Clinical trial results:
A multicenter, randomized, double-blind, placebo controlled efficacy and safety trial of intravenous zoledronic acid twice yearly compared to placebo in osteoporotic children treated with glucocorticoids.

Summary

EudraCT number	2008-001252-52
Trial protocol	GB FI BE DE PL Outside EU/EEA HU IT
Global end of trial date	05 March 2018

Results information

Result version number	v2 (current)
This version publication date	30 March 2019
First version publication date	20 September 2018
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	CZOL446H2337

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00799266
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, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000057-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	05 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 March 2018
Global end of trial reached?	Yes
Global end of trial date	05 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate that 0.05 mg/kg (max 5 mg) zoledronic acid administered every 6 months was superior to placebo for the change in lumbar spine bone mineral density (BMD) Z-score at Month 12 relative to baseline.

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	04 December 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Russian Federation: 2
Country: Number of subjects enrolled	South Africa: 3
Country: Number of subjects enrolled	United Kingdom: 3
Worldwide total number of subjects	34
EEA total number of subjects	5

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)	12
Adolescents (12-17 years)	22
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 in 12 centers in 6 countries: Australia (1), Canada (5), Hungary (1), United Kingdom (2), Russian Federation (2), and South Africa (1).

Pre-assignment

Screening details:

The Participant Flow and Baseline Characteristics were done on the Intention-to-treat (ITT) population. All efficacy analyses were done on the Modified Intention-to-treat (MITT) population and all safety analyses were based on Safety population.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Zoledronic acid

Arm description:

Twice yearly 0.05 mg/kg (max 5 mg) i.v infusion (at least 30 minutes) of zoledronic acid

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

Dosage and administration details:

Twice yearly 0.05 mg/kg (max 5 mg) i.v infusion (at least 30 minutes) of zoledronic acid

Arm title	Placebo

Arm description:

Twice yearly i.v of infusion of Placebo (similar dosing as active drug)

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in administration system
Routes of administration	Intravenous use

Dosage and administration details:

Twice yearly i.v of infusion of Placebo (similar dosing as active drug)

Number of subjects in period 1	Zoledronic acid	Placebo
Started	18	16
Modified Intention-to-treat (MITT)	17	16
Safety Set	18	16
Completed	15	15
Not completed	3	1
Subject withdrew consent	3	-
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Zoledronic acid
Reporting group description:	
Twice yearly 0.05 mg/kg (max 5 mg) i.v infusion (at least 30 minutes) of zoledronic acid	
Reporting group title	Placebo
Reporting group description:	
Twice yearly i.v of infusion of Placebo (similar dosing as active drug)	

Reporting group values	Zoledronic acid	Placebo	Total
Number of subjects	18	16	34
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	5	7	12
Adolescents (12-17 years)	13	9	22
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	13.0	12.3	
standard deviation	± 3.50	± 3.42	-
Sex: Female, Male Units: Subjects			
Female	6	5	11
Male	12	11	23
Race/Ethnicity, Customized Units: Subjects			
Caucasian	13	14	27
Black	2	1	3
Asian	2	0	2
Native American	1	1	2
Pacific Islander	0	0	0
Othe	0	0	0
Lumbar Spine Bone Mineral Density (BMD) Z-score			
Lumbar Spine Bone Mineral Density (BMD) Z-score in the Modified Intention-to-treat (MITT) population. No imputation done at Baseline.			
Units: Z-score			
arithmetic mean	-2.127	-2.379	
standard deviation	± 0.7863	± 0.8975	-
Lumbar Spine Bone Mineral Content (BMC)			

Lumbar Spine Bone Mineral Content (BMC) in the Modified Intention-to-treat (MITT) population. No imputation done at Baseline.			
Units: gram (g)			
arithmetic mean	31.886	22.605	
standard deviation	± 15.1062	± 6.6054	-
Total body Bone Mineral Content (BMC)			
Total body Bone Mineral Content (BMC) in the Modified Intention-to-treat (MITT) population. No imputation done at Baseline.			
Units: gram (g)			
arithmetic mean	1550.556	1050.610	
standard deviation	± 592.0670	± 253.0759	-
Serum Procollagen type 1 amino-terminal propeptide (P1NP)			
Serum Procollagen type 1 amino-terminal propeptide (P1NP) in the Modified Intention-to-treat (MITT) population. No imputation done at Baseline.			
Units: nanogram per milliliter (ng/mL)			
arithmetic mean	313.54	368.90	
standard deviation	± 284.541	± 235.226	-
Serum Bone specific alkaline phosphatase (BSAP)			
Serum Bone specific alkaline phosphatase (BSAP) in the Modified Intention-to-treat (MITT) population. No imputation done at Baseline.			
Units: nanogram per milliliter (ng/mL)			
arithmetic mean	31.559	43.414	
standard deviation	± 22.6619	± 32.8200	-
Serum Cross linked N-telopeptide (NTX)			
Serum Cross linked N-telopeptide (NTX) in the Modified Intention-to-treat (MITT) population. No imputation done at Baseline.			
Units: nmol BCE/L			
arithmetic mean	34.359	39.192	
standard deviation	± 22.0490	± 14.5823	-
Serum Tartrate-resistant acid phosphatase isoform 5b (TRAP-5b)			
Serum Tartrate-resistant acid phosphatase isoform 5b (TRAP-5b) in the Modified Intention-to-treat (MITT) population. No imputation done at Baseline.			
Units: U/L			
arithmetic mean	7.010	8.595	
standard deviation	± 2.9998	± 4.5650	-
Vertebral Morphometry (mid-to-posterior height ratio)			
Vertebral Morphometry (mid-to-posterior height ratio) in the Modified Intention-to-treat (MITT) population. Calculation was done using average ratio between mid-height and posterior height from L1 to L4 and analysis of covariance model was used with treatment, pooled centers, underlying condition treated with glucocordicoids and baseline value as explanatory variables and pooled centers as random effect.			
Units: mid-to-posterior height ratio			
arithmetic mean	0.982	0.976	
standard deviation	± 0.0428	± 0.0788	-
Second metacarpal cortical width			
Second metacarpal cortical width in the Modified Intention-to-treat (MITT) population. Metacarpal cortical width of "0" was not included. An analysis of covariance model used with treatment, pooled centers, underlying condition treated with glucocorticoids at baseline value as explanatory variables and pooled centers as random effect.			
Units: millimeter (mm)			
arithmetic mean	0.40	0.41	
standard deviation	± 0.194	± 0.144	-

End points

End points reporting groups	
Reporting group title	Zoledronic acid
Reporting group description:	
Twice yearly 0.05 mg/kg (max 5 mg) i.v infusion (at least 30 minutes) of zoledronic acid	
Reporting group title	Placebo
Reporting group description:	
Twice yearly i.v of infusion of Placebo (similar dosing as active drug)	

Primary: Mean Change from Baseline in Lumbar Spine Bone Mineral Density (BMD) Z-score at Month 12

End point title	Mean Change from Baseline in Lumbar Spine Bone Mineral Density (BMD) Z-score at Month 12
End point description:	
Lumbar Spine Bone Mineral Density (BMD) Z-score was determined by the central imaging vendor before first treatment and at Month 12. The methods to be used to measure Lumbar Spine BMD Z-score were described in the respective DXA Manuals provided by central imaging vendor. Positive changes from baseline indicated an improvement in condition.	
End point type	Primary
End point timeframe:	
Month 12	

End point values	Zoledronic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	16		
Units: Z-score				
least squares mean (standard error)	0.582 (± 0.1279)	0.168 (± 0.1449)		

Statistical analyses

Statistical analysis title	Lumbar Spine BMD Z-score at Month 12
Comparison groups	Placebo v Zoledronic acid
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0392
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	0.414

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.022
upper limit	0.806

Secondary: Mean Change from Baseline in Lumbar Spine Bone Mineral Density (BMD) Z-score at Month 6

End point title	Mean Change from Baseline in Lumbar Spine Bone Mineral Density (BMD) Z-score at Month 6

End point description:

Lumbar Spine Bone Mineral Density (BMD) Z-score was determined by the central imaging vendor before first treatment and at Month 6. The methods to be used to measure Lumbar Spine BMD Z-score were described in the respective DXA Manuals provided by central imaging vendor. Positive changes from baseline indicated an improvement in condition.

End point type	Secondary

End point timeframe:

Month 6

End point values	Zoledronic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	16		
Units: Z-score				
least squares mean (standard error)	0.447 (± 0.13)	0.157 (± 0.14)		

Statistical analyses

Statistical analysis title	Lumbar Spine BMD Z-score at Month 6
Comparison groups	Zoledronic acid v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1322
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.094
upper limit	0.673

Secondary: Mean Change from Baseline in Lumbar Spine BMC at Month 6 and 12	
End point title	Mean Change from Baseline in Lumbar Spine BMC at Month 6 and 12
End point description:	
Lumbar Spine BMC was determined by the central imaging vendor before first treatment and at Months 6 and 12. The methods to be used to measure BMC were described in the respective DXA Manuals.	
End point type	Secondary
End point timeframe:	
Month 6, Month 12	

End point values	Zoledronic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	16		
Units: gram (g)				
least squares mean (standard error)				
Lumbar Spine (LS) BMC Change at Month 6	4.110 (± 0.63)	2.131 (± 0.70)		
Lumbar Spine (LS) BMC Change at Month 12	6.450 (± 1.18)	4.295 (± 1.32)		

Statistical analyses

Statistical analysis title	Lumbar Spine BMC at Month 6
Comparison groups	Zoledronic acid v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0409
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	1.979
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.089
upper limit	3.869

Statistical analysis title	Lumbar Spine BMC at Month 12
Comparison groups	Zoledronic acid v Placebo

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.234
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	2.155
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.488
upper limit	5.798

Secondary: Mean Change from Baseline in total body BMC at Month 6 and 12

End point title	Mean Change from Baseline in total body BMC at Month 6 and 12

End point description:

Total body BMC was all determined by the central imaging vendor before first treatment and at Months 6 and 12. The methods to be used to measure BMC were described in the respective DXA Manuals.

End point type	Secondary

End point timeframe:

Month 6, Month 12

End point values	Zoledronic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	16		
Units: gram (g)				
least squares mean (standard error)				
Total BMC Change at Month 6	129.272 (± 24.23)	95.214 (± 28.74)		
Total BMC Change at Month 12	220.805 (± 42.74)	140.064 (± 51.90)		

Statistical analyses

Statistical analysis title	Total Body BMC at Month 6
Comparison groups	Zoledronic acid v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3827
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	34.058

Confidence interval	
level	95 %
sides	2-sided
lower limit	-45.385
upper limit	113.502

Statistical analysis title	Total Body BMC at Month 12
Comparison groups	Zoledronic acid v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2634
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	80.741
Confidence interval	
level	95 %
sides	2-sided
lower limit	-65.602
upper limit	227.084

Secondary: Mean Change from Baseline in Serum P1NP at Months 6 and 12	
End point title	Mean Change from Baseline in Serum P1NP at Months 6 and 12
End point description:	
Serum Procollagen type 1 amino-terminal propeptide (P1NP) was collected before first treatment (baseline) and at Months 6 and Month 12 according to the instructions provided in the Laboratory Manual. The samples were analyzed in batches at the laboratory.	
End point type	Secondary
End point timeframe:	
Month 6, Month 12	

End point values	Zoledronic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	16		
Units: nanogram per milliliter (ng/mL)				
least squares mean (standard error)				
P1NP Change at Month 6	-134.285 (± 48.80)	77.497 (± 56.15)		
P1NP Change at Month 12	-230.966 (± 59.1977)	150.166 (± 68.0933)		

Statistical analyses

Statistical analysis title	Serum P1NP at Month 6
Comparison groups	Zoledronic acid v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0631
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-211.782
Confidence interval	
level	95 %
sides	2-sided
lower limit	-363.765
upper limit	-59.8

Statistical analysis title	Serum P1NP at Month 12
Comparison groups	Zoledronic acid v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0049
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-381.132
Confidence interval	
level	95 %
sides	2-sided
lower limit	-565.416
upper limit	-196.848

Secondary: Mean Change from Baseline in BSAP at Months 6 and 12

End point title	Mean Change from Baseline in BSAP at Months 6 and 12

End point description:

Bone specific alkaline phosphatase (BSAP) were collected before first treatment (baseline) and at Months 6 and Month 12 according to the instructions provided in the Laboratory Manual. The samples were analyzed in batches at the laboratory.

End point type	Secondary

End point timeframe:

Month 6, Month 12

End point values	Zoledronic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	16		
Units: nanogram per milliliter (ng/mL)				
least squares mean (standard error)				
BSAP Change at Month 6	-7.413 (± 3.63)	3.810 (± 4.05)		
BSAP Change at Month 12	-13.984 (± 4.3814)	6.450 (± 4.9010)		

Statistical analyses

Statistical analysis title	Serum BSAP at Month 6
Comparison groups	Zoledronic acid v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2129
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-11.223
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.595
upper limit	0.149

Statistical analysis title	Serum BSAP at Month 12
Comparison groups	Zoledronic acid v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0215
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-20.435
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.96
upper limit	-6.909

Secondary: Mean Change from Baseline in Serum NTX at Months 6 and 12	
End point title	Mean Change from Baseline in Serum NTX at Months 6 and 12

End point description:

Serum Cross linked N-telopeptide (NTX) were collected before first treatment (baseline) and at Months 6 and Month 12 according to the instructions provided in the Laboratory Manual. The samples were analyzed in batches at the laboratory.

End point type	Secondary

End point timeframe:

Month 6, Month 12

End point values	Zoledronic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	16		
Units: nmol BCE/L				
least squares mean (standard error)				
NTX Change at Month 6	-13.746 (± 4.23)	7.192 (± 4.74)		
NTX Change at Month 12	-20.134 (± 3.76)	7.440 (± 4.23)		

Statistical analyses

Statistical analysis title	Serum NTX at Month 6
Comparison groups	Zoledronic acid v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0254
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-20.938
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.766
upper limit	-8.11

Statistical analysis title	Serum NTX at Month 12
Comparison groups	Zoledronic acid v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0002
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-27.574

Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.037
upper limit	-16.111

Secondary: Mean Change from Baseline in Serum TRAP-5b at Months 6 and 12

End point title	Mean Change from Baseline in Serum TRAP-5b at Months 6 and 12

End point description:

Serum Tartrate-resistant acid phosphatase isoform 5b (TRAP 5b) was collected before first treatment (baseline) and at Months 6 and Month 12 according to the instructions provided in the Laboratory Manual. The samples were analyzed in batches at the laboratory.

End point type	Secondary

End point timeframe:

Month 6, Month 12

End point values	Zoledronic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	16		
Units: U/L				
least squares mean (standard error)				
TRAP 5b Change at Month 6	-1.561 (± 0.65)	0.313 (± 0.74)		
TRAP 5b Change at Month 12	-1.728 (± 0.73)	0.109 (± 0.81)		

Statistical analyses

Statistical analysis title	Serum TRAP-5b at Month 6
Comparison groups	Zoledronic acid v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2178
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-1.874
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.931
upper limit	0.182

Statistical analysis title	Serum TRAP-5b at Month 12
Comparison groups	Zoledronic acid v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.184
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-1.837
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.103
upper limit	0.429

Secondary: Mean Change from Baseline in Vertebral morphometry at Month 12	
End point title	Mean Change from Baseline in Vertebral morphometry at Month 12
End point description:	
Vertebral morphometry (or concave index) was calculated using the average ratio between mid-height and posterior height from L1 to L4 and performed by a central reader.	
End point type	Secondary
End point timeframe:	
Month 12	

End point values	Zoledronic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	16		
Units: Ratio				
least squares mean (standard error)	-0.018 (± 0.01)	-0.0003 (± 0.01)		

Statistical analyses

Statistical analysis title	Vertebral morphometry at Month 12
Comparison groups	Zoledronic acid v Placebo

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.318
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-0.018
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.055
upper limit	0.019

Secondary: Percentage of Patients with reduction in Pain at Months 3, 6, 9 and 12

End point title	Percentage of Patients with reduction in Pain at Months 3, 6, 9 and 12

End point description:

Pain was evaluated at each visit (in office and telephone visit) at randomization, Months 3, 6, 9 and 12 using the Faces Pain Scale-Revised (FPS-R). Children were selecting the face that best fits their pain. The pain score ranged from 0 (No Pain) to 10 (Very Much Pain). The reduction in pain from baseline by visit was evaluated based on whether or not patients had a decrease in their FPS-R from baseline. If pain remained the same or worsened from baseline a patient was classified as '0' and if the pain scale decreased then the patient was classified as '1'.

End point type	Secondary

End point timeframe:

Month 3, Month 6, Month 9 and Month 12

End point values	Zoledronic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	16		
Units: Percentage of Patients				
number (not applicable)				
Month 3	37.5	53.8		
Month 6	37.5	50.0		
Month 9	33.3	46.2		
Month 12	31.3	57.1		

Statistical analyses

Statistical analysis title	Reduction in Pain at Month 3
Comparison groups	Zoledronic acid v Placebo

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5226
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	5.2

Statistical analysis title	Reduction in Pain at Month 6
Comparison groups	Zoledronic acid v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.522 [1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	999.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	999.99

Notes:

[1] - >999.99 (<0.01, >999.99)

Statistical analysis title	Reduction in Pain at Month 9
Comparison groups	Zoledronic acid v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6019
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	6.22

Statistical analysis title	Reduction in Pain at Month 12

Comparison groups	Zoledronic acid v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9652 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.45
Confidence interval	
level	Other: 0.97 %
sides	2-sided
lower limit	0.01
upper limit	999.99

Notes:

[2] - 0.45 (<0.01, >999.99)

Secondary: Mean Change from Baseline in 2nd metacarpal cortical width at Month 12

End point title	Mean Change from Baseline in 2nd metacarpal cortical width at Month 12

End point description:

Left posteroanterior (PA) hand/wrist X-ray were taken at Visit 1 and at the Month 12 visit to assess bone age and the between-treatment differences for change in 2nd metacarpal cortical width at Month 12 relative to baseline. If a fracture of the left upper extremity precluded radiographic imaging, then the right hand was evaluated for this purpose. In this case, the right hand was be imaged at both Visit 1 and at Month 12. The information was used in the assessment of bone density.

End point type	Secondary

End point timeframe:

Month 12

End point values	Zoledronic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	16		
Units: millimeter (mm)				
least squares mean (standard error)	-0.01 (± 0.040)	0.03 (± 0.047)		

Statistical analyses

Statistical analysis title	2nd metacarpal cortical width at Month 12
Comparison groups	Zoledronic acid v Placebo

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5165
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.09

Secondary: Urinary concentration of zoledronic acid at Month 12

End point title	Urinary concentration of zoledronic acid at Month 12[3]

End point description:

Urine was collected overnight or for at least 4 waking hours from all patients able to provide specimens, to measure urinary concentration of zoledronic acid at Month 12. Only descriptive analysis done.

End point type	Secondary

End point timeframe:

Month 12

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Urinary concentration of Zoledronic acid is only collected/apllicable for treatment arm "Zoledronic Acid"

End point values	Zoledronic acid			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: ng/mL				
arithmetic mean (standard deviation)	1643.3 (± 2846.34)			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety of zoledronic acid for the treatment of osteoporotic children treated with glucocorticoids

End point title	Safety of zoledronic acid for the treatment of osteoporotic children treated with glucocorticoids

End point description:

Analysis of absolute and relative frequencies for treatment emergent Adverse Event (AE), Serious Adverse Event (SAE) and Deaths by primary System Organ Class (SOC) to demonstrate that zoledronic acid is safe for the treatment of osteoporotic children treated with glucocorticoids through the monitoring of relevant clinical and laboratory safety parameters. Only descriptive analysis done.

End point type	Secondary

End point timeframe:

Baseline through Month 12

End point values	Zoledronic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	16		
Units: Percentage of Participants				
number (not applicable)				
AEs by Primary System Organ Class (SOC)	83.3	75.0		
SAEs by Primary System Organ Class (SOC)	27.8	6.3		
Deaths by Primary System Organ Class (SOC)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with new vertebral fractures at Month 12

End point title	Number of participants with new vertebral fractures at Month 12

End point description:

New vertebral fractures were defined as fractures of Genant Grade 1 or higher that occurred at lumbar or thoracic spine from first dose infusion to the end of the study.

End point type	Secondary

End point timeframe:

Month 12

End point values	Zoledronic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	16		
Units: Participants	0	2		

Statistical analyses

Statistical analysis title	New vertebral fractures at Month 12
Comparison groups	Zoledronic acid v Placebo

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2258
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All AEs reported in this record are from date of First Patient First Treatment until Last Patient Last Visit) up to approximately 9 years

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Zoledronic acid

Reporting group description:

Zoledronic acid

Reporting group title	Placebo

Reporting group description:

Placebo

Serious adverse events	Zoledronic acid	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 18 (27.78%)	1 / 16 (6.25%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Weight decreased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			

subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Acute phase reaction			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (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	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	2 / 18 (11.11%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Clostridium difficile infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella zoster virus infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (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	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 18 (77.78%)	12 / 16 (75.00%)	

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Acute phase reaction			
subjects affected / exposed	2 / 18 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Chills			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	1 / 18 (5.56%)	2 / 16 (12.50%)	
occurrences (all)	1	2	
Pain			
subjects affected / exposed	3 / 18 (16.67%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
Pyrexia			
subjects affected / exposed	3 / 18 (16.67%)	1 / 16 (6.25%)	
occurrences (all)	5	2	
Thirst			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Food allergy			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Cough			

subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Obstructive airways disorder			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Sneezing			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Sleep talking			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood iron decreased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Transaminases increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Fracture			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Fracture displacement			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Joint dislocation			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Ligament sprain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Muscle strain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Skin abrasion			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Tooth fracture			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Tibia fracture			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Cardiac disorders			
Tachycardia			

subjects affected / exposed	3 / 18 (16.67%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Depressed level of consciousness			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	3 / 18 (16.67%)	1 / 16 (6.25%)	
occurrences (all)	3	1	
Lethargy			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Eye disorder			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Eye pruritus			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Lacrimation increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 18 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Abdominal pain upper			

subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Dental caries			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	2 / 18 (11.11%)	2 / 16 (12.50%)	
occurrences (all)	2	2	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	2 / 18 (11.11%)	2 / 16 (12.50%)	
occurrences (all)	2	2	
Tooth erosion			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	3 / 18 (16.67%)	1 / 16 (6.25%)	
occurrences (all)	4	1	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Keratosis pilaris			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Mechanical urticaria			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Adrenal insufficiency			

subjects affected / exposed	3 / 18 (16.67%)	0 / 16 (0.00%)	
occurrences (all)	4	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 18 (27.78%)	1 / 16 (6.25%)	
occurrences (all)	5	1	
Back pain			
subjects affected / exposed	4 / 18 (22.22%)	1 / 16 (6.25%)	
occurrences (all)	6	1	
Flank pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Limb discomfort			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal discomfort			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	2 / 18 (11.11%)	1 / 16 (6.25%)	
occurrences (all)	4	1	
Musculoskeletal pain			
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Pain in extremity			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Polyarthritis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Herpes zoster			

subjects affected / exposed	0 / 18 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Influenza			
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Localised infection			
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Nasopharyngitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Otitis media			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	2 / 18 (11.11%)	2 / 16 (12.50%)	
occurrences (all)	2	3	
Varicella zoster virus infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Hypocalcaemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Dehydration			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Vitamin B12 deficiency			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 July 2008	Amendment 1 clarified and amended the osteoporosis inclusion criteria including one or more low-trauma lower extremity long bone fractures and/or two or more low-trauma upper extremity long bone fractures. The following items were also amended to refine the protocol and further ensure patient safety: measuring bone-age at screening and Month 12; collecting pain assessment by FPS-R at baseline, Months 3, 6, 9 and 12; sitting height measured at baseline, Months 6 and 12 and implementing a DMC.
23 September 2008	Amendment 2 allowed patients to receive their first study drug infusion (Visit 2) in the out-patient setting at the clinical discretion of the study investigators. In addition, clarification was provided for the definition of "vitamin D and calcium supplementation" and "low trauma fracture".
15 July 2010	Amendment 3 updated the original Schwartz Formula to the updated Schwartz formula: GFR (mL/min/1.73 m2) = k [height (m)/Scr (mg/dl)] k = 0.41 Amendment 3 also incorporated changes, which only applied to the UK sites for the enrollment of female patients of childbearing potential. These changes incorporated additional information on theoretical risks to a developing fetus in the pregnancy section and an additional supervised urine pregnancy test at Week 12.
16 August 2013	Amendment 4 extended the study population to include patients with GIO associated with underlying conditions other than chronic inflammatory disorders, relaxed the lumbar spine BMD Z-score inclusion criteria from -1.0 to -0.5 or worse, and included an assessment of zoledronic acid urine concentrations 6 months after dosing.
26 October 2015	Amendment 5 (based on Health Authority request) provided a risk/benefit statement previously included in the introduction section and then presented in a separate section in the protocol and allowed more countries to apply the contraceptive wording originally provided for UK sites only.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported