurement; n = number of subjects with evaluable data at the time point of interest
Vertical lines represent the standard deviation.
Source: Figure 14-4.1.6

CHMP comment:

The Assessor agrees that there may be a trend for dose response as measured by Lumbar Spine BMD but conclusions cannot be drawn due to sample size and variability between subjects.

4.7. Lumbar Spine Bone Mineral Content

There was a trend of dose-related changes in lumbar spine BMC with increase in mean percentage change from baseline ranging from 7.68% to 18.16% at day 85 and from 12.64% to 21.29% at day 169 for the adolescents, and from 8.41% to 16.03% at day 85 and from 7.98% to 12.42% at day 169 for the children.

CHMP comment:

The Assessor agrees that there may be a trend for dose response as measured by Lumbar Spine BMD but conclusions cannot be drawn due to sample size and variability between subjects.

4.8. Lumbar Spine Bone Area

No clear dose-related changes in lumbar spine bone area were observed. The mean percent change in lumbar spine bone area from baseline ranged from 2.72% to 6.23% at day 85 and from 4.53% to 6.87% at day 169 for the adolescents, and from 0.80% to 3.44% at day 85 and from -0.09% to 1.92% at day 169 for the children.

CHMP comment

No clear dose-related changes in lumbar spine bone area can be observed. Conclusions cannot be drawn due to sample size and variability.

4.9. Bone Mineral Density Z-score at Lumbar Spine

Most subjects, both adolescents and children, also showed increased lumbar spine BMD Z-scores after 3 monthly doses of romosozumab, with increase in mean BMD Z-scores from baseline ranging from 0.20 to 0.50 at day 85 and from 0.23 to 0.48 at day 169 in the adolescents, and from 0.33 to 0.53 at day 85 and from 0.25 to 0.50 at day 169 in the children.

CHMP comment:

The Assessor agrees that lumbar spine BMD-Z scores increases after 3 monthly doses of romozumab. A placebo controlled trial is needed in order to be able to draw conclusions about efficacy.

5. Safety results

5.1. Exposure to Romosozumab

Of 25 subjects, 24 received 3 doses of romosozumab and 1 subject received 1 dose of romosozumab. The mean (SD) cumulative romosozumab exposure was 168.1 (68.2) mg in cohort 1, 59.0 (17.0) mg in cohort 2, 598.5 (40.6) mg in cohort 3, 186.5 (105.0) mg in cohort 4, 659.3 (182.3) mg in cohort 5, and 257.4 (70.9) mg in cohort 6.

5.2. Assessment of Safety

In Study 20160227, all safety endpoints were assessed using safety analysis set (all subjects who received at least 1 dose of romosozumab).

5.3. Overview of adverse events

5.3.1. Overall Adverse Events

Twelve of 25 subjects (48.0%) who enrolled in the study had treatment-emergent adverse events (TEAEs) during the study including 3-month follow-up period. All treatment-emergent adverse events were mild or moderate in severity. Serious treatment-emergent adverse events (STEAEs, preferred terms: femur fracture and lower limb fracture) were reported for 2 subjects (8.0%). None of these serious treatment-emergent adverse events were considered related to the investigational product by the investigator. Additionally, 1 subject in cohort 6 and another subject in cohort 5 reported nonserious treatment-emergent adverse events (nsTEAE) of femur fracture and ankle fracture respectively. These events were considered as not related to the investigational product. No treatment-emergent adverse events led to discontinuation of investigational product or were fatal. There was no specific pattern of any reported adverse events identified.

5.3.2. Adverse events related to drug

Treatment-emergent adverse events considered as related to romosozumab by the investigator were reported for 3 subjects (12.0%); 1 subject in cohort 5 reported events of injection site erythema, injection site swelling, 1 subject in cohort 6 reported events of injection site erythema, injection site pain, and injection site swelling, nasopharyngitis, and pain in extremity and another subject in cohort 6 reported events of muscle swelling and pain in extremity. All these events were mild or moderate in severity and none of these events were serious.

5.3.3. Common Adverse Events

Treatment-emergent adverse events by preferred term reported for ≥ 2 subjects overall were pain in extremity (3 subjects; 12.0%); and coronavirus disease 2019, nasopharyngitis, femur fracture, upper respiratory tract infection, arthralgia, back pain, injection site erythema, injection site swelling, pyrexia, cough, and headache, (2 subjects; 8.0% each).

5.3.4. Serious Adverse Events

Serious treatment-emergent adverse events were reported for 2 subjects (8.0%). Of these, 1 subject in cohort 4 had serious treatment-emergent adverse event of femur fracture, and another subject in

cohort 2 had lower limb fracture. None of these were considered related to the investigational product by the investigator.

5.3.5. Deaths

No subjects had fatal adverse events during the study.

5.3.6. Other Significant Adverse Events/ Adverse events of special interest

Events of interest under the category of hypersensitivity searched using narrow search strategy in standardized Medical Dictionary for Regulatory Activities (MedDRA) queries were reported for 1 subject (4.0%) in cohort 4 (preferred term: rash maculo-papular).

Events of interest under the category of injection site reactions searched using Amgen-defined MedDRA search strategies were reported for 2 subjects (8.0%). These events by preferred term were injection site erythema (2 subjects), injection site swelling (2 subjects), and injection site pain (1 subject). All these events were reported in cohort 5 and cohort 6.

5.3.7. Laboratory Assessments and Vital Signs

No clinically meaningful changes in laboratory or vital sign parameters were observed in this study. No subject met the criteria for Hy's law.

5.3.8. Electrocardiogram

No clinically meaningful change in mean from baseline to end-of-study were observed for electrocardiogram parameters during the study.

5.3.9. Cranial Nerve Examination

Among the 6 facial examination parameters, only 1 parameter (closing of lips) was abnormal but not clinically significant for 1 subject in cohort 2 on day 85. The Study 20160227 CSR provides further details of the safety analysis and results.

Table 4. Summary of Subject Incidence of Treatment-emergent Adverse Events (TEAEs).

	Romosozumab [redacted] SC 12 - < 18 years of Age (N = 4)	Romosozumab [redacted] SC 5 - < 12 years of Age (N = 4)	Romosozumab [redacted] SC 12 - < 18 years of Age (N = 4)	Romosozumab [redacted] SC 5 - < 12 years of Age (N = 5)	Romosozumab [redacted] SC 12 - < 18 years of Age (N = 4)	Romosozumab [redacted] SC 5 - < 12 years of Age (N = 4)	Overall (N = 25)
All treatment-emergent adverse events	1 (25.0)	1 (25.0)	2 (50.0)	4 (80.0)	1 (25.0)	3 (75.0)	12 (48.0)
Severity Grade[a]							
Mild	1 (25.0)	0 (0.0)	2 (50.0)	4 (80.0)	1 (25.0)	3 (75.0)	11 (44.0)
Moderate	0 (0.0)	1 (25.0)	0 (0.0)	1 (20.0)	1 (25.0)	1 (25.0)	4 (16.0)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse events	0 (0.0)	1 (25.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	2 (8.0)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related treatment-emergent adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	2 (50.0)	3 (12.0)
Severity Grade[a]							
Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	2 (50.0)	3 (12.0)
Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (4.0)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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CRF = case report form; SC = subcutaneous
Included adverse events starting on or after first dose of investigational product as determined by the flag on the CRF and up to the end of study date. .
[a]The severity grade is based on Severity Intensity Scale for Adverse Events
Source: Modified from Table 14-6.1.1

Table 5. Summary of Subject Incidence of Treatment-emergent Adverse Events of Interest.

Event of Interest	Romosozumab [redacted] SC 12 - < 18 Years of Age (N = 4) n (%)	Romosozumab [redacted] SC 5 - < 12 Years of Age (N = 4) n (%)	Romosozumab [redacted] SC 12 - < 18 Years of Age (N = 4) n (%)	Romosozumab [redacted] SC 5 - < 12 Years of Age (N = 5) n (%)	Romosozumab [redacted] SC 12 - < 18 Years of Age (N = 4) n (%)	Romosozumab [redacted] SC 5 - < 12 Years of Age (N = 4) n (%)	Overall (N = 25) n (%)
Adjudicated positive ONJ							
Adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiovascular event							
Adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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N = Number of subjects who received ≥ 1 dose of investigational product.
n = Number of subjects with observed data.
Adverse events were identified based on current MedDRA search strategies using MedDRA version 26.0.
Hypersensitivity and malignancy includes only treatment-emergent adverse events as a result of a narrow search/scope in standardized MedDRA queries (SMQ).
Hypocalcemia, injection site reactions, hyperostosis, and osteoarthritis includes only treatment-emergent adverse events as a result of Amgen-defined MedDRA search strategies.
Serious cardiovascular adverse events were identified using cardiac and vascular system organ class (SOC) in MedDRA.
ONJ = osteonecrosis of the jaw.

Program: /userdata/stat/amg785/earlydev/20160227/analysis/final/tables/t-ae-inc-eoi.sas
Output: t14-06-001-002-ae-inc-eoi.rtf (Date Generated: 14JUN23:03:46:22) Source: adam.adsl, adam.adae

Table 6. Most common Treatment-emergent Adverse Events by Preferred Term.

Preferred Term	Romosozumab [redacted] SC 12 - < 18 years of Age (N = 4)	Romosozumab [redacted] SC 5 - < 12 years of Age (N = 4)	Romosozumab [redacted] SC 12 - < 18 years of Age (N = 4)	Romosozumab [redacted] SC 5 - < 12 years of Age (N = 5)	Romosozumab [redacted] SC 12 - < 18 years of Age (N = 4)	Romosozumab [redacted] SC 5 - < 12 years of Age (N = 4)	Overall (N = 25)
Number of subjects reporting treatment-emergent adverse events	1 (25.0)	1 (25.0)	2 (50.0)	4 (80.0)	1 (25.0)	3 (75.0)	12 (48.0)
COVID-19	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	1 (25.0)	0 (0.0)	2 (8.0)
Nasopharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (25.0)	2 (8.0)
Upper respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)	2 (8.0)
Femur fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (25.0)	2 (8.0)
Pain in extremity	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	2 (50.0)	3 (12.0)
Arthralgia	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (25.0)	2 (8.0)
Back pain	0 (0.0)	0 (0.0)	1 (25.0)	1 (20.0)	0 (0.0)	0 (0.0)	2 (8.0)
Injection site erythema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (25.0)	2 (8.0)
Injection site swelling	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (25.0)	2 (8.0)
Pyrexia	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	1 (25.0)	2 (8.0)
Cough	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)	2 (8.0)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)	2 (8.0)

COVID-19 = coronavirus 2019; MedDRA = Medical Dictionary for Regulatory Activities; SARS-CoV-2 = severe acute respiratory syndrome coronavirus; SC = subcutaneous
System organ classes and preferred terms were sorted by descending order of frequency in the total and coded using MedDRA version 26.0.
Source: Modified from Table 14-6.2.1

5.3.10. Conclusion Safety results

CHMP comment:

Overall, TEAEs were reported in 12/25 paediatric patients (48%) and STEAEs were reported in 2/14 patients (8%). No cardiovascular or fatal events were observed.

It is agreed by the Assessor that there is no reasonable relation between the TEAEs or STEAEs reported and the investigational product.

In addition, the Assessor agrees that there seem to be no reasonable relation between nsTEAEs and the investigational product.

Treatment-emergent adverse events related to investigational product were reported for 3 subjects (12%) but were mild or moderate in severity. None of these events were serious.

The Assessor agrees that no specific pattern of any reported adverse event can be identified. The Assessor also agrees that TEAEs related to romosozumab were mild or moderate and none of these were serious.

Overall, the Assessor agrees with the conclusion that no safety signals were identified among peadiatric patients treated with romosozumab.

6. Discussion on clinical aspects

This is a CSR for Study 20160227 which is a phase 1b, open-label, ascending multiple-dose study to evaluate safety, tolerability, pharmacokinetics, and pharmacodynamics of Romosozumab in children (5 to <12 years of age) and adolescents (12 to <18 years of age) with Osteogenesis Imperfecta as part of a clinical development program for new indication of Evenity in children (in addition to indication for the treatment of osteoporosis in postmenopausal women).

A second study, Study 20200105, is planned as part of the clinical development program. Study 20200105 is a phase 3, open label, multicenter, randomized study to evaluate the efficacy and safety of romosozumab in children (5 to <12 years of age) and adolescents (12 to <18 years of age) with OI and enrolment for Study 20200105 is planned to start September 2023. Data from Study 20200105 will be presented separately. Subsequently, this CSR only addresses data from Study 20160227.

The pharmacokinetics of romosozumab was observed in 25 paediatric OI patients. Descriptive statistics for PK parameters per cohort (age and dose dependent) were reported. Due to the limited sample size per cohort, dose or age differences should be interpreted with caution. Nonetheless, there seem to be a slight trend that the mean AUCtau, per dose group, were lower in patients 5 to < 12 years compared to patients 12 to <18 years of age indicating that romosozumab PK may not be linear with respect to body weight.

No safety signals were identified in study sample, paediatric subjects treated with romosozumab. More safety data on the use of romosozumab is expected from future studies.

Bone turnover markers were evaluated as secondary endpoints. No conclusions can be made due to small sample size.

TEAEs were reported in 12/25 paediatric patients (48%) and STEAEs were reported in 2/14 patients (8%). All TEAEs and STAEs were mild or moderate. No cardiovascular events or deaths were observed. Assessor acknowledges that there seem to be no reasonable relation between TEAEs, STEAs or nsTEAEs and the investigational product.

Treatment-emergent adverse events related to investigational product were reported for 3 subjects (12%) but were mild or moderate in severity. None of these events were serious.

No specific pattern of any reported adverse event can be identified.

Overall, no safety signals were identified among peadiatric patients treated with romosozumab.

More safety data on the use of romosozumab in paediatric OI patients is expected in future clinical studies.

7. Rapporteur’s overall conclusion and recommendation

Study 20160227 was submitted according to paediatric investigational plan. No further action required.

☒ **Fulfilled**

8. Request for supplementary information

None.