EU Clinical Trials Register

Clinical trial results:
A 1-year, multicenter, open-label, extension to CZOL446H2337 to evaluate safety and efficacy of zoledronic acid twice yearly in osteoporotic children treated with glucocorticoids

Summary

EudraCT number	2010-020399-41
Trial protocol	GB HU
Global end of trial date	27 February 2019

Results information

Result version number	v1 (current)
This version publication date	04 September 2019
First version publication date	04 September 2019

Trial information

Trial identification

Sponsor protocol code	CZOL446H2337E1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01197300
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)	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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 February 2019
Global end of trial reached?	Yes
Global end of trial date	27 February 2019
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 zoledronic acid given long-term, over an additional 12 months from the Core study (CZOL446H2337), was safe for the treatment of osteoporotic children treated with glucocorticoids (GCs).

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	25 October 2010
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	Australia: 4
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Russian Federation: 2
Country: Number of subjects enrolled	South Africa: 3
Worldwide total number of subjects	25
EEA total number of subjects	3

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)	8
Adolescents (12-17 years)	17
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 10 centers in 6 countries: Australia (1), Canada (4), Hungary (1), United Kingdom (1), Russian Federation (2), and South Africa (1).

Pre-assignment

Screening details:

This was an open label extension to the Core study CZOL446H2337 (NCT00799266), where all patients received zoledronic acid. However, the study groups from the Core study were used to compare the patient populations within this extension phase, who received the same treatment under each particular group during the duration of core study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Core treatment 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	Core treatment: Placebo

Arm description:

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

Arm type	Placebo
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

Number of subjects in period 1	Core treatment Zoledronic acid	Core treatment: Placebo
Started	10	15
Completed	10	13
Not completed	0	2
Protocol deviation	-	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups

Reporting group title	Core treatment 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	Core treatment: Placebo
Reporting group description:	
Twice yearly 0.05 mg/kg (max 5 mg) i.v infusion (at least 30 minutes) of zoledronic acid	

Reporting group values	Core treatment Zoledronic acid	Core treatment: Placebo	Total
Number of subjects	10	15	25
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)	1	7	8
Adolescents (12-17 years)	9	8	17
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Age at extension informed consent			
Units: Years			
arithmetic mean	15.3	13.2	
standard deviation	± 2.58	± 3.38	-
Sex: Female, Male			
Units: Subjects			
Female	3	5	8
Male	7	10	17
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	8	13	21
Black	2	1	3
Native American	0	1	1
Lumbar Spine Bone Mineral Density (BMD) Z-score			
Lumbar Spine Bone Mineral Density (BMD) Z-score in the Full Analysis (FAS) population. Extension baseline was defined as the last non-missing measurement on or prior to the date of first study drug infusion in the extension study. Bone mass, as measured by DXA, is reported as BMC (g) or areal BMD (g/cm2). These values are compared with reference values from healthy youth of similar age, sex, and race/ ethnicity to calculate a z score, the number of SDs from the expected mean. A BMC or BMD z score that is >2 SDs below expected (< −2.0) is referred to as "low for age".			
Units: Z-score			
arithmetic mean	-1.568	-2.291	
standard deviation	± 1.0196	± 1.0712	-
Lumbar Spine Bone Mineral Content			

(BMC)			
Lumbar Spine Bone Mineral Content (BMC) in the Full Analysis (FAS) population. Extension baseline was defined as the last non-missing measurement on or prior to the date of first study drug infusion in the extension study.			
Units: gram (g)			
arithmetic mean	42.106	25.890	
standard deviation	± 15.6967	± 7.3089	-
Total body Bone Mineral Content (BMC)			
Total body Bone Mineral Content (BMC) in the Full Analysis (FAS) population. Extension baseline was defined as the last non-missing measurement on or prior to the date of first study drug infusion in the extension study.			
Units: gram (g)			
arithmetic mean	1976.698	1144.613	
standard deviation	± 636.2144	± 253.5405	-
Serum Procollagen type 1 amino-terminal propeptide (P1NP)			
Serum Procollagen type 1 amino-terminal propeptide (P1NP) in the Full Analysis (FAS) population. Extension baseline was defined as the last non-missing measurement on or prior to the date of first study drug infusion in the extension study.			
Units: nanogram per milliliter (ng/mL)			
arithmetic mean	141.300	523.933	
standard deviation	± 100.8111	± 475.5547	-
Bone specific alkaline phosphatase (BSAP)			
Serum Bone specific alkaline phosphatase (BSAP) in the Full Analysis (FAS) population. Extension baseline was defined as the last non-missing measurement on or prior to the date of first study drug infusion in the extension study.			
Units: nanogram per milliliter (ng/mL)			
arithmetic mean	25.841	49.737	
standard deviation	± 14.8595	± 36.6580	-
Serum Cross linked N-telopeptide (NTX)			
Serum Cross linked N-telopeptide (NTX) in the Full Analysis (FAS) population. Extension baseline was defined as the last non-missing measurement on or prior to the date of first study drug infusion in the extension study.			
Units: nmol BCE/L			
arithmetic mean	19.092	42.217	
standard deviation	± 8.3760	± 25.2275	-
Serum Tartrate-resistant acid phosphatase isoform 5b (TRAP-5b)			
Serum Tartrate-resistant acid phosphatase isoform 5b (TRAP-5b) in the Full Analysis (FAS) population. Extension baseline was defined as the last non-missing measurement on or prior to the date of first study drug infusion in the extension study.			
Units: U/L			
arithmetic mean	5.338	8.636	
standard deviation	± 2.5097	± 5.2925	-
Second metacarpal cortical width			
Second metacarpal cortical width in the Full Analysis (FAS) 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	0.45	0.38	
standard deviation	± 0.207	± 0.163	-

End points

End points reporting groups

Reporting group title	Core treatment 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	Core treatment: Placebo
Reporting group description:	
Twice yearly 0.05 mg/kg (max 5 mg) i.v infusion (at least 30 minutes) of zoledronic acid	

Primary: Long-term Safety of zoledronic acid for the treatment of osteoporotic children treated with glucocorticoids.

End point title	Long-term Safety of zoledronic acid for the treatment of osteoporotic children treated with glucocorticoids.[1]

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 given long-term, over an additional 12 months from the Core study (CZOL446H2337), is safe for the treatment of osteoporotic children treated with glucocorticoids through the monitoring of relevant clinical and laboratory safety parameters.

End point type	Primary

End point timeframe:

Baseline 1 (Visit 1 of the Core Study) through Month 24 (Visit 15/Final Extension Visit)

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 performed.

End point values	Core treatment Zoledronic acid	Core treatment: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	15		
Units: Participants				
number (not applicable)				
On-treatment Adverse Events (AEs)	7	12		
On-treatment Serious Adverse Events (SAEs)	3	0		
On-treatment Deaths	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline 1 (Visit 1 of the Core study) in Lumbar Spine Bone Mineral Density (BMD) Z-score at Month 18 and 24 by Core treatment group.

End point title	Mean Change from Baseline 1 (Visit 1 of the Core study) in Lumbar Spine Bone Mineral Density (BMD) Z-score at Month 18 and 24 by Core treatment group.

End point description:

Lumbar Spine Bone Mineral Density (BMD) Z-score was determined by the central imaging vendor at the final visit of Core study (Visit 8) or at 1st infusion visit (Visit 9), and thereafter at Visit 12 (Month 18) and Visit 15 (Month 24) (final Extension Study visit/EOS) of Extension study. 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 Core baseline indicated an improvement in condition.

End point type	Secondary

End point timeframe:

Month 18 (Visit 12 of the Extension Study), Month 24 (Visit 15/Final Extension Visit)

End point values	Core treatment Zoledronic acid	Core treatment: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	15		
Units: Z-score				
least squares mean (standard error)				
Lumbar Spine BMD Z-score Change at Month 18	-40.648 (± 14.1205)	-44.348 (± 14.0348)		
Lumbar Spine BMD Z-score Change at Month 24	-46.161 (± 12.4486)	-67.913 (± 12.1722)		

Statistical analyses

Statistical analysis title	Lumbar Spine BMD Z-score Change at Month 18
Comparison groups	Core treatment Zoledronic acid v Core treatment: Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8505 [2]
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.242
upper limit	44.642

Notes:

[2] - An analysis of covariance (ANCOVA) model was performed with Core treatment, pooled centers, underlying condition treated with GCs and Core baseline lumbar spine BMD Z-score as explanatory variables and pooled centers as random effect.

Statistical analysis title	Lumbar Spine BMD Z-score Change at Month 24
Comparison groups	Core treatment Zoledronic acid v Core treatment: Placebo

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.218 [3]
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	21.752
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.126
upper limit	57.63

Notes:

[3] - An analysis of covariance (ANCOVA) model was performed with Core treatment, pooled centers, underlying condition treated with GCs and Core baseline lumbar spine BMD Z-score as explanatory variables and pooled centers as random effect.

Secondary: Mean Change from Baseline 1 (Visit 1 of the Core study) in Lumbar Spine Bone Mineral Content (BMC) at Month 18 and 24 by Core treatment group.

End point title	Mean Change from Baseline 1 (Visit 1 of the Core study) in Lumbar Spine Bone Mineral Content (BMC) at Month 18 and 24 by Core treatment group.

End point description:

Lumbar Spine Bone Mineral Content (BMC) was determined by the central imaging vendor at the final visit of Core study (Visit 8) or at 1st infusion visit (Visit 9), and thereafter at Visit 12 (Month 18) and Visit 15 (Month 24) (final Extension Study visit/EOS) of Extension study. The methods to be used to measure BMC were described in the respective DXA Manuals. Positive changes from Core baseline indicated an improvement in condition.

End point type	Secondary

End point timeframe:

Month 18 (Visit 12 of the Extension Study), Month 24 (Visit 15/Final Extension Visit)

End point values	Core treatment Zoledronic acid	Core treatment: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	15		
Units: gram				
least squares mean (standard error)				
Lumbar Spine BMC Change at Month 18	12.293 (± 1.7749)	9.933 (± 1.6717)		
Lumbar Spine BMC Change at Month 24	15.845 (± 2.2217)	14.666 (± 2.0500)		

Statistical analyses

Statistical analysis title	Lumbar Spine BMC Change at Month 18
Comparison groups	Core treatment Zoledronic acid v Core treatment: Placebo

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3544 [4]
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	2.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.886
upper limit	7.606

Notes:

[4] - An analysis of covariance (ANCOVA) model was performed with Core treatment, pooled centers, underlying condition treated with GCs and Core baseline lumbar spine BMD Z-score as explanatory variables and pooled centers as random effect.

Statistical analysis title	Lumbar Spine BMC Change at Month 24
Comparison groups	Core treatment Zoledronic acid v Core treatment: Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.705 [5]
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	1.179
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.281
upper limit	7.639

Notes:

[5] - An analysis of covariance (ANCOVA) model was performed with Core treatment, pooled centers, underlying condition treated with GCs and Core baseline lumbar spine BMD Z-score as explanatory variables and pooled centers as random effect.

Secondary: Mean Change from Baseline 1 (Visit 1 of the Core study) in total body BMC at Month 18 and 24 by Core treatment group.

End point title	Mean Change from Baseline 1 (Visit 1 of the Core study) in total body BMC at Month 18 and 24 by Core treatment group.

End point description:

Total body BMC were determined by the central imaging vendor at the final visit of Core study (Visit 8) or at 1st infusion visit (Visit 9), and thereafter at Visit 12 (Month 18) and Visit 15 (Month 24) (final Extension Study visit/EOS) of Extension study. The methods to be used to measure BMC were described in the respective DXA Manuals. Positive changes from Core baseline indicated an improvement in condition.

End point type	Secondary

End point timeframe:

Month 18 (Visit 12 of the Extension Study), Month 24 (Visit 15/Final Extension Visit)

End point values	Core treatment Zoledronic acid	Core treatment: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	15		
Units: gram				
least squares mean (standard error)				
Total body BMC Change at Month 18	387.721 (± 87396.2756)	266.592 (± 87396.2698)		
Total body BMC Change at Month 24	496.997 (± 120.9281)	431.323 (± 123.5462)		

Statistical analyses

Statistical analysis title	Total body BMC Change at Month 18
Comparison groups	Core treatment Zoledronic acid v Core treatment: Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.531 [6]
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	121.129
Confidence interval	
level	95 %
sides	2-sided
lower limit	-291
upper limit	533.258

Notes:

[6] - An analysis of covariance (ANCOVA) model was performed with Core treatment, pooled centers, underlying condition treated with GCs and Core baseline lumbar spine BMD Z-score as explanatory variables and pooled centers as random effect.

Statistical analysis title	Total body BMC Change at Month 24
Comparison groups	Core treatment Zoledronic acid v Core treatment: Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7347 [7]
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	65.674
Confidence interval	
level	95 %
sides	2-sided
lower limit	-344.067
upper limit	475.415

Notes:

[7] - An analysis of covariance (ANCOVA) model was performed with Core treatment, pooled centers, underlying condition treated with GCs and Core baseline lumbar spine BMD Z-score as explanatory variables and pooled centers as random effect.

Secondary: Mean Change from Baseline 1 (Visit 1 of the Core study) in Serum P1NP at Month 18 and 24 by Core treatment group.

End point title	Mean Change from Baseline 1 (Visit 1 of the Core study) in Serum P1NP at Month 18 and 24 by Core treatment group.

End point description:

Serum Procollagen type 1 amino-terminal propeptide (P1NP) was collected at the final visit Core study at Visit 8, or at 1st infusion visit (Visit 9), and thereafter at Visit 12 (Month 18) and Visit 15 (Month 24) (final Extension study Visit/EOS) of Extension study according to the instructions provided in the Laboratory Manual. The samples were analyzed in batches at the laboratory. Decrease or negative changes from Core baseline indicated a pharmacological response to therapy.

End point type	Secondary

End point timeframe:

Month 18 (Visit 12 of the Extension Study), Month 24 (Visit 15/Final Extension Visit)

End point values	Core treatment Zoledronic acid	Core treatment: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	15		
Units: nanogram per milliliter (ng/mL)				
least squares mean (standard error)				
Serum P1NP Change at Month 18	-169.837 (± 86.8640)	-22.157 (± 82.6761)		
Serum P1NP Change at Month 24	-228.068 (± 54.1402)	-95.631 (± 53.0765)		

Statistical analyses

Statistical analysis title	Serum P1NP Change at Month 24
Comparison groups	Core treatment Zoledronic acid v Core treatment: Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1266 [8]
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-132.437
Confidence interval	
level	95 %
sides	2-sided
lower limit	-286.452
upper limit	21.579

Notes:

[8] - An analysis of covariance (ANCOVA) model was performed on the transformed data with Core treatment, pooled centers, underlying condition treated with glucocorticoids and loge as explanatory variables and pooled centers as random effect.

Statistical analysis title	Serum P1NP Change at Month 18
Comparison groups	Core treatment Zoledronic acid v Core treatment: Placebo

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4143 [9]
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-147.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-394.41
upper limit	99.049

Notes:

[9] - An analysis of covariance (ANCOVA) model was performed on the transformed data with Core treatment, pooled centers, underlying condition treated with glucocorticoids and loge as explanatory variables and pooled centers as random effect.

Secondary: Mean Change from Baseline 1 (Visit 1 of the Core study) in BSAP at Month 18 and 24 by Core treatment group.

End point title	Mean Change from Baseline 1 (Visit 1 of the Core study) in BSAP at Month 18 and 24 by Core treatment group.

End point description:

Bone specific alkaline phosphatase (BSAP) was collected at the final visit Core study at Visit 8, or at 1st infusion visit (Visit 9), and thereafter at Visit 12 (Month 18) and Visit 15 (Month 24) (final Extension study Visit/EOS) of Extension study according to the instructions provided in the Laboratory Manual. The samples were analyzed in batches at the laboratory. Decrease or negative changes from Core baseline indicated a pharmacological response to therapy.

End point type	Secondary

End point timeframe:

Month 18 (Visit 12 of the Extension Study), Month 24 (Visit 15/Final Extension Visit)

End point values	Core treatment Zoledronic acid	Core treatment: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	15		
Units: nanogram per milliliter (ng/mL)				
least squares mean (standard error)				
BSAP Change at Month 18	-13.716 (± 8.5909)	3.975 (± 8.0523)		
BSAP Change at Month 24	-9.675 (± 6.4159)	-6.013 (± 5.9316)		

Statistical analyses

Statistical analysis title	BSAP Change at Month 18
Comparison groups	Core treatment Zoledronic acid v Core treatment: Placebo

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2123 [10]
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-17.691
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.925
upper limit	6.543

Notes:

[10] - An analysis of covariance (ANCOVA) model was performed on the transformed data with Core treatment, pooled centers, underlying condition treated with glucocorticoids and loge as explanatory variables and pooled centers as random effect.

Statistical analysis title	BSAP Change at Month 24
Comparison groups	Core treatment Zoledronic acid v Core treatment: Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4852 [11]
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-3.662
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.479
upper limit	14.155

Notes:

[11] - An analysis of covariance (ANCOVA) model was performed on the transformed data with Core treatment, pooled centers, underlying condition treated with glucocorticoids and loge as explanatory variables and pooled centers as random effect.

Secondary: Mean Change from Baseline 1 (Visit 1 of the Core study) in Serum NTX at Month 18 and 24 by Core treatment group.

End point title	Mean Change from Baseline 1 (Visit 1 of the Core study) in Serum NTX at Month 18 and 24 by Core treatment group.

End point description:

Serum Cross linked N-telopeptide (NTX) was collected at the final visit Core study at Visit 8, or at 1st infusion visit (Visit 9), and thereafter at Visit 12 (Month 18) and Visit 15 (Month 24) (final Extension study Visit/EOS) of Extension study according to the instructions provided in the Laboratory Manual. The samples were analyzed in batches at the laboratory. Decrease or negative changes from Core baseline indicated a pharmacological response to therapy.

End point type	Secondary

End point timeframe:

Month 18 (Visit 12 of the Extension Study), Month 24 (Visit 15/Final Extension Visit)

End point values	Core treatment Zoledronic acid	Core treatment: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	15		
Units: nmol BCE/L				
least squares mean (standard error)				
Serum NTX Change at Month 18	-17.577 (± 168.8975)	-12.916 (± 168.8965)		
Serum NTX Change at Month 24	-17.450 (± 2.3585)	-14.891 (± 2.0590)		

Statistical analyses

Statistical analysis title	Serum NTX Change at Month 18
Comparison groups	Core treatment Zoledronic acid v Core treatment: Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9009 [12]
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-4.661
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.647
upper limit	7.325

Notes:

[12] - An analysis of covariance (ANCOVA) model was performed on the transformed data with Core treatment, pooled centers, underlying condition treated with glucocorticoids and loge as explanatory variables and pooled centers as random effect.

Statistical analysis title	Serum NTX Change at Month 24
Comparison groups	Core treatment Zoledronic acid v Core treatment: Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9472 [13]
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-2.558
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.864
upper limit	3.747

Notes:

[13] - An analysis of covariance (ANCOVA) model was performed on the transformed data with Core treatment, pooled centers, underlying condition treated with glucocorticoids and loge as explanatory variables and pooled centers as random effect.

Secondary: Mean Change from Baseline 1 (Visit 1 of the Core study) in Serum TRAP-5b at Month 18 and 24 by Core treatment group.

End point title	Mean Change from Baseline 1 (Visit 1 of the Core study) in Serum TRAP-5b at Month 18 and 24 by Core treatment group.

End point description:

Serum Tartrate-resistant acid phosphatase isoform 5b (TRAP 5b) were collected at the final visit Core study at Visit 8, or at 1st infusion visit (Visit 9), and thereafter at Visit 12 (Month 18) and Visit 15 (Month 24) (final Extension study Visit/EOS) of Extension study according to the instructions provided in the Laboratory Manual. The samples were analyzed in batches at the laboratory. Decrease or negative changes from Core baseline indicated a pharmacological response to therapy.

End point type	Secondary

End point timeframe:

Month 18 (Visit 12 of the Extension Study), Month 24 (Visit 15/Final Extension Visit)

End point values	Core treatment Zoledronic acid	Core treatment: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	15		
Units: U/L				
least squares mean (standard error)				
Serum TRAP-5b Change at Month 18	-2.661 (± 0.8126)	-1.179 (± 0.7725)		
Serum TRAP-5b Change at Month 24	-2.670 (± 0.7158)	-2.260 (± 0.6701)		

Statistical analyses

Statistical analysis title	Serum TRAP-5b Change at Month 18
Comparison groups	Core treatment Zoledronic acid v Core treatment: Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.46 [14]
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-1.482
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.805
upper limit	0.841

Notes:

[14] - An analysis of covariance (ANCOVA) model was performed on the transformed data with Core treatment, pooled centers, underlying condition treated with glucocorticoids and loge as explanatory variables and pooled centers as random effect.

Statistical analysis title	Serum TRAP-5b Change at Month 24
Comparison groups	Core treatment Zoledronic acid v Core treatment: Placebo

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9236 [15]
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.423
upper limit	1.603

Notes:

[15] - An analysis of covariance (ANCOVA) model was performed on the transformed data with Core treatment, pooled centers, underlying condition treated with glucocorticoids and loge as explanatory variables and pooled centers as random effect.

Secondary: Number of participants with new vertebral fractures during the 12 month Extension period by Core treatment group.

End point title	Number of participants with new vertebral fractures during the 12 month Extension period by Core treatment group.

End point description:

New vertebral fractures are defined as fractures of Genant grade 1 or higher that occur at lumbar or thoracic spine from first extension dose infusion to the end of the study in a previously normal vertebra.

End point type	Secondary

End point timeframe:

Month 24 (Visit 15/Final Extension Visit)

End point values	Core treatment Zoledronic acid	Core treatment: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	15		
Units: Participants				
number (not applicable)	1	1		

Statistical analyses

Statistical analysis title	New vertebral fractures at Month 12 Extension
Comparison groups	Core treatment Zoledronic acid v Core treatment: Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 1
Method	Fisher exact

Secondary: Number of participants with new morphometric vertebral fractures during the 12 month Extension period by Core treatment group.

End point title	Number of participants with new morphometric vertebral fractures during the 12 month Extension period by Core treatment group.

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. A new morphometric vertebral fractures during the 12 month Extension Period was defined as a morphometric vertebral fracture present at Month 24 X-ray which was not present at the Extension Baseline (Baseline 2).

End point type	Secondary

End point timeframe:

Month 24 (Visit 15/Final Extension Visit)

End point values	Core treatment Zoledronic acid	Core treatment: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	15		
Units: Participants				
number (not applicable)	1	1		

Statistical analyses

Statistical analysis title	New morphometric vertebral fractures

Statistical analysis description:

New morphometric vertebral fractures at Month 12 Extension

Comparison groups	Core treatment Zoledronic acid v Core treatment: Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 1
Method	Fisher exact

Secondary: Percentage of Patients with reduction in Pain from Baseline 1 (Visit 1 of the Core study) at Month 15, 18, 21 and 24 by Core treatment group.

End point title	Percentage of Patients with reduction in Pain from Baseline 1 (Visit 1 of the Core study) at Month 15, 18, 21 and 24 by Core treatment group.

End point description:

Pain was evaluated at each visit (at office and telephone visit) at the final visit of the Core study and first visit of the Extension study (Visit 9), Visits 11 (Month 15), 12 (Month 18), 14 (Month 21) and 15 (Month 24) 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 Core 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 15, Month 18, Month 21, Month 24

End point values	Core treatment Zoledronic acid	Core treatment: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	15		
Units: Percentage of Patients				
number (not applicable)				
Reduction in Pain at Month 15	55.6	46.2		
Reduction in Pain at Month 18	30.0	50.0		
Reduction in Pain at Month 21	30.0	50.0		
Reduction in Pain at Month 24	30.0	38.5		

Statistical analyses

Statistical analysis title	Reduction in Pain at Month 15
Comparison groups	Core treatment Zoledronic acid v Core treatment: Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3971 [16]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	173.07

Notes:

[16] - Presented by treatment group and evaluated using a logistic regression model with Core treatment, pooled centers, underlying condition treated with glucocorticoids and Core baseline pain score as explanatory variables.

Statistical analysis title	Reduction in Pain at Month 18
Comparison groups	Core treatment Zoledronic acid v Core treatment: Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6046 [17]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	999.99

Notes:

[17] - Presented by treatment group and evaluated using a logistic regression model with Core treatment, pooled centers, underlying condition treated with glucocorticoids and Core baseline pain score as explanatory variables.

Statistical analysis title	Reduction in Pain at Month 21
Comparison groups	Core treatment Zoledronic acid v Core treatment: Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6046 [18]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	999.99

Notes:

[18] - Presented by treatment group and evaluated using a logistic regression model with Core treatment, pooled centers, underlying condition treated with glucocorticoids and Core baseline pain score as explanatory variables.

Statistical analysis title	Reduction in Pain at Month 24
Comparison groups	Core treatment Zoledronic acid v Core treatment: Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.875 [19]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	38.04

Notes:

[19] - Presented by treatment group and evaluated using a logistic regression model with Core treatment, pooled centers, underlying condition treated with glucocorticoids and Core baseline pain score as explanatory variables.

Secondary: Mean Change from Baseline (Core and Extension) in 2nd metacarpal cortical width at month 24 by Core treatment group.

End point title	Mean Change from Baseline (Core and Extension) in 2nd metacarpal cortical width at month 24 by Core treatment group.

End point description:

Left postero-anterior (PA) hand/wrist X-ray were taken at the final visit of Core study and at Visit

15/EOS (Month 24) to assess bone age. The change in 2nd metacarpal cortical width at Month 24 relative to the respective Baseline was calculated. If a fracture of the left upper extremity precluded radiographic imaging, (or precluded this X-ray in the Core study) then the right hand was evaluated for this purpose. In this case, an image of the right hand was carried out at both Visit 8 and at Visit 15/EOS (Month 24). The information was used in the assessment of bone density.

End point type	Secondary

End point timeframe:

Baseline 1 (Visit 1 of the Core Study) and Baseline 2 (Visit 9 of the Extension Study) through Month 24 (Visit 15/Final Extension Visit)

End point values	Core treatment Zoledronic acid	Core treatment: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	15		
Units: millimeter (mm)				
least squares mean (standard error)				
2nd metacarpal cortical width change from BL1	-0.04 (± 0.068)	-0.03 (± 0.054)		
2nd metacarpal cortical width change from BL2	-0.09 (± 0.089)	0.02 (± 0.063)		

Statistical analyses

Statistical analysis title	2nd metacarpal cortical width chge from BL1

Statistical analysis description:

2nd metacarpal cortical width chge from BL1 at Month 24

Comparison groups	Core treatment Zoledronic acid v Core treatment: Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9231 [20]
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.17

Notes:

[20] - An analysis of covariance (ANCOVA) model was performed with Core treatment, pooled centers, underlying condition treated with GCs and Core baseline bone age as explanatory variables and pooled centers as random effect.

Statistical analysis title	2nd metacarpal cortical width chge from BL2

Statistical analysis description:

2nd metacarpal cortical width chge from BL2 at Month 24

Comparison groups	Core treatment Zoledronic acid v Core treatment: Placebo

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2694 [21]
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.1

Notes:

[21] - An analysis of covariance (ANCOVA) model was performed with Core treatment, pooled centers, underlying condition treated with GCs and Extension baseline bone age as explanatory variables and pooled centers as random effect.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events and serious adverse events were collected for the maximum actual duration of treatment exposure and follow up for a participant per the protocol for approximately 13 months.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Core Treatment Placebo
Reporting group description:	
Core Treatment Placebo	
Reporting group title	Core Treatment Zoledronic acid
Reporting group description:	
Core Treatment Zoledronic acid	

Serious adverse events	Core Treatment Placebo	Core Treatment Zoledronic acid	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	3 / 10 (30.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Postictal state			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Core Treatment Placebo	Core Treatment Zoledronic acid	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 15 (80.00%)	7 / 10 (70.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	1 / 15 (6.67%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Secondary hypertension			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Surgical and medical procedures			

Tooth extraction			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 15 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Fatigue			
subjects affected / exposed	3 / 15 (20.00%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Infusion site pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	3 / 15 (20.00%)	2 / 10 (20.00%)	
occurrences (all)	3	2	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 15 (13.33%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Hypoxia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	3	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 15 (6.67%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Insomnia			

subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	1	0
Sleep disorder		
subjects affected / exposed	2 / 15 (13.33%)	0 / 10 (0.00%)
occurrences (all)	2	0
Suicide attempt		
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	1
Investigations		
Liver function test increased		
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	1	0
Therapeutic agent urine positive		
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	1
Vitamin B12 decreased		
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	1	0
Injury, poisoning and procedural complications		
Fall		
subjects affected / exposed	2 / 15 (13.33%)	0 / 10 (0.00%)
occurrences (all)	2	0
Joint dislocation		
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	1
Skin abrasion		
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	1
Cardiac disorders		
Tachycardia		
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	2
Nervous system disorders		
Epileptic aura		
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	1

Headache		
subjects affected / exposed	2 / 15 (13.33%)	3 / 10 (30.00%)
occurrences (all)	2	3
Postictal state		
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	4
Sciatica		
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	1	0
Tremor		
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	1
Ear and labyrinth disorders		
Ear pain		
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	1
Eye disorders		
Ocular hyperaemia		
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	1	0
Gastrointestinal disorders		
Abdominal pain		
subjects affected / exposed	2 / 15 (13.33%)	2 / 10 (20.00%)
occurrences (all)	2	2
Abdominal pain lower		
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	1
Abdominal pain upper		
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	1
Constipation		
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	1
Diarrhoea		
subjects affected / exposed	1 / 15 (6.67%)	1 / 10 (10.00%)
occurrences (all)	1	1
Gastrooesophageal reflux disease		

subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	1	0
Nausea		
subjects affected / exposed	3 / 15 (20.00%)	1 / 10 (10.00%)
occurrences (all)	3	1
Vomiting		
subjects affected / exposed	1 / 15 (6.67%)	2 / 10 (20.00%)
occurrences (all)	1	2
Skin and subcutaneous tissue disorders		
Butterfly rash		
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	1
Ingrowing nail		
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	1	0
Rash		
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	1	0
Skin discolouration		
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	1
Endocrine disorders		
Adrenal insufficiency		
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	1	0
Musculoskeletal and connective tissue disorders		
Arthralgia		
subjects affected / exposed	5 / 15 (33.33%)	0 / 10 (0.00%)
occurrences (all)	8	0
Arthritis		
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	1
Back pain		
subjects affected / exposed	3 / 15 (20.00%)	1 / 10 (10.00%)
occurrences (all)	5	1
Bone pain		

subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	1	0
Flank pain		
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	1
Myalgia		
subjects affected / exposed	2 / 15 (13.33%)	0 / 10 (0.00%)
occurrences (all)	2	0
Neck pain		
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	1
Pain in extremity		
subjects affected / exposed	1 / 15 (6.67%)	1 / 10 (10.00%)
occurrences (all)	2	1
Scoliosis		
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	1
Spinal pain		
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	1	0
Trismus		
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	1	0
Infections and infestations		
Bronchitis		
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	1	0
Candida infection		
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	1	0
Gastroenteritis		
subjects affected / exposed	2 / 15 (13.33%)	0 / 10 (0.00%)
occurrences (all)	2	0
Herpes virus infection		
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)
occurrences (all)	1	0

Influenza			
subjects affected / exposed	3 / 15 (20.00%)	1 / 10 (10.00%)	
occurrences (all)	3	1	
Nasopharyngitis			
subjects affected / exposed	2 / 15 (13.33%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 15 (6.67%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Urinary tract infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Hypocalcaemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Hypophosphataemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Insulin resistance			
subjects affected / exposed	0 / 15 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 November 2012	Amendment 1 applied to UK sites only, regarding contraception and pregnancy in female patients of child bearing potential
15 January 2014	The rationale for Amendment 2 was to reflect the changes in the Core (CZOL446H2337) protocol v04 which extended the study population to include patients with underlying conditions other than chronic inflammatory disorders e.g. Duchenne muscular dystrophy (DMD).
18 May 2016	The rationale for Amendment 3 was to reflect the changes in the Core protocol (CZOL446H2337) v05 which has been amended to address Health Authority requests to provide a Risk Benefit statement, and allow more countries to apply the contraceptive wording originally provided for United Kingdom (UK) sites only.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported