



Clinical trial results:

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

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

Summary

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CZOL446H2202 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00063479 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

| | |
|--|----------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMEA-000024-PIP01-07 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

Results analysis stage

| | |
|--|-------------|
| Analysis stage | Final |
| Date of interim/final analysis | 09 May 2007 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 09 May 2007 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator:

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

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 2 |
| Children (2-11 years) | 104 |
| Adolescents (12-17 years) | 44 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 20 centers in 9 countries.

Pre-assignment

Screening details:

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

Period 1

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

Arms

| | |
|------------------------------|-----------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Zoledronic acid |

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|-------------|
| Arm title | Pamidronate |
|------------------|-------------|

Arm description:

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

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|------------------------|
| Investigational medicinal product name | Pamidronate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

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

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

Baseline characteristics

Reporting groups

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

Reporting group description:

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

| | |
|-----------------------|-------------|
| Reporting group title | Pamidronate |
|-----------------------|-------------|

Reporting group description:

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

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

End points

End points reporting groups

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

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

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

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

Statistical analyses

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

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

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point timeframe:
Baseline, Month 6, Month 12

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

Statistical analyses

No statistical analyses for this end point

Secondary: Number of clinical fractures during 12 Months

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|--|
| End point title | Number of subjects with bone pain scores at Month 6 and Month 12 |
|-----------------|--|

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Month 6, Month 12

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

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first fracture during 12 Months

| | |
|-----------------|---|
| End point title | Time to first fracture during 12 Months |
|-----------------|---|

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1 to Month 12

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 10.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------|
| Reporting group title | Zoledronic Acid |
|-----------------------|-----------------|

Reporting group description:

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

| | |
|-----------------------|-------------|
| Reporting group title | Pamidronate |
|-----------------------|-------------|

Reporting group description:

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

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

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

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

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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

Notes:

