



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 | v1 |
| This version publication date | 20 September 2018 |
| First version publication date | 20 September 2018 |

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) | EMA-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 | Australia: 6 |
| Country: Number of subjects enrolled | Canada: 18 |
| Country: Number of subjects enrolled | Hungary: 2 |
| 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, Data analyst, Carer, 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 BMD Z-score (MITT) | | | |
| Lumbar spine BMD Z-score (MITT) (n=17,16) | | | |
| Units: Score on a scale | | | |
| arithmetic mean | -2.127 | -2.379 | - |
| standard deviation | ± 0.7863 | ± 0.8975 | - |
| Lumbar spine BMC (MITT) | | | |
| Lumbar spine BMC (MITT) (n=17,16) | | | |
| Units: gram (g) | | | |

| | | | |
|--|------------|------------|---|
| arithmetic mean | 31.886 | 22.605 | |
| standard deviation | ± 15.1062 | ± 6.6054 | - |
| Total body BMC (MITT) | | | |
| Total body BMC (MITT) (n=16,14) | | | |
| Units: gram (g) | | | |
| arithmetic mean | 1550.556 | 1050.610 | |
| standard deviation | ± 592.0670 | ± 253.0759 | - |
| Serum P1NP (MITT) | | | |
| Serum P1NP (MITT) (n=16,14) | | | |
| Units: nanogram per milliliter (ng/mL) | | | |
| arithmetic mean | 313.54 | 368.90 | |
| standard deviation | ± 284.541 | ± 235.226 | - |
| Serum BSAP (MITT) | | | |
| Serum BSAP (MITT) (n=16, 14) | | | |
| Units: nanogram per milliliter (ng/mL) | | | |
| arithmetic mean | 31.559 | 43.414 | |
| standard deviation | ± 22.6619 | ± 32.8200 | - |
| Serum NTX (MITT) | | | |
| Serum NTX (MITT) (n=16, 14) | | | |
| Units: nmol BCE/L | | | |
| arithmetic mean | 34.359 | 39.192 | |
| standard deviation | ± 22.0490 | ± 14.5823 | - |
| Serum TRAP-5b (MITT) | | | |
| Serum TRAP-5b (MITT) (n=16, 14) | | | |
| Units: U/L | | | |
| arithmetic mean | 7.010 | 8.595 | |
| standard deviation | ± 2.9998 | ± 4.5650 | - |
| Vertebral morphometry (MITT) | | | |
| Vertebral morphometry (MITT) (n=10, 13) | | | |
| Units: Ratio | | | |
| arithmetic mean | 0.982 | 0.976 | |
| standard deviation | ± 0.0428 | ± 0.0788 | - |
| Metacarpal cortical width (MITT) | | | |
| Metacarpal cortical width (MITT) (n=9, 12) | | | |
| 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: Score on a scale | | | | |
| least squares mean (standard error) | 0.607 (± 0.13) | 0.182 (± 0.15) | | |

Statistical analyses

| | |
|---|--------------------------------------|
| Statistical analysis title | Lumbar Spine BMD Z-score at Month 12 |
| Comparison groups | Zoledronic acid v Placebo |
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.038 |
| Method | ANCOVA |
| Parameter estimate | Difference in LS mean |
| Point estimate | 0.425 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.026 |
| upper limit | 0.825 |

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: Score on a scale | | | | |
| 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: Score on a scale | | | | |
| least squares mean (standard error) | | | | |
| LS Change at Month 6 (n=16, 15) | 4.110 (± 0.63) | 2.131 (± 0.70) | | |
| LS Change at Month 12 (n=16, 15) | 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: Score on a scale | | | | |
| least squares mean (standard error) | | | | |
| Total BMC Change at Month 6 (n=15,13) | 129.272 (± 24.23) | 95.214 (± 28.74) | | |
| Total BMC Change at Month 12 (n=15,12) | 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 (n=14,15) | -134.285 (± 48.80) | 77.497 (± 56.15) | | |
| P1NP Change at Month 12 (n=15,15) | -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 (n=14,15) | -7.413 (\pm 3.63) | 3.810 (\pm 4.05) | | |
| BSAP Change at Month 12 (n=15,15) | -13.984 (\pm 4.3814) | 6.450 (\pm 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 (n=14,15) | -13.746 (\pm 4.23) | 7.192 (\pm 4.74) | | |
| NTX Change at Month 12 (n=15,15) | -20.134 (\pm 3.76) | 7.440 (\pm 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 (n=14,15) | -1.561 (± 0.65) | 0.313 (± 0.74) | | |
| TRAP 5b Change at Month 12 (n=14,15) | -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: New vertebral fractures at Month 12

| | |
|------------------------|---|
| End point title | 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: Percentage of new vertebral fractures | | | | |
| number (not applicable) | 0 | 13.3 | | |

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 |

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 | 10 | 13 | | |
| Units: Ratio | | | | |
| least squares mean (standard error) | -0.018 (\pm 0.01) | -0.0003 (\pm 0.01) | | |

Statistical analyses

| | |
|---|-----------------------------------|
| Statistical analysis title | Vertebral morphometry at Month 12 |
| Comparison groups | Zoledronic acid v Placebo |
| Number of subjects included in analysis | 23 |
| 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 |
|-----------------|---|

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 (n=16,13) | 37.5 | 53.8 | | |
| Month 6 (n=16,14) | 37.5 | 50.0 | | |
| Month 9 (n=15,13) | 33.3 | 46.2 | | |
| Month 12 (n=16,14) | 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 | 9 | 11 | | |
| Units: millimeter (mm) | | | | |
| least squares mean (standard error) | -0.01 (\pm 0.040) | 0.03 (\pm 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 | 20 |
| 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 |
|-----------------|--|

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

| End point values | Zoledronic acid | Placebo | | |
|--------------------------------------|-----------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 17 | 0 ^[3] | | |
| Units: Percent below LLOQ (10 ng/mL) | | | | |
| number (not applicable) | 11.8 | | | |

Notes:

[3] - Only collected in 'Zoledronic Acid' arm

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 SOC (n=15,12) | 83.3 | 75.0 | | |
| SAEs by Primary SOC (n=5,1) | 27.8 | 6.3 | | |
| Deaths by Primary SOC (n=0,0) | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

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 | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo

| | |
|-----------------------|-----------------|
| Reporting group title | Zoledronic acid |
|-----------------------|-----------------|

Reporting group description:

Zoledronic acid

| Serious adverse events | Placebo | Zoledronic acid | |
|---|----------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 5 / 18 (27.78%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 18 (5.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 18 (5.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 18 (5.56%) | |
| 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 / 16 (0.00%) | 1 / 18 (5.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Acute phase reaction | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 18 (5.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 18 (5.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 18 (5.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Crohn's disease | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 2 / 18 (11.11%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 18 (5.56%) | |
| 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 / 16 (0.00%) | 1 / 18 (5.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 18 (5.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Psychiatric disorders | | | |
| Abnormal behaviour | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 18 (5.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 18 (5.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 18 (5.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 18 (5.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Varicella zoster virus infection | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 18 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 18 (5.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Placebo | Zoledronic acid | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 16 (75.00%) | 14 / 18 (77.78%) | |

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

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

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

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

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

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

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

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: $\text{GFR (mL/min/1.73 m}^2\text{)} = k [\text{height (m)}/\text{Scr (mg/dl)}]$ $k = 0.41$ 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