



Clinical trial results:

An international, multicenter, randomized, open-label, parallel efficacy, and safety trial of intravenous zoledronic acid compared to intravenous pamidronate in children with severe osteogenesis imperfect

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> complete trial results.

Summary

EudraCT number	2015-003539-37
Trial protocol	Outside EU/EEA
Global end of trial date	09 May 2007

Results information

Result version number	v1 (current)
This version publication date	07 July 2018
First version publication date	07 July 2018

Trial information

Trial identification

Sponsor protocol code	CZOL446H2202
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00063479
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)	Yes
EMA paediatric investigation plan number(s)	EMA-000024-PIP01-07
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	09 May 2007
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	09 May 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary efficacy objective was to assess the percentage (%) change in lumbar spine (LS) bone mineral density (BMD) at month 12 relative to baseline in zoledronic acid-treated pediatric patients with severe OI compared to pamidronate-treated pediatric patients who were 1 to 17 years of age.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator:

Pamidronate was established as an off-label therapy for treating children with OI as there was no approved therapy for this indication. Based on severity of disease in this pediatric population, it was ethically difficult for parents/guardians to give consent for participation in the study if their child had the possibility of being randomized to placebo.

Actual start date of recruitment	26 June 2003
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 51
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	Finland: 14
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	South Africa: 8
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Poland: 17
Worldwide total number of subjects	150
EEA total number of subjects	76

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)	2
Children (2-11 years)	104
Adolescents (12-17 years)	44
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 20 centers in 9 countries.

Pre-assignment

Screening details:

A total of 155 subjects were randomized in the study. 150 patients were in the ITT group. The trial analysis was performed on intent to treat (ITT) population defined as all randomized subjects who had a least one post-baseline efficacy assessment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Zoledronic acid

Arm description:

Subjects were peripherally intravenously (i.v.) infused with doses of zoledronic acid based on age and body weight. Subjects aged from 1 to <3 years received 0.025 milligram (mg)/kilogram (kg) diluted in 50 milliliter (mL) of normal saline up to a maximum dose of at a frequency of 30 to 45 minute infusion every 3 months. Subjects aged from 3 to 17 years received 0.05 mg/kg diluted in 100 mL of normal saline up to a maximum of 4 mg at a frequency of 30 minute infusion every 3 months. All subjects were hospitalized for 48 hours at the first infusion of zoledronic acid and post-dose symptoms were assessed. A total of 4 infusions were received during the study treatment period.

Arm type	Experimental
Investigational medicinal product name	Zoledronic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects aged 1 to <3 years received a dose of 0.025 mg/kg up to a maximum of 2 mg every 3 months. Subjects aged 3 to 17 years received 0.05 mg/kg of zoledronic acid up to a maximum of 4 mg every 3 months. Zoledronic acid was provided in 5 mg/100 mL vials; for older children 5mg/5mL vials were used. The calculated dose of zoledronic acid was diluted to 50 mL with normal saline and infused over 30 to 45 minutes for children <3 years old; and diluted to 100 mL with normal saline for infusion over 30 minutes in subjects aged 3 to 17 years. All Subjects were hospitalised for 48 hours at the first infusion of zoledronic acid and post-dose symptoms were assessed. A total of 4 infusions were received during the study treatment period.

Arm title	Pamidronate
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Arm description:

Subjects were peripherally i.v. infused with doses of pamidronate based on age and body weight. Subjects aged from 1 to <2 years received 0.5 mg/kg/day at frequency of 4 hour infusion on each of 3 successive days, every 2 months. Subjects aged 2 years received 0.75 mg/kg/day at a frequency of 4 hour infusion on each of 3 successive days, every 3 months. Subjects aged from 3 to 17 years received 1 mg/kg/day at a frequency of 4 hour infusion on each of 3 successive days, every 3 months. Subjects received a maximum daily dose of up to 60 mg.

Arm type	Active comparator
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Investigational medicinal product name	Pamidronate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Subjects aged 1 to <2 years received a daily dose of 0.5 mg/kg up to a maximum of 60 on each of 3 successive days, every 2 months. Subjects aged 2 and 3 to 17 years received a daily dose of 0.75 mg/kg and 1 mg/kg of pamidronate, respectively up to a maximum of 60 mg on each of 3 successive days, every 3 months. Each 90 mg vial of lyophilized pamidronate was reconstituted with 10.0 mL of sterile water for injection.

Number of subjects in period 1	Zoledronic acid	Pamidronate
Started	74	76
Completed	68	69
Not completed	6	7
Consent withdrawn by subject	3	3
Adverse event, non-fatal	2	2
Lost to follow-up	1	2

Baseline characteristics

Reporting groups

Reporting group title	Zoledronic acid
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Reporting group description:

Subjects were peripherally intravenously (i.v.) infused with doses of zoledronic acid based on age and body weight. Subjects aged from 1 to <3 years received 0.025 milligram (mg)/kilogram (kg) diluted in 50 milliliter (mL) of normal saline up to a maximum dose of at a frequency of 30 to 45 minute infusion every 3 months. Subjects aged from 3 to 17 years received 0.05 mg/kg diluted in 100 mL of normal saline up to a maximum of 4 mg at a frequency of 30 minute infusion every 3 months. All subjects were hospitalized for 48 hours at the first infusion of zoledronic acid and post-dose symptoms were assessed. A total of 4 infusions were received during the study treatment period.

Reporting group title	Pamidronate
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Reporting group description:

Subjects were peripherally i.v. infused with doses of pamidronate based on age and body weight. Subjects aged from 1 to <2 years received 0.5 mg/kg/day at frequency of 4 hour infusion on each of 3 successive days, every 2 months. Subjects aged 2 years received 0.75 mg/kg/day at a frequency of 4 hour infusion on each of 3 successive days, every 3 months. Subjects aged from 3 to 17 years received 1 mg/kg/day at a frequency of 4 hour infusion on each of 3 successive days, every 3 months. Subjects received a maximum daily dose of up to 60 mg.

Reporting group values	Zoledronic acid	Pamidronate	Total
Number of subjects	74	76	150
Age categorical			
150 patients were in the ITT group. The trial analysis was performed on intent to treat (ITT) population defined as all randomized subjects who had a least one post-baseline efficacy assessment.			
Units: Subjects			
Infants and toddlers (28 days-23 months)	1	1	2
Children (2-11 years)	49	55	104
Adolescents (12-17 years)	24	20	44
Age continuous			
150 patients were in the ITT group. The trial analysis was performed on intent to treat (ITT) population defined as all randomized subjects who had a least one post-baseline efficacy assessment.			
Units: years			
arithmetic mean	8.6	8.5	
standard deviation	± 4.25	± 4.2	-
Gender categorical			
150 patients were in the ITT group. The trial analysis was performed on intent to treat (ITT) population defined as all randomized subjects who had a least one post-baseline efficacy assessment.			
Units: Subjects			
Female	36	31	67
Male	38	45	83

End points

End points reporting groups

Reporting group title	Zoledronic acid
Reporting group description: Subjects were peripherally intravenously (i.v.) infused with doses of zoledronic acid based on age and body weight. Subjects aged from 1 to <3 years received 0.025 milligram (mg)/kilogram (kg) diluted in 50 milliliter (mL) of normal saline up to a maximum dose of at a frequency of 30 to 45 minute infusion every 3 months. Subjects aged from 3 to 17 years received 0.05 mg/kg diluted in 100 mL of normal saline up to a maximum of 4 mg at a frequency of 30 minute infusion every 3 months. All subjects were hospitalized for 48 hours at the first infusion of zoledronic acid and post-dose symptoms were assessed. A total of 4 infusions were received during the study treatment period.	
Reporting group title	Pamidronate
Reporting group description: Subjects were peripherally i.v. infused with doses of pamidronate based on age and body weight. Subjects aged from 1 to <2 years received 0.5 mg/kg/day at frequency of 4 hour infusion on each of 3 successive days, every 2 months. Subjects aged 2 years received 0.75 mg/kg/day at a frequency of 4 hour infusion on each of 3 successive days, every 3 months. Subjects aged from 3 to 17 years received 1 mg/kg/day at a frequency of 4 hour infusion on each of 3 successive days, every 3 months. Subjects received a maximum daily dose of up to 60 mg.	

Primary: Percent change from baseline in lumbar spine bone mineral density (BMD) at Month 12

End point title	Percent change from baseline in lumbar spine bone mineral density (BMD) at Month 12
End point description: BMD was measured by dual energy x-ray absorptiometry (DEXA) at specified visits. The skeletal scanning sites was anteroposterior (AP) lumbar spine (L1-L4) in infant to ≤ 17 years of age. The analysis was performed on intent to treat (ITT) population defined as all randomized subjects who had at least one post-baseline efficacy assessment. The missing values were imputed using the last post-baseline observation carried forward (LOCF) approach.	
End point type	Primary
End point timeframe: Baseline, Month 12	

End point values	Zoledronic acid	Pamidronate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	68		
Units: Percentage change				
number (not applicable)	42.71	34.65		

Statistical analyses

Statistical analysis title	Change in lumbar spine BMD at month 12
Comparison groups	Zoledronic acid v Pamidronate

Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	8.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	15.71
Variability estimate	Standard error of the mean

Secondary: Change from baseline in lumbar spine Z-score at Month 12

End point title	Change from baseline in lumbar spine Z-score at Month 12
End point description:	
Z-score was defined as the comparison of BMD in subjects with osteoporosis to a healthy subject of similar age and body size. It is the number of standard deviations of the BMD measurement above or below that of healthy subject. A Z-score above 2.0 was considered normal according to the International Society for Clinical Densitometry (ISCD). Positive values shows improvement. Subjects aged greater than or equal to 3 years were imaged on the Hologic equipment and subjects aged greater than or equal to 5 years were imaged on the Lunar equipment with validated normalized ranges. The analysis was performed on ITT population. The missing values were imputed using the LOCF approach.	
End point type	Secondary
End point timeframe:	
Baseline, Month 12	

End point values	Zoledronic acid	Pamidronate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	49		
Units: Gram (g)/Centimeter (cm)^2				
least squares mean (standard error)	1.57 (± 0.13)	1.31 (± 0.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in femoral neck bone mineral content (BMC) at Month 6 and 12

End point title	Change from baseline in femoral neck bone mineral content (BMC) at Month 6 and 12
End point description:	
Femoral neck BMD was measured by DEXA, using skeletal scanning in infant to subjects aged ≤17 years. The analysis was performed on ITT population. The missing values were imputed using the last post-baseline observation carried forward (LOCF).	
End point type	Secondary

End point timeframe:
Baseline, Month 6, Month 12

End point values	Zoledronic acid	Pamidronate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	45		
Units: Gram (g)				
least squares mean (standard error)				
Month 6	0.31 (\pm 0.04)	0.26 (\pm 0.04)		
Month 12	0.47 (\pm 0.04)	0.4 (\pm 0.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of clinical fractures during 12 Months

End point title	Number of clinical fractures during 12 Months
End point description: Subjects were evaluated for any new fractures over an year using X-ray technique. The analysis was performed on ITT population. The missing values were imputed using the LOCF approach.	
End point type	Secondary
End point timeframe: Day 1 to Month 12	

End point values	Zoledronic acid	Pamidronate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	67		
Units: Number of clinical fractures				
arithmetic mean (standard deviation)	1.04 (\pm 3)	0.67 (\pm 1.21)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in serum C-terminal telopeptide of type I collagen (CTx) at Month 6 and Month 12

End point title	Percent change from baseline in serum C-terminal telopeptide of type I collagen (CTx) at Month 6 and Month 12
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End point description:

C-terminal telopeptide of type I collagen (CTx) was bone resorption biomarker measured in subjects aged ≥ 3 years. Percent change from baseline was measured as $100 \times (\text{endpoint} - \text{baseline}) / \text{baseline}$. Negative change indicated improvement in bone resorption. The analysis was performed on ITT

population. Here 'n' signifies number of subjects evaluated for C-telopeptide at the specified time-points.

End point type	Secondary
End point timeframe:	
Baseline, Month 6, Month 12	

End point values	Zoledronic acid	Pamidronate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: Nanogram (ng)/ milliliter (mL)				
arithmetic mean (standard deviation)				
Month 6 (n=44,49)	-34.288 (± 19.199)	3.07 (± 79.661)		
Month 12 (n=40,49)	-34.228 (± 20.775)	9.377 (± 99.581)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in N-terminal propeptide of type I collagen (P1NP) at Month 6 and Month 12

End point title	Percent change from baseline in N-terminal propeptide of type I collagen (P1NP) at Month 6 and Month 12
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End point description:

P1NP was the bone formation biomarker in serum measured in subjects aged ≥3 years. Percent change from baseline was measured as 100*(Month 6 or 12 - baseline)/baseline values. Negative change indicated improvement in bone formation. The analysis was performed on ITT population. Here, 'n' signifies number of subjects evaluated for P1NP at Month 6 and 12.

End point type	Secondary
End point timeframe:	
Baseline, Month 6, Month 12	

End point values	Zoledronic acid	Pamidronate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: ng/mL				
arithmetic mean (standard deviation)				
Month 6 (n=44,48)	-36.809 (± 26.137)	-21.958 (± 26.693)		
Month 12 (n= 40, 50)	-45.59 (± 21.302)	-27.703 (± 34.907)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in bone specific alkaline phosphatase (BALP) at Month 6 and Month 12

End point title	Percent change from baseline in bone specific alkaline phosphatase (BALP) at Month 6 and Month 12
End point description: BALP was the bone formation biomarker in serum measured in subjects aged ≥ 3 years. Percent change from baseline was measured as $100 \times (\text{Month 6 or 12} - \text{baseline}) / \text{baseline values}$. Negative change indicated improvement in bone formation. The analysis was performed on ITT population. Here, 'n' signifies number of subjects evaluated for BALP at Month 6 and 12.	
End point type	Secondary
End point timeframe: Baseline, Month 6, Month 12	

End point values	Zoledronic acid	Pamidronate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: ng/mL				
arithmetic mean (standard deviation)				
Month 6 (n=44,49)	-25.387 (\pm 27.118)	-19.687 (\pm 22.468)		
Month 12 (n= 40, 50)	-34.77 (\pm 20.821)	-26.849 (\pm 25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in supine height at Month 6 and Month 12

End point title	Change from baseline in supine height at Month 6 and Month 12
End point description: Supine height was measured using a stadiometer. Average of two height measurements were taken in millimeters (mm). If the two measurements differed by greater than 4 mm then two additional measurements were recorded and the average of the four height measurements was used for the analysis. The effect of zoledronic acid on the change in supine length was compared to pamidronate in children aged ≥ 1 year to ≤ 17 years. The analysis was performed on ITT population.	
End point type	Secondary
End point timeframe: Baseline, Month 6, Month 12	

End point values	Zoledronic acid	Pamidronate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	74		
Units: Centimeter				
arithmetic mean (standard deviation)				
Month 6	3.26 (± 3.06)	4.108 (± 7.18)		
Month 12	6.041 (± 5.264)	6.527 (± 7.009)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with bone pain scores at Month 6 and Month 12

End point title	Number of subjects with bone pain scores at Month 6 and Month 12
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End point description:

Bone pain in pediatric was assessed by using Wong-Baker FACES Pain Rating questionnaires. The questionnaires included a face scale of six categories (faces) based on pain intensity rating from "No Hurt" to "Hurts Worst". Face scale was rated as: Face 0 - very happy because no pain at all; Face 1 - hurts just a little bit; Face 2 - hurts a little more; Face 3 - hurts even more; Face 4 - hurts a whole lot; Face 5 - hurts as much as can be imagined, although you don't have to be crying to feel this bad. The analysis was performed on ITT population.

End point type	Secondary
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End point timeframe:

Baseline, Month 6, Month 12

End point values	Zoledronic acid	Pamidronate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: Subjects				
Month 6 (No hurt)	52	55		
Month 6 (Hurts little bit)	13	12		
Month 6 (Hurts little more)	5	1		
Month 6 (Hurts even more)	0	0		
Month 6 (Hurts whole lot)	0	1		
Month 6 (Hurts worst)	0	1		
Month 6 (Missing)	4	6		
Month 12 (No hurt)	54	49		
Month 12 (Hurts little bit)	7	7		
Month 12 (Hurts little more)	0	5		
Month 12 (Hurts even more)	2	2		
Month 12 (Hurts whole lot)	0	1		
Month 12 (Hurts worst)	0	0		
Month 12 (Missing)	11	12		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first fracture during 12 Months

End point title	Time to first fracture during 12 Months
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End point description:

Subjects were evaluated for time to first fracture after infusion of the treatment drug. Subjects with no fractures were reported and censored at day 365 or the last visit, whichever was earlier and the fractures occurred after 365 days were truncated at Day 365. The analysis was performed on ITT population. Here, '99999' in median and confidence interval represents the non-estimable data.

End point type	Secondary
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End point timeframe:

Day 1 to Month 12

End point values	Zoledronic acid	Pamidronate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: Days				
median (confidence interval 95%)	99999 (334 to 99999)	99999 (326 to 99999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events are monitored from date of First Subject First Visit (FSFV) until Last Subject Last Visit (LSLV). All other adverse events are monitored from First Subject First Treatment until LSLV.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	10.0
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Reporting groups

Reporting group title	Zoledronic Acid
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Reporting group description:

Subjects were peripherally i.v. infused with doses of zoledronic acid based on age and body weight. Subjects aged from 1 to <3 years received 0.025 mg/kg diluted in 50 mL of normal saline up to a maximum dose of at a frequency of 30 to 45 minute infusion every 3 months. Subjects aged from 3 to 17 years received 0.05 mg/kg diluted in 100 mL of normal saline up to a maximum of 4 mg at a frequency of 30 minute infusion every 3 months.

Reporting group title	Pamidronate
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Reporting group description:

Subjects were peripherally i.v. infused with doses of pamidronate based on age and body weight. Subjects aged from 1 to <2 years received 0.5 mg/kg/day at frequency of 4 hour infusion on each of 3 successive days, every 2 months. Subjects aged 2 years received 0.75 mg/kg/day at a frequency of 4 hour infusion on each of 3 successive days, every 3 months. Subjects aged from 3 to 17 years received 1 mg/kg/day at a frequency of 4 hour infusion on each of 3 successive days, every 3 months. Subjects received a maximum daily dose of up to 60 mg.

Serious adverse events	Zoledronic Acid	Pamidronate	
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 74 (32.43%)	15 / 78 (19.23%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood calcium decreased			
subjects affected / exposed	1 / 74 (1.35%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 74 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			

subjects affected / exposed	1 / 74 (1.35%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	10 / 74 (13.51%)	5 / 78 (6.41%)	
occurrences causally related to treatment / all	0 / 13	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture displacement			
subjects affected / exposed	0 / 74 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 74 (1.35%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	2 / 74 (2.70%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site haematoma			
subjects affected / exposed	1 / 74 (1.35%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 74 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 74 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device complication			

subjects affected / exposed	1 / 74 (1.35%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle strain			
subjects affected / exposed	0 / 74 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 74 (1.35%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			
subjects affected / exposed	2 / 74 (2.70%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 74 (1.35%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 74 (1.35%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	1 / 74 (1.35%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 74 (1.35%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vasculitis			

subjects affected / exposed	0 / 74 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral disorder			
subjects affected / exposed	0 / 74 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 74 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	0 / 74 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 74 (1.35%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 74 (2.70%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 74 (1.35%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	1 / 74 (1.35%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 74 (1.35%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint instability			
subjects affected / exposed	0 / 74 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint range of motion decreased			
subjects affected / exposed	0 / 74 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint swelling			
subjects affected / exposed	0 / 74 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb deformity			
subjects affected / exposed	1 / 74 (1.35%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 74 (1.35%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudarthrosis			

subjects affected / exposed	1 / 74 (1.35%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb deformity			
subjects affected / exposed	1 / 74 (1.35%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	1 / 74 (1.35%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	6 / 74 (8.11%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Zoledronic Acid	Pamidronate	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 74 (91.89%)	72 / 78 (92.31%)	
Investigations			
Blood calcium decreased			
subjects affected / exposed	2 / 74 (2.70%)	5 / 78 (6.41%)	
occurrences (all)	3	8	
Body temperature increased			
subjects affected / exposed	5 / 74 (6.76%)	1 / 78 (1.28%)	
occurrences (all)	5	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 74 (2.70%)	4 / 78 (5.13%)	
occurrences (all)	3	4	
Fall			
subjects affected / exposed	2 / 74 (2.70%)	5 / 78 (6.41%)	
occurrences (all)	4	8	
Femur fracture			
subjects affected / exposed	9 / 74 (12.16%)	4 / 78 (5.13%)	
occurrences (all)	14	6	
Fibula fracture			
subjects affected / exposed	4 / 74 (5.41%)	1 / 78 (1.28%)	
occurrences (all)	4	1	
Foot fracture			
subjects affected / exposed	2 / 74 (2.70%)	5 / 78 (6.41%)	
occurrences (all)	2	5	
Hand fracture			
subjects affected / exposed	6 / 74 (8.11%)	2 / 78 (2.56%)	
occurrences (all)	6	3	
Humerus fracture			
subjects affected / exposed	1 / 74 (1.35%)	6 / 78 (7.69%)	
occurrences (all)	1	7	
Limb injury			
subjects affected / exposed	0 / 74 (0.00%)	4 / 78 (5.13%)	
occurrences (all)	0	4	
Tibia fracture			

subjects affected / exposed occurrences (all)	9 / 74 (12.16%) 9	3 / 78 (3.85%) 5	
Upper limb fracture subjects affected / exposed occurrences (all)	1 / 74 (1.35%) 1	5 / 78 (6.41%) 5	
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	6 / 74 (8.11%) 6	4 / 78 (5.13%) 4	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	4 / 74 (5.41%) 4	3 / 78 (3.85%) 3	
Headache subjects affected / exposed occurrences (all)	16 / 74 (21.62%) 24	15 / 78 (19.23%) 20	
General disorders and administration site conditions Acute phase reaction subjects affected / exposed occurrences (all)	4 / 74 (5.41%) 4	5 / 78 (6.41%) 5	
Chills subjects affected / exposed occurrences (all)	1 / 74 (1.35%) 1	4 / 78 (5.13%) 4	
Fatigue subjects affected / exposed occurrences (all)	11 / 74 (14.86%) 12	6 / 78 (7.69%) 6	
Influenza like illness subjects affected / exposed occurrences (all)	2 / 74 (2.70%) 2	5 / 78 (6.41%) 5	
Infusion site pain subjects affected / exposed occurrences (all)	0 / 74 (0.00%) 0	7 / 78 (8.97%) 10	
Pain subjects affected / exposed occurrences (all)	5 / 74 (6.76%) 5	8 / 78 (10.26%) 10	
Pyrexia			

subjects affected / exposed occurrences (all)	43 / 74 (58.11%) 52	42 / 78 (53.85%) 56	
Gastrointestinal disorders			
Abdominal pain upper subjects affected / exposed occurrences (all)	8 / 74 (10.81%) 10	4 / 78 (5.13%) 4	
Diarrhoea subjects affected / exposed occurrences (all)	5 / 74 (6.76%) 6	5 / 78 (6.41%) 5	
Nausea subjects affected / exposed occurrences (all)	9 / 74 (12.16%) 11	10 / 78 (12.82%) 15	
Vomiting subjects affected / exposed occurrences (all)	21 / 74 (28.38%) 22	12 / 78 (15.38%) 13	
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	5 / 74 (6.76%) 7	4 / 78 (5.13%) 5	
Epistaxis subjects affected / exposed occurrences (all)	3 / 74 (4.05%) 4	5 / 78 (6.41%) 5	
Nasal congestion subjects affected / exposed occurrences (all)	3 / 74 (4.05%) 3	4 / 78 (5.13%) 5	
Pharyngolaryngeal pain subjects affected / exposed occurrences (all)	2 / 74 (2.70%) 2	4 / 78 (5.13%) 5	
Skin and subcutaneous tissue disorders			
Rash subjects affected / exposed occurrences (all)	4 / 74 (5.41%) 5	4 / 78 (5.13%) 4	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	19 / 74 (25.68%) 28	17 / 78 (21.79%) 23	

Back pain			
subjects affected / exposed	14 / 74 (18.92%)	14 / 78 (17.95%)	
occurrences (all)	15	15	
Bone pain			
subjects affected / exposed	12 / 74 (16.22%)	4 / 78 (5.13%)	
occurrences (all)	20	6	
Muscle spasms			
subjects affected / exposed	4 / 74 (5.41%)	1 / 78 (1.28%)	
occurrences (all)	4	3	
Musculoskeletal chest pain			
subjects affected / exposed	6 / 74 (8.11%)	2 / 78 (2.56%)	
occurrences (all)	10	2	
Musculoskeletal pain			
subjects affected / exposed	9 / 74 (12.16%)	3 / 78 (3.85%)	
occurrences (all)	15	4	
Neck pain			
subjects affected / exposed	2 / 74 (2.70%)	4 / 78 (5.13%)	
occurrences (all)	2	4	
Pain in extremity			
subjects affected / exposed	21 / 74 (28.38%)	19 / 78 (24.36%)	
occurrences (all)	35	30	
Scoliosis			
subjects affected / exposed	2 / 74 (2.70%)	5 / 78 (6.41%)	
occurrences (all)	2	5	
Infections and infestations			
Ear infection			
subjects affected / exposed	4 / 74 (5.41%)	4 / 78 (5.13%)	
occurrences (all)	5	5	
Influenza			
subjects affected / exposed	8 / 74 (10.81%)	2 / 78 (2.56%)	
occurrences (all)	10	2	
Nasopharyngitis			
subjects affected / exposed	12 / 74 (16.22%)	9 / 78 (11.54%)	
occurrences (all)	16	13	
Otitis media			

subjects affected / exposed	4 / 74 (5.41%)	1 / 78 (1.28%)	
occurrences (all)	5	1	
Pharyngitis			
subjects affected / exposed	2 / 74 (2.70%)	4 / 78 (5.13%)	
occurrences (all)	3	5	
Pharyngitis streptococcal			
subjects affected / exposed	4 / 74 (5.41%)	4 / 78 (5.13%)	
occurrences (all)	5	4	
Sinusitis			
subjects affected / exposed	5 / 74 (6.76%)	0 / 78 (0.00%)	
occurrences (all)	6	0	
Upper respiratory tract infection			
subjects affected / exposed	6 / 74 (8.11%)	7 / 78 (8.97%)	
occurrences (all)	8	11	
Urinary tract infection			
subjects affected / exposed	4 / 74 (5.41%)	1 / 78 (1.28%)	
occurrences (all)	5	1	
Viral infection			
subjects affected / exposed	3 / 74 (4.05%)	4 / 78 (5.13%)	
occurrences (all)	4	4	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	5 / 74 (6.76%)	8 / 78 (10.26%)	
occurrences (all)	7	8	
Hypocalcaemia			
subjects affected / exposed	11 / 74 (14.86%)	7 / 78 (8.97%)	
occurrences (all)	11	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 February 2003	The amendment was issued 4 months before the first subject first visit. The amendment complied with an Food and Drug Administration (FDA) written request requiring the inclusion of children in the 1-3 year age group. Safety related changes were also added as per the suggestion of the Data Safety Monitoring Board (DSMB) concerning definitions and tests for renal abnormalities. The amendment also added six infants, 3 to 11 months of age, to be treated with zoledronic acid at (a) pre-designated site(s). Nine infants were screened, but none met the inclusion/exclusion criteria.
02 February 2004	The amendment was issued after data were reviewed for the first 36 subjects enrolled in the study. The amendment included change in the conduct of the study based on the recommendations of the DSMB. The amendment included: <ul style="list-style-type: none">• The ionized calcium assessments and required hospitalisations for subjects were amended to reflect the standard of treatment.• A re-test for the pathologic proteinuria exclusion criterion was allowed.• Approval was granted for enrollment of subjects aged 1 to 3 years at all study sites. Subjects aged 3 to 11 months were to be enrolled at a pre-designated site.• For subjects less than 3 years old randomized to zoledronic acid treatment, 5 mg/100 mL plastic vials (rather than 5 mg/5 mL vials) were used to ensure greater accuracy for these subjects who were to receive smaller doses of zoledronic acid.
19 January 2006	The amendment included: <ul style="list-style-type: none">• The lower age entry criterion for infants was removed and upper limit increased to 12 months (from 11 months).• An exclusion criterion for urine protein/creatinine ratio of >0.4 for infants was added.• The urine sample collected for urine protein/creatinine ratio assessment was to be a first morning void.• The number of subjects randomized was increased to approximately 154 subjects to evaluate all primary endpoints.
31 January 2007	The amendment was to clarify and implement the DSMB recommendations, when they reviewed un-blinded efficacy and safety data. Subjects with type I OI, regardless of study drug assignment received no further study drug due to an observed increased incidence of femur fracture, while all other subjects (type III or IV OI) continued to receive their assigned study drug.

Notes:

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.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> complete trial results.

Notes:

