Clinical trial results:
An international, multicenter, randomized, open-label, safety and efficacy trial of intravenous zoledronic acid administered either once or twice yearly in children with severe osteogenesis imperfecta, a 1-year extension to CZOL446H2202

Summary

EudraCT number	2004-001666-40
Trial protocol	HU GB BE
Global end of trial date	01 May 2007

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	CZOL446H2202E1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00131118
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 May 2007
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 May 2007
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to examine the long-term general and renal safety of once yearly or twice yearly zoledronic acid (ZOL) over a 12 month extension treatment period in children aged 1 to 17 years with severe osteogenesis imperfecta (OI) who had completed one year of treatment with either ZOL or pamidronate (PAM) in the core CZOL446H2202 study.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 August 2004
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Finland: 11
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Poland: 13
Country: Number of subjects enrolled	South Africa: 7
Country: Number of subjects enrolled	United States: 41
Worldwide total number of subjects	103
EEA total number of subjects	46

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	61
Adolescents (12-17 years)	42
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 16 centres in 8 countries.

Pre-assignment

Screening details:

The study enrolled a total of 103 subjects who completed the core study (CZOL446H2202).

Period 1

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

Blinding implementation details:

This was an open-label study. However, the Novartis clinical trial team, data analysts and vendor personnel were blinded to the subject treatment groups until the study database was locked.

Arms

Are arms mutually exclusive?	Yes
Arm title	ZOL-ZOL once yearly

Arm description:

Subjects who received ZOL in core study received ZOL based on age and body weight in extension study. Subjects aged 3 to 17 years received 0.05 milligram/kilogram (mg/kg) of ZOL up to a maximum of 4 mg once yearly. Subjects aged 1 to less than (<) 3 years received a lower ZOL dose of 0.025 mg/kg up to a maximum of 2 mg once yearly, until they reached their third birthday when the dose was increased to 0.05 mg/kg at the next scheduled dose administration visit.

Arm type	Experimental
Investigational medicinal product name	Zoledronic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Intravenous use

Dosage and administration details:

ZOL 0.025 mg/kg or 0.05mg/kg intravenous (i.v.) infusion was administered once a year.

Arm title	ZOL-ZOL twice yearly

Arm description:

Subjects who received ZOL in core study received ZOL based on age and body weight in extension study. Subjects aged 3 to 17 years received 0.05 mg/kg of ZOL up to a maximum of 4 mg twice yearly at 6 month intervals. Subjects aged 1 to < 3 years received a lower ZOL dose of 0.025 mg/kg up to a maximum of 2 mg twice yearly at 6 month intervals, until they reached their third birthday when the dose was increased to 0.05 mg/kg at the next scheduled dose administration visit.

Arm type	Experimental
Investigational medicinal product name	Zoledronic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Intravenous use

Dosage and administration details:

ZOL 0.025 mg/kg or 0.05mg/kg i.v. infusion was administered twice yearly at 6 months intervals.

Arm title	PAM-ZOL once yearly

Arm description:

Subjects who received pamidronate (PAM) in core study received ZOL based on age and body weight in

extension study. Subjects aged 3 to 17 years received 0.05 mg/kg of ZOL up to a maximum of 4 mg once yearly. Subjects aged 1 to less than < 3 years received a lower ZOL dose of 0.025 mg/kg up to a maximum of 2 mg once yearly, until they reached their third birthday when the dose was increased to 0.05 mg/kg at the next scheduled dose administration visit.

Arm type	Experimental
Investigational medicinal product name	Zoledronic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Intravenous use

Dosage and administration details:

ZOL 0.025 mg/kg or 0.05mg/kg intravenous (i.v.) infusion was administered once a year.

Arm title	PAM-ZOL twice yearly

Arm description:

Subjects who received PAM in core study received ZOL based on age and body weight in extension study. Subjects aged 3 to 17 years received 0.05 mg/kg of ZOL up to a maximum of 4 mg twice yearly at 6 month intervals. Subjects aged 1 to < 3 years received a lower ZOL dose of 0.025 mg/kg up to a maximum of 2 mg twice yearly at 6 month intervals, until they reached their third birthday when the dose was increased to 0.05 mg/kg at the next scheduled dose administration visit.

Arm type	Experimental
Investigational medicinal product name	Zoledronic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Intravenous use

Dosage and administration details:

ZOL 0.025 mg/kg or 0.05mg/kg i.v. infusion was administered twice yearly at 6 months intervals.

Number of subjects in period 1	ZOL-ZOL once yearly	ZOL-ZOL twice yearly	PAM-ZOL once yearly
Started	25	27	24
Completed	23	24	21
Not completed	2	3	3
Consent withdrawn by subject	2	1	-
Administrative problems	-	2	3
Lost to follow-up	-	-	-

Number of subjects in period 1	PAM-ZOL twice yearly
Started	27
Completed	24
Not completed	3
Consent withdrawn by subject	-
Administrative problems	2
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	ZOL-ZOL once yearly
Reporting group description:	
Subjects who received ZOL in core study received ZOL based on age and body weight in extension study. Subjects aged 3 to 17 years received 0.05 milligram/kilogram (mg/kg) of ZOL up to a maximum of 4 mg once yearly. Subjects aged 1 to less than (<) 3 years received a lower ZOL dose of 0.025 mg/kg up to a maximum of 2 mg once yearly, until they reached their third birthday when the dose was increased to 0.05 mg/kg at the next scheduled dose administration visit.	
Reporting group title	ZOL-ZOL twice yearly
Reporting group description:	
Subjects who received ZOL in core study received ZOL based on age and body weight in extension study. Subjects aged 3 to 17 years received 0.05 mg/kg of ZOL up to a maximum of 4 mg twice yearly at 6 month intervals. Subjects aged 1 to < 3 years received a lower ZOL dose of 0.025 mg/kg up to a maximum of 2 mg twice yearly at 6 month intervals, until they reached their third birthday when the dose was increased to 0.05 mg/kg at the next scheduled dose administration visit.	
Reporting group title	PAM-ZOL once yearly
Reporting group description:	
Subjects who received pamidronate (PAM) in core study received ZOL based on age and body weight in extension study. Subjects aged 3 to 17 years received 0.05 mg/kg of ZOL up to a maximum of 4 mg once yearly. Subjects aged 1 to less than < 3 years received a lower ZOL dose of 0.025 mg/kg up to a maximum of 2 mg once yearly, until they reached their third birthday when the dose was increased to 0.05 mg/kg at the next scheduled dose administration visit.	
Reporting group title	PAM-ZOL twice yearly
Reporting group description:	
Subjects who received PAM in core study received ZOL based on age and body weight in extension study. Subjects aged 3 to 17 years received 0.05 mg/kg of ZOL up to a maximum of 4 mg twice yearly at 6 month intervals. Subjects aged 1 to < 3 years received a lower ZOL dose of 0.025 mg/kg up to a maximum of 2 mg twice yearly at 6 month intervals, until they reached their third birthday when the dose was increased to 0.05 mg/kg at the next scheduled dose administration visit.	

Reporting group values	ZOL-ZOL once yearly	ZOL-ZOL twice yearly	PAM-ZOL once yearly
Number of subjects	25	27	24
Age categorical Units: Subjects			
2- <3 years	1	0	0
3- <9 years	13	12	9
9 years or older	11	15	15
Age continuous Units: years			
arithmetic mean	8.9	9.9	10
standard deviation	± 4.98	± 4.29	± 4.81
Gender categorical Units: Subjects			
Female	11	14	11
Male	14	13	13

Reporting group values	PAM-ZOL twice yearly	Total	
Number of subjects	27	103	

Age categorical Units: Subjects			
2- <3 years	1	2	
3- <9 years	8	42	
9 years or older	18	59	
Age continuous Units: years			
arithmetic mean	10		
standard deviation	± 3.97	-	
Gender categorical Units: Subjects			
Female	9	45	
Male	18	58	

End points

End points reporting groups

Reporting group title	ZOL-ZOL once yearly

Reporting group description:

Subjects who received ZOL in core study received ZOL based on age and body weight in extension study. Subjects aged 3 to 17 years received 0.05 milligram/kilogram (mg/kg) of ZOL up to a maximum of 4 mg once yearly. Subjects aged 1 to less than (<) 3 years received a lower ZOL dose of 0.025 mg/kg up to a maximum of 2 mg once yearly, until they reached their third birthday when the dose was increased to 0.05 mg/kg at the next scheduled dose administration visit.

Reporting group title	ZOL-ZOL twice yearly

Reporting group description:

Subjects who received ZOL in core study received ZOL based on age and body weight in extension study. Subjects aged 3 to 17 years received 0.05 mg/kg of ZOL up to a maximum of 4 mg twice yearly at 6 month intervals. Subjects aged 1 to < 3 years received a lower ZOL dose of 0.025 mg/kg up to a maximum of 2 mg twice yearly at 6 month intervals, until they reached their third birthday when the dose was increased to 0.05 mg/kg at the next scheduled dose administration visit.

Reporting group title	PAM-ZOL once yearly

Reporting group description:

Subjects who received pamidronate (PAM) in core study received ZOL based on age and body weight in extension study. Subjects aged 3 to 17 years received 0.05 mg/kg of ZOL up to a maximum of 4 mg once yearly. Subjects aged 1 to less than < 3 years received a lower ZOL dose of 0.025 mg/kg up to a maximum of 2 mg once yearly, until they reached their third birthday when the dose was increased to 0.05 mg/kg at the next scheduled dose administration visit.

Reporting group title	PAM-ZOL twice yearly

Reporting group description:

Subjects who received PAM in core study received ZOL based on age and body weight in extension study. Subjects aged 3 to 17 years received 0.05 mg/kg of ZOL up to a maximum of 4 mg twice yearly at 6 month intervals. Subjects aged 1 to < 3 years received a lower ZOL dose of 0.025 mg/kg up to a maximum of 2 mg twice yearly at 6 month intervals, until they reached their third birthday when the dose was increased to 0.05 mg/kg at the next scheduled dose administration visit.

Primary: Number of subjects with adverse events (AEs) and serious adverse events (SAEs)

End point title	Number of subjects with adverse events (AEs) and serious adverse events (SAEs)[1]

End point description:

An AE was defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of study drug, whether or not related to study drug. A SAE was defined as an event which was fatal or life threatening, required or prolonged hospitalization, was significantly or permanently disabling or incapacitating, constituted a congenital anomaly or a birth defect, or encompassed any other clinically significant event that could jeopardize the subject or require medical or surgical intervention to prevent one of the aforementioned outcomes. Analysis was performed in safety population (SAF), defined as the subjects who received at least one dose of study medication in the extension study and had at least one post-baseline safety assessment.

End point type	Primary

End point timeframe:

From start of study treatment (extension phase) to end of study (extension phase)

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: Only descriptive analysis was planned for this outcome measure.

End point values	ZOL-ZOL once yearly	ZOL-ZOL twice yearly	PAM-ZOL once yearly	PAM-ZOL twice yearly
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	27	24	27
Units: Number of subjects				
AEs	24	24	17	20
SAEs	5	6	3	5

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change from baseline in lumbar spine bone mineral density (BMD) at months 18 and 24

End point title	Percentage change from baseline in lumbar spine bone mineral density (BMD) at months 18 and 24

End point description:

Bone-mineral density (BMD) was estimated dual energy X-ray absorptiometry (DEXA) method. Percent change from core baseline in lumbar spine BMD was calculated by using the formula: 100 (endpoint - core baseline)/core baseline. The analysis was performed in Intent-to-treat (ITT) population, defined as all randomized subjects who received at least one dose of study drug and had at least one post baseline efficacy assessment on the efficacy variable. The 'n' signifies those subjects with lumbar spine BMD measurements at both baseline and the respective specified time points, as determined by the visit window after last observation carried forward (LOCF) imputation for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline (core study), Month 18, Month 24 (core+extension study)

End point values	ZOL-ZOL once yearly	ZOL-ZOL twice yearly	PAM-ZOL once yearly	PAM-ZOL twice yearly
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	27	24	27
Units: grams/ square centimetres				
arithmetic mean (standard deviation)				
Change from baseline to Month 18(n=22,21, 22,22)	58.61 (± 28.871)	49.043 (± 19.43)	43.659 (± 27.492)	50.721 (± 33.172)
Change from baseline to Month 24(n=22,21, 22,22)	64.569 (± 30.373)	59.1 (± 21.338)	52.538 (± 31.341)	62.202 (± 44.71)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in lumbar spine bone mineral density (BMD) Z-scores at months 18 and 24

End point title	Change from baseline in lumbar spine bone mineral density (BMD) Z-scores at months 18 and 24

End point description:

The BMD Z-score was used to diagnose low bone mass in young adults and children. Z-score was determined as: (Measured BMD - Age-matched mean BMD)/ Age matched population standard deviation. Lumbar spine Z-scores were available only for subjects aged 3 years or older using a Hologic imaging equipment, and subjects aged 5 years or older were imaged using the Lunar equipment. The analysis was performed in ITT population. The 'n' signifies those subjects with lumbar spine BMD Z-score measurements at both baseline and the respective specified time points, as determined by the visit window after LOCF imputation for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline (core study), Month 18, Month 24 (core+extension study)

End point values	ZOL-ZOL once yearly	ZOL-ZOL twice yearly	PAM-ZOL once yearly	PAM-ZOL twice yearly
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	27	24	27
Units: Units on a scale				
arithmetic mean (standard deviation)				
Change from baseline to Month 18(n=13,12, 12,18)	2.459 (± 1.017)	2.073 (± 0.963)	1.198 (± 0.576)	2.017 (± 1.333)
Change from baseline to Month 24(n=13,12, 12,18)	2.633 (± 0.991)	2.253 (± 1.211)	1.411 (± 0.685)	2.238 (± 1.465)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in bone mineral content (BMC) of the total body at months 18 and 24

End point title	Change from baseline in bone mineral content (BMC) of the total body at months 18 and 24

End point description:

Bone mineral content (BMC) was used to diagnose the bone loss in the study subjects. Percent change from core baseline in BMC was calculated by using the formula: 100*(endpoint - core baseline)/core baseline. The analysis was performed in ITT population. The 'n' signifies those subjects with total BMC measurements at both baseline and the respective specified time points, as determined by the visit window after LOCF imputation for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline (core study), Month 18, Month 24 (core+extension study)

End point values	ZOL-ZOL once yearly	ZOL-ZOL twice yearly	PAM-ZOL once yearly	PAM-ZOL twice yearly
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	27	24	27
Units: grams				
arithmetic mean (standard deviation)				

Change from baseline to Month 18(n=24, 27, 23, 24)	299.379 (± 205.819)	329.843 (± 236.744)	366.794 (± 192.875)	346.233 (± 161.58)
Change from baseline to Month 24(n=24, 27, 23, 24)	365.499 (± 239.374)	422.261 (± 278.864)	431.069 (± 234.943)	435.566 (± 240.497)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of clinical fractures per subject

End point title	Number of clinical fractures per subject

End point description:

The total number of clinical fractures per subject was determined from the sum of all anatomic sites captured in the radiographic interpretation report. Analysis was performed in ITT population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Extension Period (12 months) and Core+Extension period (24 months)

End point values	ZOL-ZOL once yearly	ZOL-ZOL twice yearly	PAM-ZOL once yearly	PAM-ZOL twice yearly
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	27	24	27
Units: fractures/subject				
arithmetic mean (standard deviation)				
Extension Period (12 months)(n=8, 8, 9, 12)	1.6 (± 0.74)	2.5 (± 2.07)	1.4 (± 0.88)	1.9 (± 1.31)
Core+Extension period (24 months)(n=14,15,17,17)	4.1 (± 6.02)	2.6 (± 2.77)	1.5 (± 0.94)	2.7 (± 2.87)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change from baseline in serum biomarkers of bone turnover at months 15, 18, 21 and 24

End point title	Percentage change from baseline in serum biomarkers of bone turnover at months 15, 18, 21 and 24

End point description:

Serum biomarkers i.e bone resorption marker C-telopeptide (beta-CTx), bone formation markers N-terminal propeptide of type I collagen (P1NP) and bone-specific alkaline phosphatase (BSAP) were measured in children aged 3 years or older. Percent change from core baseline in serum biomarkers was calculated by using the formula: 100*(endpoint - core baseline)/core baseline. Analysis was performed in ITT population. The 'n' signifies those subjects with total Serum biomarkers measurements at both baseline and the respective specified time points, as determined by available data..

End point type	Secondary

End point timeframe:

Baseline (core study), Month 15, 18, 21, 24 (core+extension study)

End point values	ZOL-ZOL once yearly	ZOL-ZOL twice yearly	PAM-ZOL once yearly	PAM-ZOL twice yearly
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	27	24	26
Units: nanogram/milliilitre(ng/mL)				
arithmetic mean (standard deviation)				
Month 15, Serum beta–CTx(n=14,13,16,13)	-24.951 (± 39.382)	-20.94 (± 27.039)	-14.459 (± 68.783)	48.943 (± 182.127)
Month 18, Serum beta–CTx (n=19,17,16,18)	-18.889 (± 37.431)	-28.666 (± 23.101)	-17.07 (± 69.033)	62.38 (± 213.296)
Month 21, Serum beta–CTx (n=16,16,15,18)	-14.523 (± 34.039)	-21.682 (± 31.279)	-2.691 (± 73.35)	8.255 (± 105.953)
Month 24, Serum beta–CTx (n=16,17,16,17)	-24.787 (± 29.412)	-15.167 (± 37.279)	-9.097 (± 61.236)	15.116 (± 119.355)
Month 15, Serum P1NP (n=14,13,16,14)	-47.028 (± 41.699)	-35.236 (± 18.03)	-57.439 (± 17.025)	-25.991 (± 54.741)
Month 18, Serum P1NP (n=18,17,16,18)	-42.705 (± 38.071)	-40.015 (± 21.195)	-52.307 (± 25.034)	-15.926 (± 65.164)
Month 21, Serum P1NP (n=15,16,15,18)	-41.123 (± 36.322)	-40.727 (± 35.033)	-44.831 (± 36.28)	-34.64 (± 47.944)
Month 24, Serum P1NP (n=15,17,16,17)	-53.948 (± 18.645)	-39.928 (± 29.892)	-44.852 (± 35.594)	-25.532 (± 53.942)
Month 15, Serum BSAP (n=14,13,16,14)	-43.016 (± 25.058)	-24.88 (± 21.182)	-42.306 (± 21.196)	-30.919 (± 28.386)
Month 18, Serum BSAP (n=19,17,16,18)	-32.095 (± 25.962)	-27.017 (± 22.682)	-43.864 (± 24.084)	-15.189 (± 38.864)
Month 21, Serum BSAP (n=16,16,15,18)	-27.6 (± 32.165)	-31.117 (± 18.021)	-35.627 (± 31.915)	-32.154 (± 30.217)
Month 24, Serum BSAP (n=16,17,16,17)	-30.81 (± 28.518)	-33.915 (± 19.387)	-34.481 (± 32.976)	-26.107 (± 38.807)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in supine length at months 15, 18, 21 and 24

End point title	Change from baseline in supine length at months 15, 18, 21 and 24

End point description:

Supine length was measured by using stadiometer. Two to four measurements were taken and the average length measurements were used if the two measurements differed by >4 millimetre (mm), two additional measurements were recorded. Change from core baseline in supine length was calculated by using the formula: (endpoint - core baseline). Analysis was performed in ITT population. The 'n' signifies those subjects with vertebral spine length measurements at both baseline and the respective specified time points, as determined by the visit window after LOCF imputation for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline (core study), Month 15, Month 18, Month 21, Month 24 (core+extension study)

End point values	ZOL-ZOL once yearly	ZOL-ZOL twice yearly	PAM-ZOL once yearly	PAM-ZOL twice yearly
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	27	24	27
Units: centimetres (cm)				
arithmetic mean (standard deviation)				
Change from baseline to Month 15(n=24, 27,24,27)	8.292 (± 7.16)	6.63 (± 3.488)	7.5 (± 5.158)	7.815 (± 3.962)
Change from baseline to Month 18(n=24, 27,24,27)	9.417 (± 7.199)	8.296 (± 4.017)	9.167 (± 5.475)	9.407 (± 6.253)
Change from baseline to Month 21(n=24, 27,24,27)	10.5 (± 6.846)	8.704 (± 4.103)	9.625 (± 5.64)	11.926 (± 7.849)
Change from baseline to Month 24(n=24, 27, 24, 27)	9.125 (± 15.358)	9.963 (± 4.238)	10.583 (± 5.778)	12.926 (± 7.706)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with bone pain

End point title	Percentage of subjects with bone pain

End point description:

The Wong-Baker FACES pain rating scale was used to assess bone pain in all subjects. For very young children, their parent or guardian was rated the bone pain scale and the older subjects were self-rated the bone pain scale. There were 6 categories of pain intensity described from "no hurt" to "hurts worst", Face 0: no hurt, face 1: hurts little bit, face 2: hurts little more, face 3: hurts even more, face 4: hurts whole lot and face 5: hurts worst. Analysis was performed in ITT population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline (core study), Month 12, Month 24 (core+extension study)

End point values	ZOL-ZOL once yearly	ZOL-ZOL twice yearly	PAM-ZOL once yearly	PAM-ZOL twice yearly
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	27	24	27
Units: Percentage of subjects				
number (not applicable)				
Month 12 No hurt	92	74.1	75	74.1
Month 12 Hurts little bit	8	22.2	12.5	11.1
Month 12 Hurts little more	0	0	8.3	7.4
Month 12 Hurts even more	0	3.7	4.2	3.7
Month 12 Hurts whole lot	0	0	0	3.7
Month 12 Hurts worst	0	0	0	0
Month 24 No Hurt	72	63	75	63
Month 24 Hurts little bit	4	18.5	8.3	18.5
Month 24 Hurts little more	0	3.7	0	0
Month 24 Hurts even more	4	0	4.2	0
Month 24 Hurts whole lot	4	0	0	0

Month 24 Hurts worst	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in cortical bone thickness at month 24

End point title	Change from baseline in cortical bone thickness at month 24

End point description:

Cortical bone thickness was used to diagnose the bone loss in the study subjects. X-rays of the vertebral spine were used to determine cortical bone thickness. Change from core baseline in cortical bone thickness was calculated by using the formula: (endpoint - core baseline). Analysis was performed in ITT population. The number of subjects analysed (N) signifies those subjects with cortical bone thickness measurements at both baseline and the respective specified time points, as determined by the visit window after LOCF imputation for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline (core study), Month 24 (core+extension study)

End point values	ZOL-ZOL once yearly	ZOL-ZOL twice yearly	PAM-ZOL once yearly	PAM-ZOL twice yearly
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	18	12	18
Units: millimetre (mm)				
arithmetic mean (standard deviation)	-0.05 (± 0.126)	-0.017 (± 0.079)	0.008 (± 0.051)	0.011 (± 0.076)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in vertebral spine length at month 24

End point title	Change from baseline in vertebral spine length at month 24

End point description:

The X-rays of the spine and hand were used to determine the changes in vertebral spine length. Change from core baseline vertebral spine length was calculated by using the formula: (endpoint - core baseline). Analysis was performed in ITT population. The number of subjects analysed (N) signifies those subjects with vertebral spine length measurements at both baseline and the respective specified time points, as determined by the visit window after LOCF imputation for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline (core study), Month 24 (core+extension study

End point values	ZOL-ZOL once yearly	ZOL-ZOL twice yearly	PAM-ZOL once yearly	PAM-ZOL twice yearly
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	13	13	14
Units: centimetre (cm)				
arithmetic mean (standard deviation)	4.703 (± 2.037)	4.075 (± 6.939)	4.774 (± 6.959)	2.642 (± 5.006)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in grip strength at month 15, 18, 21 and 24

End point title	Change from baseline in grip strength at month 15, 18, 21 and 24

End point description:

Grip strength assessed by hand dynamometry in subjects aged 3 years or older. The assessment was made from the best of three measurements attained with the dominant hand. The Change from core baseline in grip strength was calculated by using the formula: (endpoint - core baseline). Analysis was performed in ITT population. The 'n' signifies those subjects with grip strength measurements at both baseline and the respective specified time points, as determined by the visit window after LOCF imputation for each group, respectively.

End point type	Secondary

End point timeframe:

Baseline (core study), Month 15, Month 18, Month 21, Month 24 (core+extension study)

End point values	ZOL-ZOL once yearly	ZOL-ZOL twice yearly	PAM-ZOL once yearly	PAM-ZOL twice yearly
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	27	24	26
Units: Grams(g)				
arithmetic mean (standard deviation)				
Change from baseline to Month 15 (n=17,20,18,23)	2.418 (± 2.848)	2.675 (± 3.512)	2.611 (± 5.217)	2.37 (± 6.572)
Change from baseline to Month 18 (n=17,20,18,23)	3.371 (± 2.026)	3.425 (± 4.836)	3.778 (± 5.236)	2.739 (± 6.473)
Change from baseline to Month 21 (n=17,20,18,23)	4.988 (± 3.904)	4.475 (± 5.333)	4.25 (± 5.899)	3.717 (± 6.694)
Change from baseline to Month 24 (n=17,20,18,23)	5.365 (± 4.04)	5.825 (± 7.276)	4.667 (± 5.773)	6.717 (± 12.902)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.1

Reporting groups

Reporting group title	Zoledronic acid: Zol 1x/yr
Reporting group description:	
Zoledronic acid: Zol 1x/yr	
Reporting group title	Zoledronic acid: Zol 2x/yr
Reporting group description:	
Zoledronic acid: Zol 2x/yr	
Reporting group title	Pamidronate: Zol 1x/yr
Reporting group description:	
Pamidronate: Zol 1x/yr	
Reporting group title	Pamidronate: Zol 2x/yr
Reporting group description:	
Pamidronate: Zol 2x/yr	

Serious adverse events	Zoledronic acid: Zol 1x/yr	Zoledronic acid: Zol 2x/yr	Pamidronate: Zol 1x/yr
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 25 (20.00%)	6 / 27 (22.22%)	3 / 24 (12.50%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 25 (0.00%)	1 / 27 (3.70%)	0 / 24 (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
Femoral neck fracture			
subjects affected / exposed	1 / 25 (4.00%)	0 / 27 (0.00%)	0 / 24 (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
Femur fracture			

subjects affected / exposed	3 / 25 (12.00%)	1 / 27 (3.70%)	2 / 24 (8.33%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			
subjects affected / exposed	0 / 25 (0.00%)	1 / 27 (3.70%)	0 / 24 (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
Medical device complication			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (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
Medical device discomfort			
subjects affected / exposed	0 / 25 (0.00%)	1 / 27 (3.70%)	0 / 24 (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
Multiple fractures			
subjects affected / exposed	0 / 25 (0.00%)	1 / 27 (3.70%)	0 / 24 (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
Post-traumatic pain			
subjects affected / exposed	0 / 25 (0.00%)	1 / 27 (3.70%)	0 / 24 (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
Radius fracture			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (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
Tibia fracture			
subjects affected / exposed	1 / 25 (4.00%)	2 / 27 (7.41%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			

subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	0 / 25 (0.00%)	1 / 27 (3.70%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillar hypertrophy			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 27 (0.00%)	0 / 24 (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
Fracture malunion			
subjects affected / exposed	1 / 25 (4.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scoliosis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 27 (3.70%)	0 / 24 (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
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			

subjects affected / exposed	0 / 25 (0.00%)	1 / 27 (3.70%)	0 / 24 (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

Serious adverse events	Pamidronate: Zol 2x/yr		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 27 (18.52%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Femoral neck fracture			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Fibula fracture			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Medical device complication			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Medical device discomfort			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Multiple fractures			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Post-traumatic pain			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radius fracture			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tibia fracture			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ulna fracture			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tonsillar hypertrophy			

subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fracture malunion			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Scoliosis			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Zoledronic acid: Zol 1x/yr	Zoledronic acid: Zol 2x/yr	Pamidronate: Zol 1x/yr
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 25 (88.00%)	19 / 27 (70.37%)	15 / 24 (62.50%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 25 (4.00%)	2 / 27 (7.41%)	1 / 24 (4.17%)
occurrences (all)	1	2	1
Femur fracture			
subjects affected / exposed	3 / 25 (12.00%)	3 / 27 (11.11%)	1 / 24 (4.17%)
occurrences (all)	3	3	1

Forearm fracture			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Hand fracture			
subjects affected / exposed	1 / 25 (4.00%)	1 / 27 (3.70%)	2 / 24 (8.33%)
occurrences (all)	1	1	3
Humerus fracture			
subjects affected / exposed	0 / 25 (0.00%)	3 / 27 (11.11%)	1 / 24 (4.17%)
occurrences (all)	0	3	1
Sunburn			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Tibia fracture			
subjects affected / exposed	4 / 25 (16.00%)	4 / 27 (14.81%)	1 / 24 (4.17%)
occurrences (all)	8	5	1
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 25 (16.00%)	1 / 27 (3.70%)	2 / 24 (8.33%)
occurrences (all)	6	1	2
Migraine			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 25 (12.00%)	1 / 27 (3.70%)	1 / 24 (4.17%)
occurrences (all)	3	1	1
Pyrexia			
subjects affected / exposed	1 / 25 (4.00%)	2 / 27 (7.41%)	3 / 24 (12.50%)
occurrences (all)	1	3	4
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 25 (0.00%)	2 / 27 (7.41%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	1 / 25 (4.00%)	2 / 27 (7.41%)	0 / 24 (0.00%)
occurrences (all)	1	2	0
Nausea			
subjects affected / exposed	3 / 25 (12.00%)	0 / 27 (0.00%)	1 / 24 (4.17%)
occurrences (all)	5	0	1
Vomiting			
subjects affected / exposed	2 / 25 (8.00%)	1 / 27 (3.70%)	2 / 24 (8.33%)
occurrences (all)	2	1	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 25 (0.00%)	2 / 27 (7.41%)	2 / 24 (8.33%)
occurrences (all)	0	3	2
Epistaxis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 25 (8.00%)	2 / 27 (7.41%)	2 / 24 (8.33%)
occurrences (all)	2	2	2
Back pain			
subjects affected / exposed	3 / 25 (12.00%)	4 / 27 (14.81%)	3 / 24 (12.50%)
occurrences (all)	4	4	3
Bone pain			
subjects affected / exposed	1 / 25 (4.00%)	2 / 27 (7.41%)	2 / 24 (8.33%)
occurrences (all)	1	2	2
Muscle spasms			
subjects affected / exposed	5 / 25 (20.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	5	0	0
Musculoskeletal chest pain			
subjects affected / exposed	2 / 25 (8.00%)	4 / 27 (14.81%)	0 / 24 (0.00%)
occurrences (all)	3	4	0
Pain in extremity			
subjects affected / exposed	4 / 25 (16.00%)	5 / 27 (18.52%)	0 / 24 (0.00%)
occurrences (all)	6	9	0
Scoliosis			

subjects affected / exposed	0 / 25 (0.00%)	2 / 27 (7.41%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Ear infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 27 (3.70%)	2 / 24 (8.33%)
occurrences (all)	0	1	2
Influenza			
subjects affected / exposed	2 / 25 (8.00%)	4 / 27 (14.81%)	2 / 24 (8.33%)
occurrences (all)	2	5	2
Nasopharyngitis			
subjects affected / exposed	5 / 25 (20.00%)	5 / 27 (18.52%)	0 / 24 (0.00%)
occurrences (all)	9	5	0
Pharyngitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Sinusitis			
subjects affected / exposed	3 / 25 (12.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	3	0	0
Upper respiratory tract infection			
subjects affected / exposed	3 / 25 (12.00%)	2 / 27 (7.41%)	1 / 24 (4.17%)
occurrences (all)	4	5	1
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 27 (3.70%)	0 / 24 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Pamidronate: Zol 2x/yr		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 27 (70.37%)		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		

Femur fracture subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Forearm fracture subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 3		
Hand fracture subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Humerus fracture subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Sunburn subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Tibia fracture subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 5		
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 5		
Migraine subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Pyrexia subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Immune system disorders			
Seasonal allergy subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	5		
Back pain			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	2		
Bone pain			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	4		
Muscle spasms			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		

Scoliosis subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1		
Infections and infestations Ear infection subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all) Pharyngitis streptococcal subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0 1 / 27 (3.70%) 1 2 / 27 (7.41%) 2 2 / 27 (7.41%) 2 0 / 27 (0.00%) 0 0 / 27 (0.00%) 0 3 / 27 (11.11%) 6		
Metabolism and nutrition disorders Hypercalcaemia subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Study was terminated prematurely at the recommendation of the independent Data Safety Monitoring Board, who after review of interim unblinded safety and efficacy data observed an excess of fracture risk that had not changed from the core study.

Notes: