

CLINICAL REVIEW

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Established Name zoledronic acid
(Proposed) Trade Name Zometa
Therapeutic Class Bisphosphonate
Applicant Novartis Pharmaceutical Corp.
Priority Designation P
Formulation 5mg per vial for IV infusion
Dosing Regimen None
Indication No indication sought
Response to Written Request
Intended Population Pediatric Patients with
Osteogenesis Imperfecta

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Clinical Review
{William Lubas, M.D., Ph.D.}
{NDA 21-223/S-006}
{Zometa (zoledronic acid)}

REFERENCES53

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Approval (AP)

1.2 Recommendation on Postmarketing Actions

None

1.2.1 Risk Management Activity

None

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Osteogenesis Imperfecta (OI) is a genetic disorder resulting in increased bone fragility and low bone mass making patients at risk for recurrent fractures. While there are currently no clinically approved medications to treat OI, bisphosphonates, are used off label for the treatment of patients with OI at high risk of fracture, and are currently the best treatment option for these patients. Before a bisphosphonate could be approved for this indication clinical trials are needed to identify effective dosing regimens describing both the duration of treatment and interval between doses needed to maintain a clinically relevant benefit. This current submission is in response to a Written Request from the agency to get pediatric data on the use of bisphosphonates in OI patients. The clinical data includes a PK study in children 1 to 17 years of age and an active comparator controlled trial comparing the use of zoledronic acid to pamidronate in children with severe OI. These results have been submitted to fulfill the requirement for an additional 6 months of Drug Exclusivity, and the sponsor is not seeking an indication for treatment of OI with this application.

1.3.2 Efficacy

This parallel-group, active-controlled, non-inferiority study randomized 155 children, between 1 and 17 years of age, with severe OI to receive one year of therapy with zoledronic acid or pamidronate. Because of the difference in dosing between the active controlled infusions it was not possible to blind the patients or treating physicians to the study drugs. However, the radiologists responsible for assessing the primary endpoints (e.g. change from baseline in LS BMD at 12 months) were blinded to treatment assignments.

The results of the study showed that zoledronic acid was not only non-inferior, but in fact superior, to pamidronate with respect to the primary endpoint in this study (e.g. percent change in LS BMD at month 12 relative to baseline). Percentage change from baseline in femoral neck BMC, total body BMC, LS-Z-score, supine length/height, vertebral spine length, and grip strength all increased during the 12 month period of the study, but there were no statistically significant differences between the zoledronic acid and pamidronate treatment groups. Bone resorption biomarker, β -CTX, and bone formation markers serum P1NP and BALP all had statistically greater reductions from baseline in the zoledronic acid group compared to the pamidronate group. There was no difference in total number of patients with fractures [e.g. 32 (43%) in the zoledronic acid group compared to 31 (41%) in the pamidronate group] nor in the time to first clinical fracture estimated using a Kaplan-Meier curve. There were numerically more OI Type I patients with fractures in the zoledronic acid group 19 (50%) compared to 10 (29%) in the pamidronate group (hazard ratio 2.1, $p=0.09$, not statistically significant), and more combined OI Type III & IV patients with fractures in the pamidronate group 21 (51%) compared to 13 (36%) in the zoledronic acid group (hazard ratio 1.7, $p=0.25$, also not statistically significant). These differences may have occurred by chance and should not be used to favor treatment with one bisphosphonate over the other. Consistent with the observed increase from baseline in LS BMD in both treatment groups, the fracture rates in both the zoledronic acid and pamidronate completer groups were much lower during the 12 months of the study than in the 12 months prior to the initiation of bisphosphonate treatment suggesting that these bisphosphonates provide a clinically beneficial treatment for pediatric patients with OI.

1.3.3 Safety

Intravenous bisphosphonates have been previously associated with the following adverse events in adults: Acute phase reactions, hypocalcemia (especially in patients with Paget's disease because of their increased rate of bone turnover), renal toxicity, bone/muscle pain, eye inflammation (iritis, uveitis and episcleritis) and osteonecrosis of the jaw (ONJ).

Acute phase reactions with short-term flu-like symptoms including: pyrexia (51%), headaches (10%), pain in extremity (8%), nausea (8%), fatigue (4%), chills (3%) and arthralgias (1%) were seen in pediatric patients during the first 3 days following the first infusion of zoledronic acid similar to what had been previously reported for adult patients. Recurrence of reactions with repeat dosing was much less common (e.g. the reporting rate for pyrexia dropped from 51% after the first dose to 3% after the second dose.)

Adverse events of hypocalcemia were reported in this study despite supplementation with calcium and vitamin D for 2 weeks prior to randomization and during the trial. More AEs of hypocalcemia were reported in the zoledronic acid treatment group (22%) than in the pamidronate group (9%). At least four of seven patients in the zoledronic acid treatment group, with serious adverse events (SAEs) of hypocalcemia or blood calcium decreased, reported symptoms of hypocalcemia, and received treatment for the hypocalcemia during hospitalizations. The lowest total calcium level reported after zoledronic acid infusions was 6.8 mg/dL and after pamidronate infusions was 7.7mg/dL. Hypocalcemia was typically seen in the first 3 days after the first infusion and was much less common with repeat dosing. In contrast to hypocalcemia, hypercalcemia was much more common with about half the patients having a lab value above the ULN of 10.28mg/dL and was seen throughout the entire length of the trial. However, no patients had serum calcium levels above 12mg/dL and none of these events was considered SAEs or required discontinuation of the study drug.

Minor elevations in serum creatinine were seen at 9-11 days after infusion with intravenous bisphosphonates, as had been previously reported in adult patients. No pediatric patients had increases in serum creatinine values to levels above 0.7mg/dL or required specific intervention because of these minor transient elevations. Only patients with normal renal function were included in this study so no information is available about the risk for renal deterioration in pediatric patients with abnormal baseline renal function or in children under 1 year of age.

Bone pain, including musculoskeletal pain and arthralgia are common findings in patients with OI so it is difficult to separate out drug-related events.

Other adverse events (AEs) that had been rarely reported in adult patients taking intravenous bisphosphonates such as ONJ and eye inflammation were not seen in this trial in pediatric OI patients. But the number of patients in this trial was too small to draw any conclusions about the relative risk for these AEs in this patient population.

In conclusion, the safety profile in pediatric OI patients, over 1 year of age, treated with zoledronic acid on a mg/kg basis was similar to what had been previously observed in adult patients receiving infusions of up to 5mg/day, but there is some data to suggest that the rate of adverse events may be somewhat higher in the pediatric population compared to the adult population.

1.3.4 Dosing Regimen and Administration

The sponsor is not seeking an indication for the treatment of patients with severe OI with this submission.

The core study, ZOL446H2202, used the following zoledronic acid dosing scheme for the first year of therapy based on age at time of the infusion:

Patients ≥ 1 to < 3 years of age were administered 0.025 mg/kg as a 30 to 45-minute intravenous infusion every 3 months.

Patients ≥ 3 years to ≤ 17 years of age were administered 0.05 mg/kg as a 30-minute intravenous infusion every 3 months.

The extension study, ZOL446H2202E1, compared once yearly to twice yearly dosing with zoledronic acid:

Patients ≥ 1 to < 3 years of age were administered 0.025 mg/kg as a 30 to 45-minute intravenous infusion every year vs. every 6 months.

Patients ≥ 3 years to ≤ 17 years of age were administered 0.05 mg/kg as a 30-minute intravenous infusion every year vs. every 6 months.

No information is available to describe the durability of the effect with yearly or biyearly dosing beyond one year of follow up.

1.3.5 Drug-Drug Interactions

No new drug-drug interaction studies were included in this submission.

1.3.6 Special Populations

All studies were performed in pediatric OI patients (see section 8.4 Pediatric). Patients with hepatic or renal insufficiency were excluded from these studies.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Zoledronic acid, is a nitrogen containing bisphosphonate which acts as an inhibitor of osteoclastic bone resorption and is intended for intravenous use. Zoledronic acid (4mg) is marketed for oncology indications [e.g. the treatment of hypercalcemia of malignancy, multiple myeloma and bone metastases] under the trade name Zometa (NDA 21-223 and 21-386). It was approved in 2002 for repeat dosing as a 4 mg dose, given no more frequently than every 7 days. Zoledronic acid (5mg) is approved for the treatment of Paget's Disease, as a one time dose and for the treatment of Postmenopausal Osteoporosis (PMO) as a once yearly dose under the trade name Reclast, since 2007 (NDA 21-817 and 22-080). The sponsor is submitting this application in order to obtain pediatric exclusivity and is not seeking an indication for the treatment of OI.

2.2 Currently Available Treatment for Indications

A 2-year, placebo-controlled trial with alendronate in pediatric OI patients, submitted as part of a Written Request, showed an improvement in spine BMD Z-score but was not able to show a reduction in fracture risk, therefore, the sponsor did not seek an indication for treatment in this population. There are currently no bisphosphonates approved for the treatment of OI, but pamidronate and other bisphosphonates are used off label for this indication, as a result of anecdotal reports in the literature that such agents can improve BMD, chronic pain and fracture incidence¹.

2.3 Availability of Proposed Active Ingredient in the United States

Zoledronic acid is available in the US at a 4mg dose under the trade name Zometa and as a 5mg dose under the trade name Reclast.

2.4 Important Issues With Pharmacologically Related Products

An increased risk of osteonecrosis of the jaw has been observed for intravenous bisphosphonates. see Oncology Drugs Advisory Committee meeting in 2005. Such information has been added to the label for Zometa and Aredia. Other safety concerns seen more frequently in clinical trials with intravenous bisphosphonates include acute phase reactions, hypocalcemia and worsening of renal function. The risk of deterioration in renal function deterioration was significantly increased when zoledronic acid was infused over 5 minutes compared with the same dose infused over 15 minutes. In addition, the risk of deteriorating renal function was significantly increased with the 8 mg dose, regardless of the 15 minute infusion time. Other concerns that have emerged with post-marketing data include the occurrence of eye inflammation (e.g. iritis,

¹ [Plotkin H, Rauch F, Bishop NJ, Montpetit K, Ruck-Gibis J, Travers R, Glorieux FH.](#) Pamidronate treatment of severe osteogenesis imperfecta in children under 3 years of age. J Clin Endocrinol Metab. 2000 May;85(5):1846-50.

uveitis and episcleritis) and bone pain, whereas gastrointestinal adverse events occur primarily with oral bisphosphonate therapy. Class labeling for bisphosphonates regarding the use of these drugs in women of childbearing age and the potential for fetal toxicity after remote exposure to the drug has recently been implemented.

A placebo-controlled trial of alendronate in pediatric patients with OI showed a similar rate of delayed fracture healing (7% alendronate vs. 9% placebo) but an increased rate of nonunion (11% alendronate vs. 0% placebo). There was also a small but significant decrease in height Z-score in the alendronate group (-3.49 at baseline to -3.71 at 2 years, for a difference of -0.22) compared to the placebo group (-3.39 at baseline to -3.47 at 2 years, for a difference of -0.08). Gastrointestinal adverse events, primarily vomiting were more common in pediatric OI patients compared to placebo, similar to what had been seen in adult patients treated with oral bisphosphonates.

2.5 Presubmission Regulatory Activity

The original Written Request was issued 19-Aug 2002 and revised twice, 19-Nov-2002 and 30-Aug-2006. The initial revision was in response to an FDA request to include children under 1 year of age in the study (e.g. >6 infants 3-11 months of age.) Under the revision these children had to meet certain renal eligibility criterion to avoid placing them at increased risk from renal toxicity during the intravenous infusions. However, it was noted during the course of this study that infants with OI consistently had elevated urine protein to creatinine ratios in the first year of life above the exclusion criterion required by the study DSMB. Therefore, it was recommended that the requirement for testing in children under 1 year of age be removed (see MO review dated 6/7/2006). The initial request also required at least 9 children in each of the age groups 1-8 years and 9-17 years. However, the sponsor had difficulty in recruiting enough patients to fulfill these requirements. Since these patients are at increased risk of infection with indwelling catheters all blood sampling has to be done with repeat venipuncture and most parents do not want to expose their children to the additional 3 to 7 blood draws which would be required to perform the PK analyses. Also there was concern over the possible trauma to these children with increased bone fragility as a result of the extra phlebotomies. Only 11 out of the 66 patients (17%) randomized to zoledronic acid were enrolled in the PK study by their parents. In response to a Briefing Book submitted to the agency describing this matter which included an analysis of the PK data on these patients, it was determined by this medical reviewer that there was sufficient reproducibility in the data, including correspondence to data observed in the adult population to permit the minimum requirement in each age range to be changed to the 4 patients in the 1-8 year age group and 7 patients in the 9-17 year age groups which had been already enrolled (see MO review dated 6/7/2006). The final WR #2 dated 30-Aug-2006, included these agreed to changes to the study protocols, and was used to determine an additional 6 months of Drug Exclusivity.

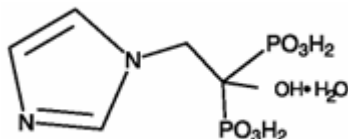
2.6 Other Relevant Background Information

None

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Zoledronic acid monohydrate is chemically designated as (1-hydroxy-2-imidazol-1-yl-phosphonoethyl) phosphonic acid monohydrate. Its structural formula is:



5mg/5mL vials of zoledronic acid (Reclast) were used in these studies. To enable accurate dosing in children, 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 patients aged 3 to 17 years. No new chemistry information was included in this submission.

3.2 Animal Pharmacology/Toxicology

See the Clinical Pharmacology review for an analysis of urine and plasma sample stability data, and RIA assay validation submitted by the sponsor.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

21-Sept-2007 submission-Original submission: Includes the clinical study report for the pivotal trial ZOL446H2202, Report DMPK(F) R99-073-stability data in urine and plasma samples, RIA assay validation, proposed labeling in PLR format, financial disclosure, copies of the Written Request letters: \\CDSESUB1\N21223\S_016\2007-09-21

20-Nov-2007 submission- SAS datasets: \\Cdsesub1\N21223\S_016\2007-11-20

15-Jan-2008 submission- 4-Month Safety Update:
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4.2 Tables of Clinical Studies

Study Name	Study Design	Number of Patients	Study Duration	Treatment groups	Primary Endpoint
ZOL446H2202	Study 1- A single-dose PK study	11 pediatric OI patients	1 day	Zoledronic acid	Plasma AUC, volume of distribution and renal clearance
	Study 2- Randomized, active controlled study	155 pediatric OI patients	1 year	Zoledronic acid (n=75) Pamidronate (n=80)	LS BMD at 12 months relative to baseline.

4.3 Review Strategy

This medical reviewer independently reviewed pivotal trial ZOL446H2202 for safety and efficacy. Dr. Lee Ping reviewed the LS BMD efficacy and fracture safety data. Dr. Vaidyanathan from clinical pharmacology, independently reviewed the PK data. The clinical, biometrics and clinical pharmacology teams collaborated on their independent findings before making final recommendations.

4.4 Data Quality and Integrity

No DSI inspections were performed. The proportion of patients with protocol deviations was similar between groups. The most common causes for protocol violations were lack of a valid baseline or 12 month LS BMD assessment.

4.5 Compliance with Good Clinical Practices

The study was conducted in accordance with FDA guidelines on “Good Clinical Practice” and the principles of the Declaration of Helsinki.

4.6 Financial Disclosures

All clinical investigators at each of the 10 US and 10 nonUS sites, who enrolled patients into the pivotal trial ZOL446H2202 responded to the financial disclosure request from the sponsor and none had any financial interests to disclose. In addition, no clinical investigators are full or part-time employees of Novartis Pharmaceuticals Corporation. Therefore, there were no financial arrangements disclosed by the sponsor that may have affected the outcome of this trial.

5 CLINICAL PHARMACOLOGY

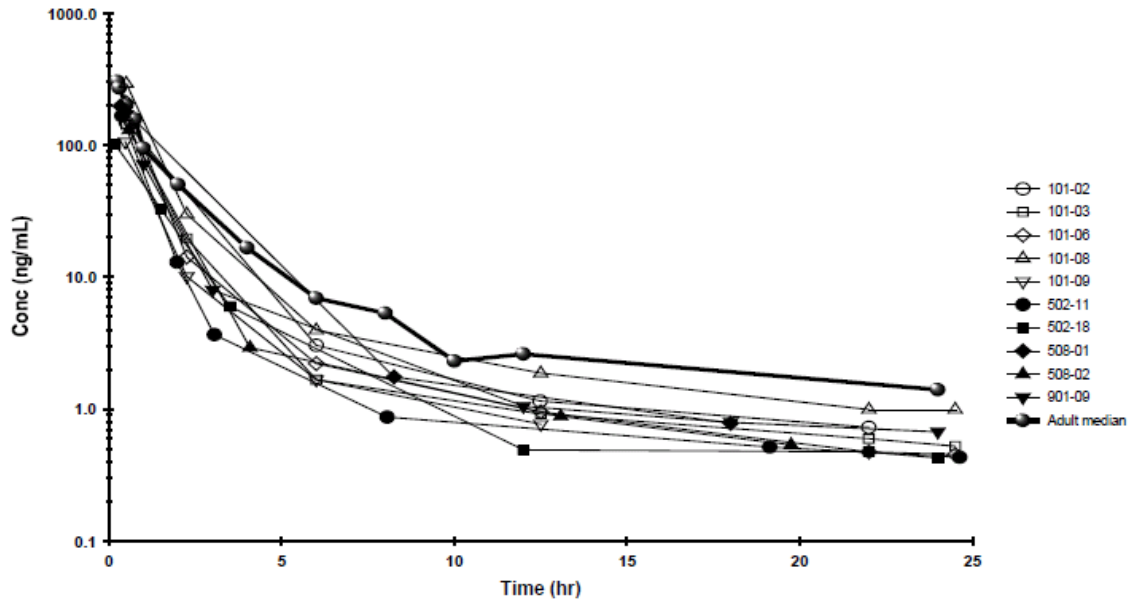
5.1 Pharmacokinetics (Study 1)

Study 1 was a single-dose study to determine the pharmacokinetics (PK) of zoledronic acid upon intravenous administration to pediatric patients with osteogenesis imperfecta (OI). A pre-dose blood sample was collected from each patient. At least 4 patients, 12 months through 8 years of age, and at least 4 patients, 9 through 17 years of age, were to complete the study. An attempt was made to include approximately equal numbers of male and female patients. Patients who were 1-2 years of age were to have three post-dose random blood samples. Patients who were 3-8 years of age were to have four post-dose random blood samples. Patients who were 9-17 years of age were to have six random post-dose blood samples. Post-dose fixed sampling was to be avoided. The timing of blood samples covered the absorption and elimination phases for the PK profiles in the different patient groups. Urine samples were only to be collected from patients 3 through 17 years of age. Zoledronic acid plasma concentration-time profiles, and zoledronic acid urinary excretion data, were characterized.

Plasma zoledronic acid concentration vs. time was plotted in **Figure 1** for 10 pediatric patients (4, age 3-8 and 6, age 9-17). The pediatric patients were dosed with 0.05mg/kg during 30 minute infusions. These data are compared to the median concentration vs. time for 16 adult cancer patients with normal renal function from studies CZOL446D0503 and CZOL446E0506 dosed with 0.05mg/kg during 15 minute IV infusions. The longer infusions in the pediatric patients probably accounted for part of the reason why their zoledronic acid levels were lower, but the shape of the curves was similar between the adult and pediatric patients.

Figure 1

Plasma zoledronic acid concentration vs. time



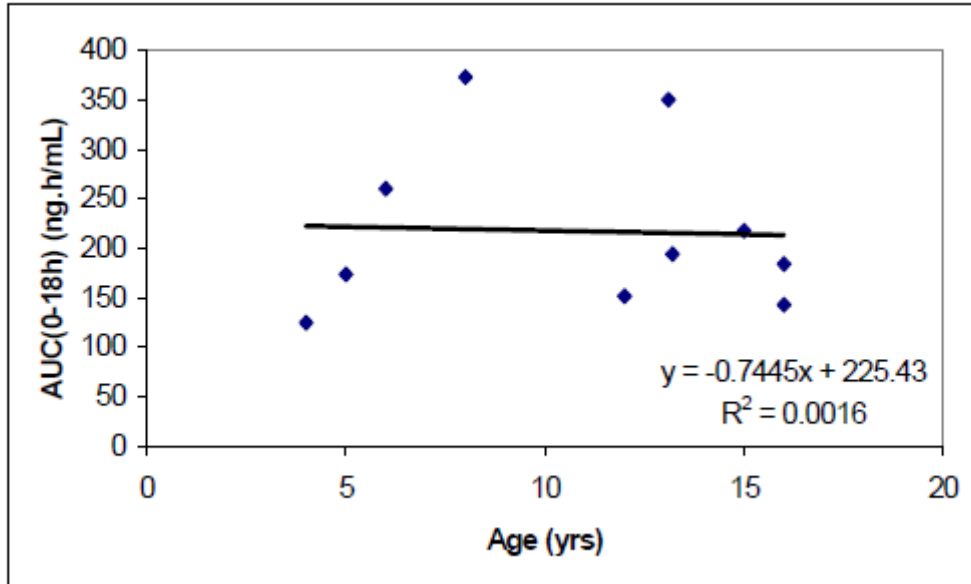
Adult median data were derived from 7 patients in Study ZOL446D0503 who received a dose of 4 mg zoledronic acid infused over 15 minutes, and 9 patients in Study ZOL446E0506 who had normal renal function and received 4 mg zoledronic acid infused over 15 minutes.

Data source Fig. 11-3 or 14.2-6.1 from clinical study report 2202.

There was no apparent difference in AUC in patients between 3 and 17 years of age (see Figure 2), although there was a good degree of variability between patients.

Figure 2

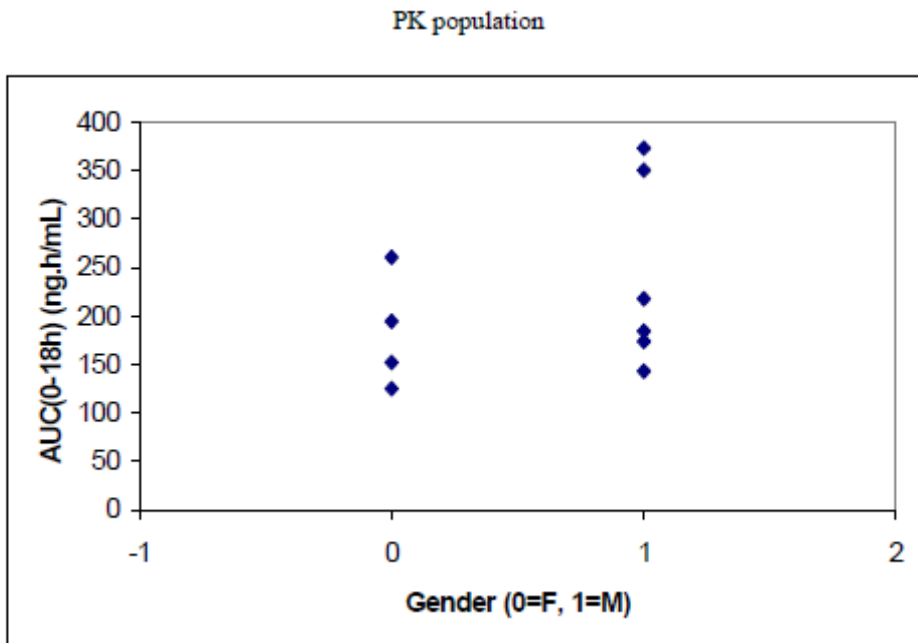
Effect of age on zoledronic acid AUC (0-18h) in pediatric patients



There was no apparent difference in AUC in pediatric patients with respect to gender (see Figure 3).

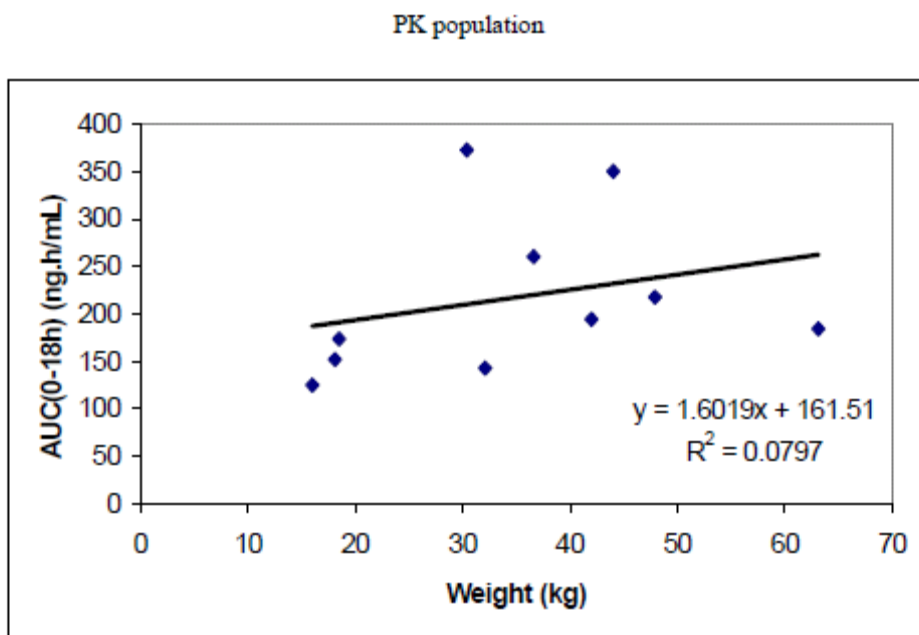
Figure 3

Effect of gender on zoledronic acid AUC (0-18h) in pediatric patients



There is a large degree of variability between patients with no apparent difference in AUC in pediatric patients with respect to body weight (see **Figure 4**).

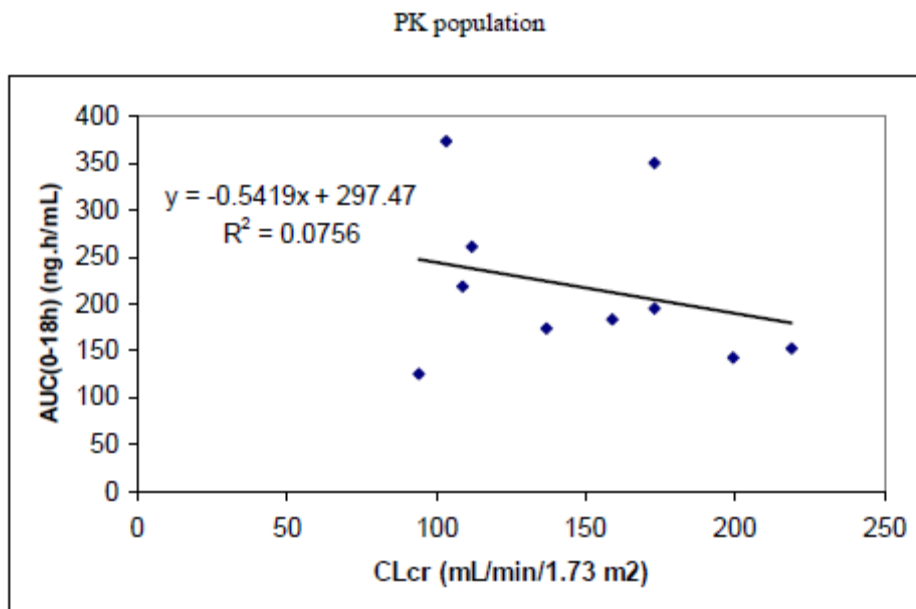
Figure 4
Effect of body weight on zoledronic acid AUC (0-18h) in pediatric patients



There is a large degree of variability between patients with no apparent effect of creatinine clearance on AUC in pediatric patients with normal renal function (see Figure 5).

Figure 5

Effect of creatinine clearance on zoledronic acid AUC (0-18h) in pediatric patients



The quality of the data on renal excretion of zoledronic acid was compromised by the failure to measure the volume of each of the urine collections. Urine volumes were roughly estimated by predicting the quantity of creatinine excreted during each collection interval using serum creatinine concentration and creatinine clearance values, then dividing by the creatinine concentration measured in each urine collection. From these estimated volumes and the concentration of zoledronic acid in urine, the amount of drug excreted in each urine collection was estimated. These data suggest that most urinary excretion occurs within the first 12 hours post dosing, with the rest of the zoledronic acid, retained in the body, likely bound up in bone. There was no difference in the pattern of urinary excretion between younger (age 3-8 years) and older children (age 9-17 years, compare Figure 6 & Figure 7).

Figure 6

Cumulative urinary excretion of zoledronic acid in pediatric patients aged 3-8 years

PK population

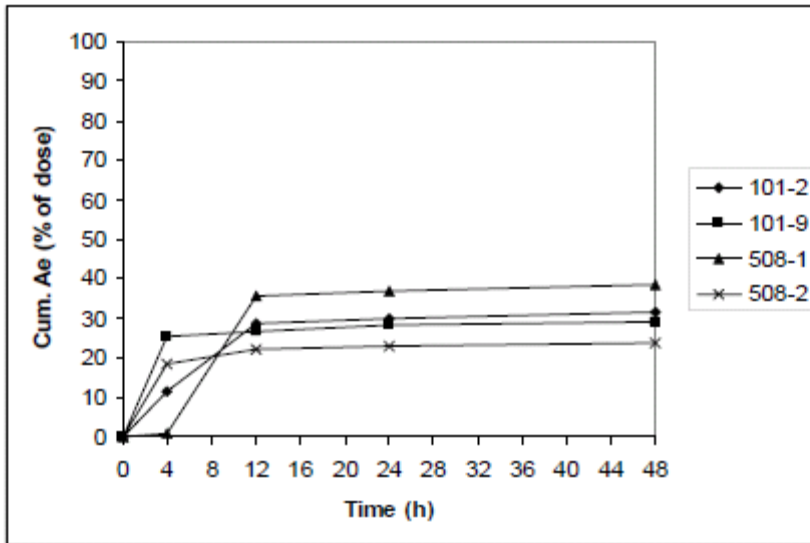
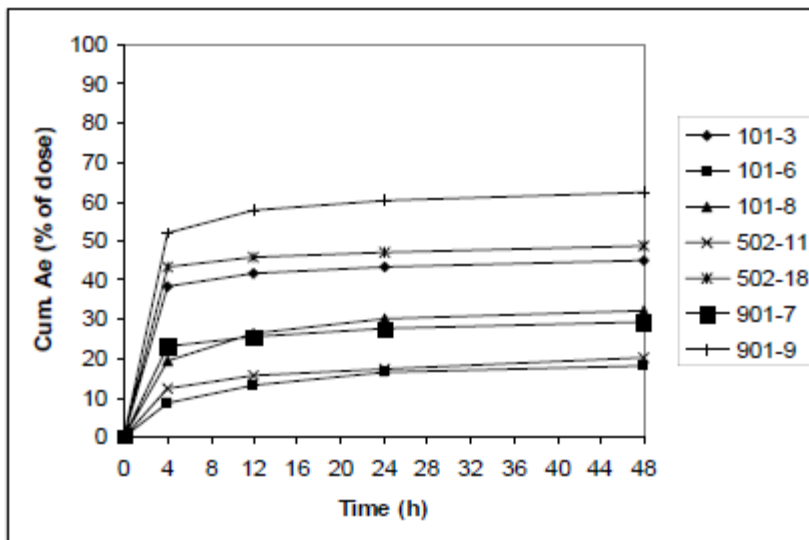


Figure 7

Cumulative urinary excretion of zoledronic acid in pediatric patients aged 9-17 years

PK population



In conclusion, there was large individual variability in the small number of pediatric patients, but in general there was no apparent effect of age, gender, body weight or creatinine clearance in

patients with normal renal function on AUC(0-18h), and most of the observed urinary excretion of zoledronic acid occurred in the first 12 hours post infusion.

5.2 Pharmacodynamics

See bone biomarker data in section 6.1.4 Efficacy findings/Secondary and exploratory endpoints

5.3 Exposure-Response Relationships

No exposure-response data was included in this submission.

6 INTEGRATED REVIEW OF EFFICACY (STUDY 2)

6.1 Indication

The sponsor is not seeking a treatment indication with this application. Pamidronate is currently used as an off-label therapy for children with OI but there is no currently approved therapy for this indication. Study ZOL446H2202 compares the effect of zoledronic acid to pamidronate on bone mineral density (BMD) in the lumbar spine (LS) of patients with moderate-to-severe OI.

6.1.1 Methods

The clinical efficacy and PK data were both obtained from study ZOL446H2202.

6.1.2 General Discussion of Endpoints

Fracture incidence, while arguably the most relevant clinical outcome, can be difficult to correlate with treatment efficacy in OI because it is affected by multiple external factors including age, mobility, capacity for ambulation and degree of limb immobilization. For example, patients feeling less bone pain as the result of a beneficial therapy may be more willing to ambulate and thereby increase their risk for a new fracture. An example of the possible disconnect between changes in BMD and fracture rates was seen in a 2-year, placebo-controlled trial with alendronate in pediatric OI patients which showed an improvement in spine BMD Z-score from -4.6 to -3.3 on alendronate compared to essentially no change on placebo (-4.6 to -4.5), yet there was no beneficial difference in fracture rates at 24 months between the treatment groups (e.g. 75% alendronate vs. 72% placebo.) Other clinical data in the literature² also support the use of BMD as a surrogate in pediatric patients with severe OI. Therefore, the Written

² [Glorieux FH](#). Experience with bisphosphonates in osteogenesis imperfecta. Pediatrics. 2007 Mar;119 Suppl 2:S163-5.

Request issued by the Agency required percentage change in LS BMD at month 12 relative to baseline as the primary efficacy variable and fracture incidence, bone pain, height or supine length and biochemical markers of bone turnover as secondary endpoints.

The two-sided 95% confidence interval based on t-distribution was planned as the primary analysis to demonstrate that zoledronic acid was not inferior to pamidronate in terms of the primary efficacy variable. Non-inferiority was concluded if the lower limit of the 95% CI for Δ was $>-13\%$ for ITT patients (last observation carried forward) who were randomized and had a valid baseline and at least one post-baseline LS BMD assessment. The superiority of zoledronic acid to pamidronate could be further assessed if non-inferiority was concluded, and demonstrated if the lower limit of the 95% CI was greater than zero.

As a secondary analysis, an analysis of covariance (ANCOVA) model was employed to compare the treatment difference of the primary efficacy variable. The model contained baseline LS BMD as a covariate, treatment, region (North America and Rest of the World), gender and pubertal stage as factors.

The following secondary endpoints were assessed:

- Change from baseline in lumbar spine Z-score at month 12: applies only to patients aged ≥ 3 years imaged on the Hologic equipment and patients aged ≥ 5 years imaged on the Lunar equipment for whom there are validated normative ranges
- Change from baseline in femoral neck BMC at month 6 and 12
- Number of clinical fractures over a year (frequency and time to first fracture)
- Relative change from baseline in biomarkers of bone turnover: serum β -CTx, P1NP and BALP at month 6 and 12 in patients ≥ 3 years of age
- Change from baseline in supine length (height) at month 6 and 12
- Summary of bone pain (Wong-Baker FACES) score at scheduled visits

The following exploratory endpoints were assessed:

- Percentage change from baseline in LS BMD at month 6
- Change from baseline in total body BMC at month 6 and 12
- Change from baseline in grip strength at month 6 and 12 in patients ≥ 3 years of age
- Change from baseline in cortical bone thickness (x-ray) at month 6 and 12
- Change from baseline in vertebral spine length (x-ray) at month 12
- Number of clinical fractures per patient over a year

The ANCOVA model, with baseline value as covariate, treatment, region, gender and pubertal stage as factors, was used to compare treatments for Z-score, BMD, BMC, supine length (height), grip strength, cortical bone thickness and vertebral spine length. For biomarkers of bone turnover, to normalize the distribution of such parameters, the \log_e transformation of the post-baseline value over the baseline value was used in the ANCOVA model with \log_e baseline value as covariate and treatment, region, gender, and pubertal stage as factors. 95% CIs and p-values were presented for analyses performed using ANCOVA models.

6.1.3 Study Design

Study 2 is a randomized, parallel-group study to compare the safety and efficacy of intravenous zoledronic acid to intravenous pamidronate in the treatment of children with moderate-to-severe OI. At least 132 patients between 1 and 17 years of age were to be randomized (1:1) to receive zoledronic acid or pamidronate. One-third of the patients were to be 12 months through 8 years of age. All patients were to receive standard medical care (e.g. supplemental calcium and vitamin D). Zoledronic acid patients ≥ 1 to < 3 years of age were to be administered 0.025 mg/kg as a 30 to 45-minute intravenous infusion every 3 months for one year. Patients ≥ 3 years to ≤ 17 years of age were to be administered 0.05 mg/kg as a 30-minute intravenous infusion every 3 months for one year. Pamidronate patients were to be administered 4-hour intravenous infusions of the study drug. Patients ≥ 1 year to < 2 years of age were to be administered 0.5 mg/kg/day on each of three consecutive days every 2 months for one year. Patients ≥ 2 years to < 3 years of age were to be administered 0.75 mg/kg/day on each of three consecutive days every 3 months for one year. Patients ≥ 3 years to ≤ 17 years of age were to be administered 1 mg/kg/day on each of three consecutive days every 3 months for one year. All patients were hospitalized for 48 hours during the first infusion and post-dose symptoms were assessed. All patients returned for follow up visits at 9 to 11 days post dosing for blood and urine sampling.

Inclusion criteria (included but not limited to)

- Children age 1 to 17
- OI type III or IV or
- OI type I with ≥ 3 minimal trauma fractures (including vertebral fractures) in the 2 previous years or with a history of limb deformity requiring surgery.
- Serum 25 hydroxy vitamin D ≥ 15 ng/mL

Exclusion criteria (included but not limited to)

- Renal disease: defined as a serum creatinine value above the upper limit of normal (age and sex-matched) or pathologic proteinuria (any patient with a urine protein to creatinine ratio of >0.3 is to be excluded) or history of prior clinically significant renal disease (e.g. nephritis or nephrotic syndrome). One repeat assessment of the urine protein to creatinine was allowed. The assessment was made within 2 weeks of the first assessment and the sample was a urine collection of a first morning void, after an overnight fast.
- Any disease or abnormality that would prevent accurate bone mineral density measurements of the lumbar spine (i.e. intra-abdominal calcification that may prohibit accurate data collection/interpretation; severe scoliosis, kyphosis, or metal implants, etc.)
- Any clinically significant clinical laboratory abnormalities at screening
- History or evidence of an intestinal malabsorption syndrome

The intent-to-treat (ITT) population included 63 patients in the zoledronic acid group and 68 patients in the pamidronate group. Patients who did not have a baseline measurement or were lost to follow-up without any post-baseline measurement were excluded from the analyses. Missing values were imputed using the last post-baseline observation carried forward (LOCF)

The per-protocol (PP) population included 51 patients in the zoledronic acid group and 55 patients in the pamidronate group. In the per-protocol analyses of the primary efficacy endpoint, missing values were not imputed.

6.1.4 Efficacy Findings

Primary endpoint

The primary endpoint was the percentage change in LS BMD at month 12 relative to baseline in the ITT (LOCF) population (see Table 1). Efficacy of zoledronic acid would be considered demonstrated if it was shown to be <13% non-inferior to pamidronate. The primary analysis of the percentage change in LS BMD at month 12 relative to baseline in the ITT (LOCF) population demonstrated that zoledronic acid was not only non-inferior, but superior, to pamidronate with an 8% greater increase in LS BMD and both 95% confidence intervals above zero. Similar results were observed in the per-protocol and completers populations.

Table 1

Percentage change from baseline in LS BMD at month 12 relative to baseline
 (Source: sponsor's Clinical Study Report Table 11-5)

Population	Treatment	N	Mean (SE) (1)	Mean difference (1)	95% CI (1)
ITT (LOCF) (2)	Zoledronic acid	63	42.71 (2.798)	8.06	0.42, 15.71
	Pamidronate	68	34.65 (2.669)		
Per-protocol	Zoledronic acid	51	45.58 (2.993)	10.02	1.46, 18.58
	Pamidronate	55	35.56 (3.094)		
Completers	Zoledronic acid	51	45.58 (2.993)	9.77	1.27, 18.26
	Pamidronate	56	35.81 (3.048)		

Note: N = number of patients with measurements at both baseline and month 12 visit, as determined by the visit windows after imputation by LOCF, the last observed value carried forward, if applicable. LOCF applied to ITT population only.

(1) Mean, mean difference (zoledronic acid minus pamidronate) and 95% CI of mean difference are based on t-distribution.

(2) ITT (LOCF) is the primary analysis.

A secondary analysis, using an analysis of covariance (ANCOVA) model was also employed to compare the treatment difference of the primary efficacy variable. The model contained baseline LS BMD as a covariate, treatment, region (North America and Rest of the World), gender and pubertal stage as factors. Whereas this analysis continued to show that zoledronic acid was not inferior to pamidronate using the -13% non inferiority margin, the LSM difference between the groups was smaller so that zoledronic acid effect was no longer superior (see Table 2).

Table 2

**Percentage change from baseline in LS BMD at month 12 relative to baseline
 Using a parametric ANCOVA model analysis (Source: sponsor's Clinical Study Report Table 11-6)**

Variable Visit	Treatment	N	Least squares mean (SE)	LSM difference (1)	95% CI (2)	P-value (2)
Percentage change from baseline in lumbar spine BMD						
Month 6	Zoledronic acid	63	29.01 (2.27)	3.79	-1.22, 8.81	0.1371
	Pamidronate	68	25.22 (2.39)			
Month 12	Zoledronic acid	63	46.46 (2.91)	5.39	-1.04, 11.82	0.0994
	Pamidronate	68	41.07 (3.07)			

The sponsor suggested that the loss of power to show superiority using the ANCOVA model was due to applying a parametric model to data that was not distributed normally. An examination of the % change in LS BMD data in the A_DXALS SAS dataset by this reviewer found that the data was not normally distributed as the sponsor had proposed. There were outliers above the 50-60% values in both treatment groups so that the mean values were consistently greater than the median values. When the sponsor repeated the analysis using a non-parametric ANCOVA model in the ITT (LOCF) population the treatment difference for % change in LS BMD in the zoledronic acid group was much greater and again superior to the data in the pamidronate group (LSM treatment difference=13.6, 95% CIs +2.9 and +24.3, and p=0.013 at the 12 month time point).

Secondary and exploratory endpoints

The secondary/exploratory variables of femoral neck BMC, total body BMC and LS Z-score were also analyzed using a parametric ANCOVA model (see Table 3). The magnitude of the LSM difference was greater in the zoledronic acid groups for each of these endpoints but the results were not statistically significant.

Table 3

Percentage change from baseline in femoral neck BMC, total body BMC, and LS Z-score at month 12 relative to baseline using a parametric ANCOVA model analysis

(Source: sponsor's Clinical Study Report Table 11-6)

Variable Visit	Treatment	N	Least squares mean (SE)	LSM difference (1)	95% CI (2)	P-value (2)
Change from baseline in femoral neck BMC						
Month 6	Zoledronic acid	42	0.31 (0.04)	0.05	-0.05, 0.14	0.3376
	Pamidronate	45	0.26 (0.04)			
Month 12	Zoledronic acid	42	0.47 (0.04)	0.08	-0.02, 0.17	0.1118
	Pamidronate	45	0.40 (0.04)			
Change from baseline in total body BMC						
Month 6	Zoledronic acid	70	143.47 (11.44)	7.14	-20.44, 34.71	0.6096
	Pamidronate	71	136.34 (12.43)			
Month 12	Zoledronic acid	70	255.59 (16.11)	24.78	-14.04, 63.61	0.2090
	Pamidronate	71	230.81 (17.50)			
Change from baseline in lumbar spine Z-score						
Month 6	Zoledronic acid	43	1.19 (0.11)	0.24	0.00, 0.49	0.0538
	Pamidronate	49	0.95 (0.10)			
Month 12	Zoledronic acid	43	1.57 (0.13)	0.27	-0.04, 0.58	0.0877
	Pamidronate	49	1.31 (0.13)			

N = number of patients with non-missing data at each specific visit, as determined by visit windows after imputation by LOCF, the last observed value carried forward

(1) LSM difference is the difference of least squares means (LSMs) between treatments (zoledronic acid minus pamidronate).

(2) 95% CI and P-value are obtained from ANCOVA model with baseline value as a covariate, treatment, region, gender and puberty stage as factors.

† Only patients aged ≥3 years imaged on the Hologic equipment and patients aged ≥5 years imaged on the Lunar equipment have Z-score values in the clinical database that could be included in this analysis, because there are no validated normative ranges available for younger children.

Source: [Table 14.2-2.1](#), [Table 14.2-2.7](#), [Table 14.2-2.9](#), [Table 14.2-2.11](#)

The secondary endpoints of relative change from baseline in biomarkers of bone turnover (serum β -CTx, P1NP and BALP, in patients ≥ 3 years of age) all had statistically significant greater reductions in the zoledronic acid group compared to the pamidronate group at both 6 and 12 months (see **Table 4**). The bone resorption marker β -CTx, produced a 34% decrease in the zoledronic acid group compared to a 9% increase in the pamidronate group at 12 months (see **Figure 8**). The bone formation marker P1NP produced a 46% decrease in the zoledronic acid group compared to only a 28% decrease in the pamidronate group at 12 months (see **Figure 9**). The bone formation marker BALP produced a produced a 35% decrease in the zoledronic acid group compared to only a 27% increase in the pamidronate group at 12 months (see **Figure 10**).

Table 4

Relative change from baseline in serum bone biomarkers β -CTx, P1NP and BALP at month 6 and 12 in patients ≥ 3 years (ITT, source Clinical Study Report Fig. 11-8)

Variable Visit	Treatment	N	Exp (LSM) (1)	Difference (2)	95% CI of ratio (3)	P-value (3)
β-CTx						
Month 6	Zoledronic acid	44	0.64	0.72	0.63, 0.82	<0.0001
	Pamidronate	49	0.88			
Month 12	Zoledronic acid	40	0.58	0.69	0.60, 0.79	<0.0001
	Pamidronate	49	0.84			
P1NP						
Month 6	Zoledronic acid	44	0.59	0.81	0.70, 0.93	0.0028
	Pamidronate	48	0.72			
Month 12	Zoledronic acid	40	0.46	0.79	0.68, 0.91	0.0011
	Pamidronate	50	0.59			
BALP						
Month 6	Zoledronic acid	44	0.63	0.89	0.80, 0.99	0.0314
	Pamidronate	49	0.71			
Month 12	Zoledronic acid	40	0.54	0.88	0.78, 1.00	0.0457
	Pamidronate	50	0.61			

N = number of patients with non-missing data at each specific visit, as determined by visit windows.

(1) Back transformed Least Squares Mean (LSM).

(2) Relative treatment difference = exponential of the difference in LSM on the log(e) scale or the geometric LSM on the original scale. For values less than 1, zoledronic acid has a greater reduction than pamidronate.

(3) The 95% CI is calculated by inverting the log(e)(ratio) transformation. The ratio = endpoint/baseline. The p-value is obtained from an analysis of covariance on log(e)(ratio) with log(e) baseline as covariate, treatment, region, gender and puberty stage as factors.

Source: [Table 14.2-4.1](#), [Table 14.2-4.3](#), [Table 14.2-4.5](#)

Figure 8 Mean % Change in b-CTX (Source Clinical Study Report Table 14.2-4.2)

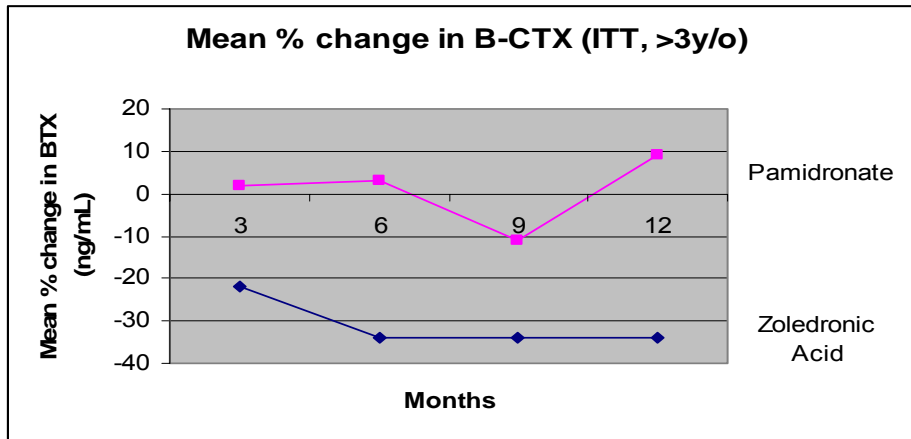


Figure 9 Mean % Change in P1NP (Source Clinical Study Report Table 14.2-4.4)

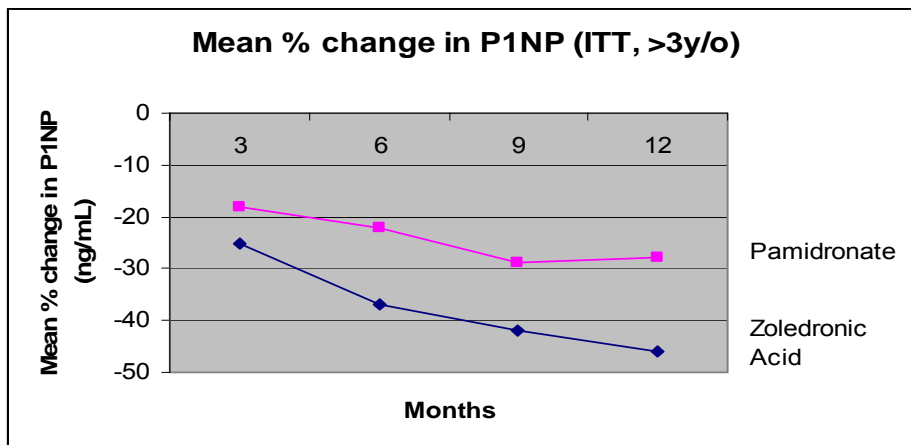
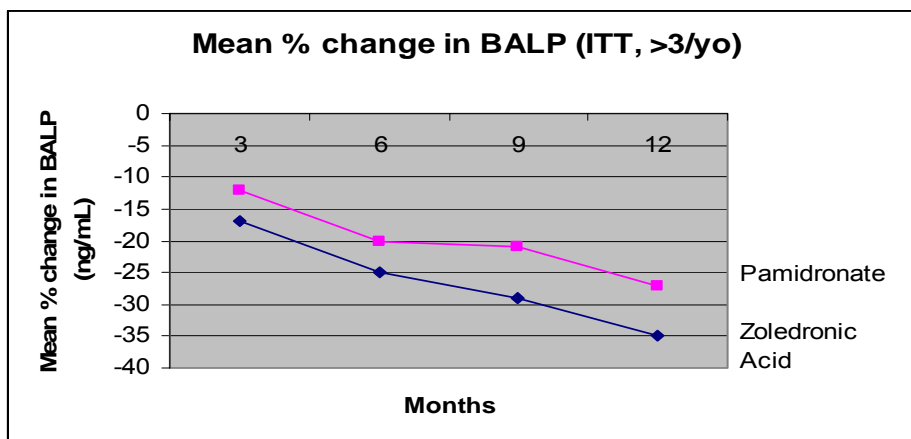


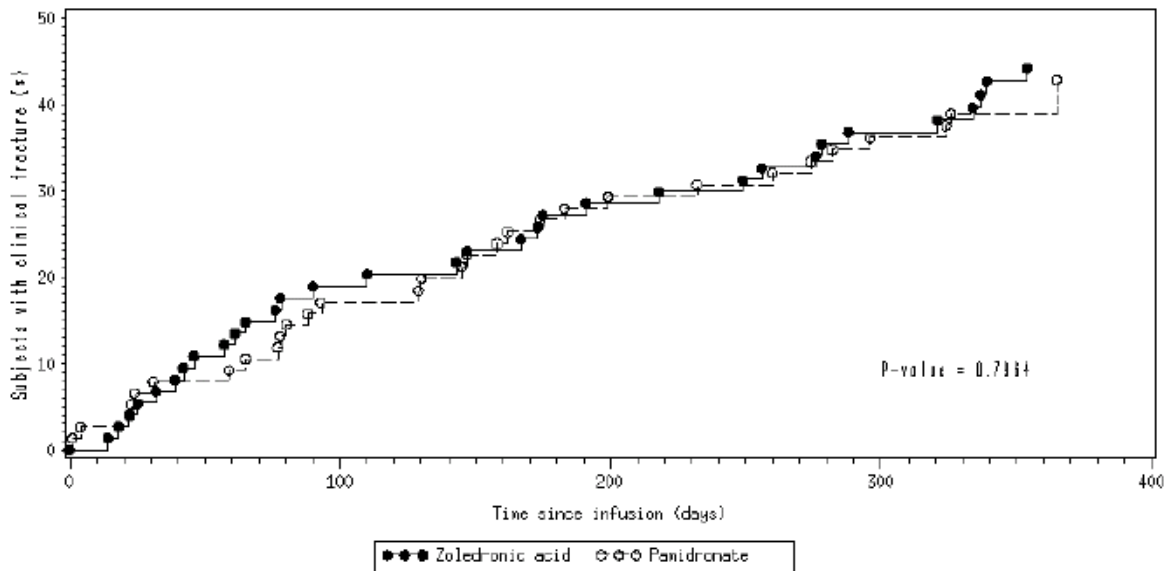
Figure 10 Mean % Change in BALP (Source Clinical Study Report Table 14.2-4.6)



Time to first clinical fracture, plotted using a Kaplan-Meier curve, showed no difference between treatment groups (see **Figure 11**). Similarly, there was no difference in total number of patients with fractures [e.g. 32 (43%) in the zoledronic acid group compared to 31 (41%) in the pamidronate group]. There were, however, numerically more OI type I patients with fractures in the zoledronic acid group 19 (50%) compared to 10 (29%) in the pamidronate group (hazard ratio 2.1, $p=0.09$, not statistically significant), which led to a DSMB recommendation for premature termination of the trial due to safety concerns. In contrast, there were numerically more OI type III & IV patients with fractures in the pamidronate group 21 (51%) compared to 13 (36%) in the zoledronic acid group (hazard ratio 1.7, $p=0.25$, also not statistically significant).

Figure 11

Kaplan-Meier estimate of time to first clinical fracture after first infusion
(ITT, source Clinical Study Report Fig. 11-2)



P-value is from Kaplan-Meier log-rank test.

Source: [Figure 14.2-5.1](#), [Table 14.2-5.1](#)

Medical Officer's comments-

It is not clear if the apparent increase in fractures seen in Type I OI patients treated with zoledronic acid represents a real finding or was a chance occurrence. The same can be said for the apparent higher rate of fractures with pamidronate in Type III & IV OI patients.

Assuming bone resorption markers are useful surrogates for risk of fracture, the greater reductions in bone resorption biomarkers seen in the zoledronic acid treatment group would have predicted a lower relative fracture rate. This was only the case for Type III & IV patients treated with zoledronic acid, even though the serum β -CTX was statistically

lower at 6, 9 and 12 months in the zoledronic acid group for both Type I ($p=.0002$) and Type III & IV patients ($p=.005$). It may be that the greater reduction in the bone formation biomarkers, seen in the zoledronic acid group may have cancelled out any benefit in Type I patients. Still it is hard to explain why there was a difference in the fracture rates between Type I and Type III & IV OI patients when zoledronic acid caused consistently greater reductions in all the bone biomarkers tested in both disease subgroups. This suggests to this reviewer that the difference in fracture rates was a chance finding.

Subjects with tibial or femoral fractures during the study had lower mean baseline LS BMDs (see Table 5). Similarly, those with lower LS BMD values as a group at the end of the study were also more likely to have had a femoral or tibial fracture during the study suggesting that LS BMD may be a useful surrogate for tibial or femoral fractures in the OI population.

Table 5

**Mean LS BMD at baseline and month 12 (LOCF)
 segregated by history of tibial or femoral fracture during the study
 (source Clinical Study Report Tables 14.2-2a and 2b)**

	Baseline LS BMD (g/cm ²)		12 month LS BMD (g/cm ²) (LOCF)	
	yes	no	yes	no
Tibial Fracture				
Zoledronic acid	0.35	0.42	0.45	0.59
Pamidronate	0.33	0.45	0.45	0.59
Femoral Fracture	yes	no	yes	no
Zoledronic acid	0.33	0.44	0.48	0.61
Pamidronate	0.36	0.46	0.5	0.59

Consistent with this, LS BMD values increased for both zoledronic acid and pamidronate treatment groups during the course of the study, and as expected the fracture rates in both treatment groups during the 12 months of the study were much lower than observed in patients in the 12 months prior to the initiation of bisphosphonate treatment. Baseline LS BMD was slightly lower in the zoledronic acid Type I patients compared to the pamidronate patients (0.428 g/cm² vs. 0.485 g/cm²) which may have imparted a slightly higher risk of fracture in the zoledronic acid group, but the % increase in LS BMD was higher in the zoledronic acid group (e.g. 41% vs. 30% for Type I patients at month 12), which should have been associated with a lower fracture risk in the Type I OI patients, in contrast to the findings seen in this study.

In summary, the findings of a reduction in bone biomarkers and an increase in LS BMD in the zoledronic acid treatment group are consistent with the lower fracture risk seen in all OI patients including Type I and Types III & IV, in this study compared to the 12 months prior to the start of therapy. However, the greater reductions in bone biomarkers and greater increase in LS BMD seen in the zoledronic acid group compared to the

pamidronate group do not correlate with the observation of a relative increase in fractures Type I patients with zoledronic acid and a relative increase in fractures in Type III & IV patients with pamidronate. It is this reviewer's impression that the difference in fracture rates, which was not statistically significant, was a chance finding.

Bone Pain was assessed using the Wong-Baker FACES at baseline, 6 and 12 months (see Table 6). Most patients had no pain or minimal pain at baseline and at the end of the study. No statistically significant differences were identified between treatment groups. Type 1 patients in the zoledronic acid group reported slightly less pain than in the pamidronate group at both the start and the end of the study which did not correlate with the greater number of Type 1 patients with fractures in this study in the zoledronic acid group. It is this reviewer's interpretation that bone pain assessments in an open-label study of OI patients are of limited value.

Table 6

Bone Pain (Wong-Baker FACES) scored by visit and treatment

Visit Wong-Baker FACES	Zoledronic acid			Pamidronate		
	All N=74	OI Type I N=38	OI Type III / IV N=36	All N=76	OI Type I N=35	OI Type III / IV N=41
Baseline						
No hurt	50 (67.6)	30 (78.9)	20 (55.6)	46 (60.5)	21 (60.0)	25 (61.0)
Hurts little bit	15 (20.3)	6 (15.8)	9 (25.0)	20 (26.3)	9 (25.7)	11 (26.8)
Hurts little more	4 (5.4)	1 (2.6)	3 (8.3)	8 (10.5)	5 (14.3)	3 (7.3)
Hurts even more	2 (2.7)	0	2 (5.6)	1 (1.3)	0	1 (2.4)
Hurts whole lot	1 (1.4)	1 (2.6)	0	0	0	0
Hurts worst	1 (1.4)	0	1 (2.8)	0	0	0
Missing	1 (1.4)	0	1 (2.8)	1 (1.3)	0	1 (2.4)
Month 6						
No hurt	52 (70.3)	29 (76.3)	23 (63.9)	55 (72.4)	25 (71.4)	30 (73.2)
Hurts little bit	13 (17.6)	4 (10.5)	9 (25.0)	12 (15.8)	6 (17.1)	6 (14.6)
Hurts little more	5 (6.8)	2 (5.3)	3 (8.3)	1 (1.3)	1 (2.9)	0
Hurts even more	0	0	0	0	0	0
Hurts whole lot	0	0	0	1 (1.3)	0	1 (2.4)
Hurts worst	0	0	0	1 (1.3)	1 (2.9)	0
Missing	4 (5.4)	3 (7.9)	1 (2.8)	6 (7.9)	2 (5.7)	4 (9.8)
Month 12						
No hurt	54 (73.0)	29 (76.3)	25 (69.4)	49 (64.5)	23 (65.7)	26 (63.4)
Hurts little bit	7 (9.5)	2 (5.3)	5 (13.9)	7 (9.2)	2 (5.7)	5 (12.2)
Hurts little more	0	0	0	5 (6.6)	3 (8.6)	2 (4.9)
Hurts even more	2 (2.7)	0	2 (5.6)	2 (2.6)	1 (2.9)	1 (2.4)
Hurts whole lot	0	0	0	1 (1.3)	0	1 (2.4)
Hurts worst	0	0	0	0	0	0
Missing	11 (14.9)	7 (18.4)	4 (11.1)	12 (15.8)	6 (17.1)	6 (14.6)

Source: [Table 14.2-5.3](#) and [Table 14.2-5.4](#)

No statistically significant differences between zoledronic acid and pamidronate were found for supine length/height, vertebral spine length or grip strength all of which increased during the 12 month period of the study. No statistically significant differences between zoledronic acid and pamidronate were found for cortical bone thickness which remained unchanged during the course of the study.

6.1.5 Clinical Microbiology

Not applicable

6.1.6 Efficacy Conclusions

- 1) Zoledronic acid was not only non-inferior, but superior, to pamidronate with respect to the primary endpoint in this study [e.g. percent change in LS BMD at month 12 relative to baseline (ITT, LOCF)].
- 2) Percentage change from baseline in femoral neck BMC, total body BMC, LS Z-score, supine length/height, vertebral spine length and grip strength all increased during the 12 month period of the study but there were no statistically significant differences between zoledronic acid and pamidronate treatment groups.
- 3) Bone resorption biomarker, β -CTX, and bone formation markers serum PINP and BALP all had statistically greater reductions from baseline in the zoledronic acid group compared to the pamidronate group.
- 4) There was no difference in total number of patients with fractures [e.g. 32 (43%) in the zoledronic acid group compared to 31 (41%) in the pamidronate group] nor in the time to first clinical fracture estimated using a Kaplan-Meier curve. There were numerically more OI Type I patients with fractures in the zoledronic acid group 19 (50%) compared to 10 (29%) in the pamidronate group (hazard ratio 2.1, $p=0.09$, not statistically significant), and more OI Type III & IV patients with fractures in the pamidronate group 21 (51%) compared to 13 (36%) in the zoledronic acid group (hazard ratio 1.7, $p=0.25$, also not statistically significant). These differences may have occurred by chance and should not be used to favor treatment with one bisphosphonate over the other.
- 5) Consistent with the observed increase from baseline in LS BMD in both treatment groups, the fracture rates in both the zoledronic acid and pamidronate completer groups were much lower during the 12 months of the study than in the 12 months prior to the initiation of bisphosphonate treatment suggesting that both of these bisphosphonates provide a clinically beneficial treatment for pediatric patients with OI.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

There were no deaths in either treatment group during the course of this study.

7.1.2 Other Serious Adverse Events

Serious adverse events occurred more commonly in the zoledronic acid group (24/74=32%) compared to the pamidronate group (15/78=19%, see Table 7) and were mainly due to higher rates of femur fracture and hypocalcemia in the zoledronic acid group.

Table 7

**Serious adverse events by preferred term occurring in > 1pt/treatment group
(Source- Clinical Study Report Table 12-8)**

Preferred terms	Zoledronic acid N=74 n (%)	Pamidronate N=78 n (%)
Patients with any SAE	24 (32.4)	15 (19.2)
Femur fracture	10 (13.5)	5 (6.4)
Hypocalcemia	6 (8.1)	0
Humerus fracture	2 (2.7)	1 (1.3)
Skull fracture	2 (2.7)	0
Pyrexia	2 (2.7)	0

The six cases of hypocalcemia and one case of blood calcium decreased reported as SAEs in zoledronic acid patients, all occurred in the 3 days after the first zoledronic acid infusion and did not recur after subsequent infusions. At least four of the seven zoledronic acid patients, with SAEs of hypocalcemia or blood calcium decreased, reported symptoms of hypocalcemia, and received treatment for the hypocalcemia during hospitalizations. Other AEs associated with the hypocalcemia included: hypokalemia, hypophosphatemia, tachycardia, fever, headache, vomiting, abdominal pain, weakness, bone pain, and general malaise.

7.1.3 Dropouts and Other Significant Adverse Events

Two patients in the zoledronic acid group had AEs leading to discontinuation including: one patient who had bone pain in the right tibia, and one patient who had a left arm fracture. Both patients received 3 infusions of study drug before discontinuation and both AEs were considered serious AEs.

Two patients in the pamidronate group also had AEs leading to discontinuation including: one 16 y/o female who became pregnant one month after her second infusion, and gave birth to a healthy 37 wk old normal baby boy, and one patient who had worsening of preexisting post traumatic stress disorder after her third dose of the study drug.

7.1.4 Other Search Strategies

None

7.1.5 Common Adverse Events

Adverse events occurring in at least 10% of patients in either group are listed in Table 8.

Table 8

Adverse Events occurring in $\geq 10\%$ of patients in either treatment group (Safety population)

	Zoledronic acid N=74 n (%)	Pamidronate N=78 n (%)
Patients with AE(s)	71 (95.9)	76 (97.4)
Preferred term:		
Pyrexia	45 (60.8)	42 (53.8)
Pain in extremity	21 (28.4)	19 (24.4)
Vomiting	21 (28.4)	12 (15.4)
Arthralgia	19 (25.7)	17 (21.8)
Femur fracture	18 (24.3)	9 (11.5)
Headache	16 (21.6)	15 (19.2)
Hypocalcemia	16 (21.6)	7 (9.0)
Back pain	14 (18.9)	14 (17.9)
Bone pain	13 (17.6)	4 (5.1)
Nasopharyngitis	12 (16.2)	9 (11.5)
Fatigue	11 (14.9)	6 (7.7)
Tibia fracture	10 (13.5)	4 (5.1)
Musculoskeletal pain	9 (12.2)	3 (3.8)
Nausea	9 (12.2)	10 (12.8)
Abdominal pain upper	8 (10.8)	4 (5.1)
Influenza	8 (10.8)	2 (2.6)
Anorexia	5 (6.8)	8 (10.3)
Pain	5 (6.8)	8 (10.3)

Preferred terms are arranged in descending order of frequency in the zoledronic acid group

Source: [Table 14.3.1-1.6](#)

Events occurring in 5% or greater of the patients in the zoledronic acid group compared to the pamidronate group were in order of greatest difference between groups: ~13% (vomiting, femur fracture, hypocalcemia, and bone pain), ~8% (tibial fracture, musculoskeletal pain, and influenza), ~7% (fatigue and pyrexia), and ~6% (upper abdominal pain). No events occurred in 5% or greater of the patients in the pamidronate group compared to the zoledronic acid group.

Medical officer's comments-

Adverse reactions seen more commonly in pediatric patients compared to adults included pyrexia (61%), hypocalcemia (22%) and headache (22%). These reactions occurred most frequently within three days after the first infusion and became less common with repeat dosing (see Table 9).

Table 9

Comparative Rates of Common Adverse Events associated with the use of Zoledronic Acid

% of AEs Reported from clinical trials with Zoledronic Acid (Source Zometa and Reclast PIs)								
AE	Bone Metastases		Hypercalcemia of Malignancy	Pagets Dz	PMO		Pediatric IO	
	Placebo	Zometa 4mg			Reclast 5mg	Placebo	All	<3 days
Pyrexia/fever	20	32	44	9	18	5	61	51
Nausea	38	46	29	9	9	5	12	8
Vomiting	27	32	14	2	5	3	28	18
hypocalcemia	NA	NA	NA	3	NA	NA	22	22
Headache	11	19	NA	11	12	8	22	10
Fatigue/ Lethargy	29	39	NA	5	5	4	15	5
Abdominal pain upper	11	14	16	2	5	3	11	NA
Influenza/Influ like illness	NA	NA	NA	7-11	9	3	11	1
Anorexia	23	22	9	2	2	1	7	3
Arthralgia	21	16	NA	9	24	20	26	7

NA- not available in PIs. The highest value in each row is highlighted.

Acute-phase reaction

Most acute phase reaction-related AEs (pyrexia, vomiting, headache, nausea, tachycardia, chills and influenza like illness) and episodes of hypocalcemia and/or hypophosphatemia were observed within the first 3-6 days after dosing (early onset) and were much less common thereafter (later onset, see Table 10) even with repeat dosing.

Table 10

Adverse Events occurring in ≥5% of patients in either treatment group (Safety population)

Preferred term	Early onset †		Later onset ‡	
	Zoledronic acid N=74 n (%)	Pamidronate N=78 n (%)	Zoledronic acid N=74 n (%)	Pamidronate N=78 n (%)
1st infusion				
Pyrexia	38 (51.4)	38 (48.7)	5 (6.8)	4 (5.1)
Hypocalcemia	16 (21.6)	6 (7.7)	0	0
Vomiting	13 (17.6)	8 (10.3)	6 (8.1)	1 (1.3)
Headache	7 (9.5)	8 (10.3)	5 (6.8)	2 (2.6)
Nausea	6 (8.1)	7 (9.0)	2 (2.7)	2 (2.6)
Pain in extremity	6 (8.1)	5 (6.4)	5 (6.8)	5 (6.4)
Tachycardia	5 (6.8)	2 (2.6)	0	1 (1.3)
Acute phase reaction	4 (5.4)	5 (6.4)	0	0
Fatigue	4 (5.4)	2 (2.6)	3 (4.1)	1 (1.3)
Hypophosphatemia	4 (5.4)	1 (1.3)	0	0
Pain	4 (5.4)	3 (3.8)	0	3 (3.8)
Blood calcium decreased	3 (4.1)	5 (6.4)	0	0
Anorexia	2 (2.7)	5 (6.4)	2 (2.7)	2 (2.6)
Back pain	2 (2.7)	4 (5.1)	4 (5.4)	4 (5.1)
Chills	2 (2.7)	4 (5.1)	0	0
Arthralgia	1 (1.4)	4 (5.1)	5 (6.8)	7 (9.0)
Influenza like illness	1 (1.4)	4 (5.1)	0	0
2nd infusion				
Pain in extremity	3 (4.1)	4 (5.1)	8 (10.8)	1 (1.3)
Pyrexia	2 (2.7)	4 (5.1)	3 (4.1)	4 (5.1)
Infusion site pain	0	5 (6.4)	0	0

† For zoledronic acid, infusion took place over 30 minutes, so early onset refers to events occurring within ≤3 days of study drug infusion start. For pamidronate, infusion took place over 3 days, so early onset refers to events occurring within ≤6 days of study drug infusion start.

‡ For zoledronic acid, later onset refers to events occurring >3 days of study drug infusion start. For pamidronate, infusion took place over 3 days, so later onset refers to events occurring >6 days of study drug infusion start.

Preferred terms are arranged in descending order of frequency in the early onset zoledronic acid group.

Source: [Table 14.3.1-1.7](#)

Musculoskeletal pain-

Post-marketing reports of musculoskeletal pain have been described infrequently with the use of zoledronic acid and other bisphosphonates. However, because of the nature of the bone disease seen with OI, it is fairly common to identify bone pain in these patients, making it more difficult to assign an etiology to musculoskeletal pain that was seen during this trial. The bone pain assessment using the Wong-Baker FACES (see Table 6) did not identify a clear increase in bone pain compared to baseline nor did it identify a clear difference between treatment groups.

Medical officer's comments-

The variability in the reports of bone pain in this study was not surprising given that this was an open-label trial and relied on pediatric patients to give subjective responses to a questionnaire.

7.1.6 Less Common Adverse Events

Eye disorders-

Uveitis and episcleritis are known side effects associated with the use of intravenous bisphosphonates. The clinical database was searched for the terms “uveitits” and “episcleritis” and no cases were found. Most of the eye disorders in the zoledronic acid group were confined to two patients: USA/0508/00002- 4 events (e.g. eye pruritus, eye irritation, lacrimation increased, and ocular hyperaemia) and FIN/0901/00011- 2 events (e.g. eye irritation and eye irritation).

Table 11

Eye Disorders in the Study ZOL446H2202

Primary system organ class Preferred term	Zoledronic acid N=74 n (%)	Pamidronate N=78 n (%)	Total N=152 n (%)
Eye disorders			
-Total	6 (8.1)	3 (3.8)	9 (5.9)
Eye irritation	3 (4.1)	0	3 (2.0)
Conjunctivitis	1 (1.4)	0	1 (0.7)
Eye pruritus	1 (1.4)	0	1 (0.7)
Lacrimation increased	1 (1.4)	0	1 (0.7)
Ocular hyperaemia	1 (1.4)	0	1 (0.7)
Retinal dystrophy	1 (1.4)	0	1 (0.7)

Medical officer’s comments-

There were no clear eye-related safety concerns identified in this trial, but because of the small size of this trial this does not rule out the possibility that bisphosphonates might precipitate such an event in this patient population.

Osteonecrosis of the jaw (ONJ)-

ONJ is a rare finding associated with the use of intravenous bisphosphonates primarily in cancer patients undergoing dental procedures. No cases of ONJ were seen in this trial.

Medical officer’s comments-

Because ONJ is such a rare finding, it was not unexpected not to see any events in this small trial, but this does not rule out the possibility that bisphosphonates might precipitate such an event in this patient population.

7.1.7 Laboratory Findings

Hypocalcemia/Hypercalcemia-

Hypocalcemia has been associated with bisphosphonate use especially with intravenous bisphosphonates and particularly in patients with Paget’s disease. To avoid placing subjects at risk of severe hypocalcemia in this study, patients with baseline calcium levels below the normal age-matched range or evidence of vitamin D deficiency (serum 25 (OH) Vit D < 15ng/mL) were excluded. All patients were provided with mandatory calcium (500mg-1500mg/day, dose

adjusted for age) and vitamin D (200IU/day) supplementation for 2 weeks prior to randomization and throughout the duration of the study.

Despite the supplementation with calcium and vitamin D there were still a few cases of hypocalcemia (CALC <2.1mmol/L) that were mostly considered mild/moderate in severity. The lowest reported calcium value was 7.4 mg/dL in the zoledronic acid group and 7.7 mg/dL in the pamidronate group. 14 of the 17 cases occurred within the first 2 weeks of treatment. Only one patient in the zoledronic acid group had a repeat episode of hypocalcemia after a later infusion.

High calcium levels were unexpectedly more prevalent than low calcium levels in this study. This may have been due to the required supplementation with calcium and vitamin D prior to and during the study. In contrast to the cases of hypocalcemia which were seen primarily following the first infusion, cases of hypercalcemia were seen throughout the length of the study. Despite the large number of elevated calcium lab values only four cases, two in each group, were also described as AEs (a_lrs.xpt, PATIENT_TXT=hypercalcemia/high calcium level).

Table 12

Abnormal Calcium Values during Study ZOL446H2202

Serum Calcium Level Abnormalities		Zoledronic Acid Patient # (%)	Pamidronate Patient # (%)
Hypercalcemia†			
>3 mmol/L (12mg/dL)	Severe	0	0
>2.875 mmol/L (11.5mg/dL)	Moderate	2(3%)	1 (1%)
>2.75 mmol/L (11mg/dL)	Moderate	5 (7%)	9 (11%)
>2.64 mmol/L (10.56mg/dL)	Mild	16 (21%)	23 (29%)
>2.57 mmol/L (10.28mg/dL) ULN	Mild	31 (41%)	47 (59%)
Hypocalcemia			
<2.1 mmol/L (8.4mg/dL) LLN	Mild	11‡ (15%)	7 (9%)
<1.75mmo/L (7.0mg/dL)	Moderate	1‡ (1%)	0
<1.525 mmol/L (6.1mg/dL)	Severe	0	0

A_LRS.xpt, PARNAM1C=CALC, DAY_1N>0, † Patients could be counted more than once if they had values in each subset. The total number of patients with data in the zoledronic acid group was 75 and in the pamidronate group 80.
 ‡ Includes one patient [0502-00011] with a calcium value of 7.9 mg/dL reported as an SAE in a case narrative but not included in SAS dataset.
 †Includes one patient [0401-00002] with a calcium value of 6.8 mg/dL reported as an SAE in a case narrative but not included in SAS dataset. These occurred possibly because the lab values were recorded in the hospital and not measured in the central clinical lab.
 In addition, six patients in the zoledronic acid group [0515-00010, 0601-00002, 0601-00004, 0601-00005, 0901-00007, and 0901-00011] had low ionized calcium values [ranging from 3.0mg/dL to 4.2mg/dL] reported as AEs with normal total calcium levels within a few days of receiving their first dose of study drug. Five of these six patients were hospitalized and received treatment for hypocalcemia/low calcium level. Eight patients in the pamidronate group had low ionized calcium levels [ranging from 3.6 to 4.4 mg/dL] reported as AEs with normal total calcium levels within a few days of receiving their first dose of study drug. None of these patients were hospitalized but at least 2 patients received additional supplementation to treat the condition.

Medical officer's comments-

There are additional AEs associated with low and high calcium levels shown in Table 13 which were captured from the AE dataset (A_AEV.xpt or see sponsor's table 14.3-1.7). Table 12 identified only those events reported from the central laboratory (see A_LRS.xpt). Again most of these hypocalcemia AEs occurred in the first two weeks associated with the first infusion and were of mild/moderate severity.

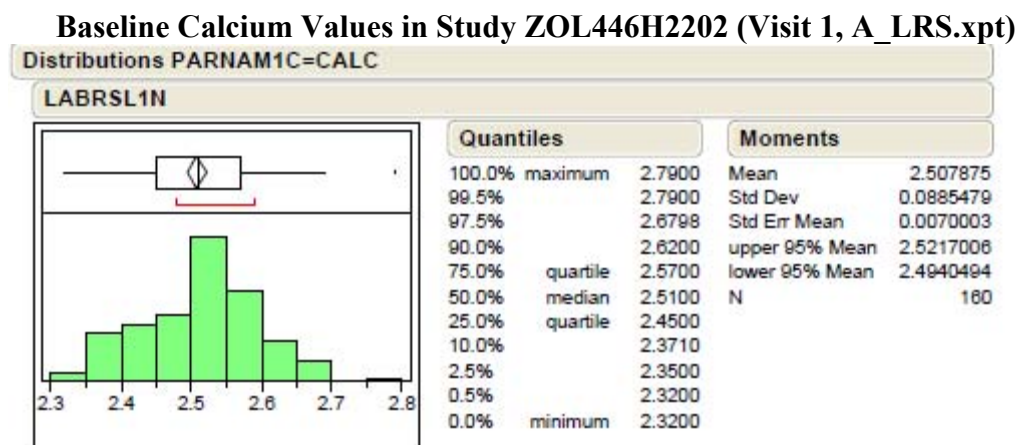
Table 13
Calcium-Related Adverse Events in Study

PT_TXT (A_AEV.xpt)	Total patients	Zoledronic acid patients	Pamidronate patients
Low Calcium			
Hypocalcaemia	23	16 (21%)	7 (9%)
Blood calcium decreased	8	3 (4%)	5 (6%)
Calcium ionised decreased	2	1 (1%)	1 (1%)
High Calcium			
Hypercalcaemia	3	2 (3%)	1 (1%)
Blood calcium increased	2	1 (1%)	1 (1%)

Source A_AEV.xpt. (PT_TXT= Hypocalcaemia, Blood calcium decreased, Calcium ionised decreased, Hypercalcaemia, or Blood calcium increased)
 Per Patient ID (STYSID1A)

Given that the risk of hypocalcemia seems largely confined to the first drug infusion, whereas the risk of hypercalcemia persists throughout the study, it might be useful to reduce calcium and vitamin supplementation after the first infusion in patients with baseline calcium values >2.57 mmol/L. Approximately, 25% of patients had baseline calcium levels >2.57 mmol/L, the ULN for the central laboratory (see Figure 12).

Figure 12



Liver Function Tests-

Two patients, one in each treatment group had SGPT/ALT values during the study that were >3xULN. Patient CZOL446H2202_0801_00015 in the zoledronic acid group had a diagnosis of “mild hepatopathy” which was believed to be unrelated to the study drug. The SGPT value was 1682 U/L (42X>ULN) and the SGOT value was 1944 U/L (57X>ULN) on study day 275, three months after the third study drug dose. Despite this elevation the patient received the final fourth dose of the drug and repeat SGPT at the final visit, Day 365, was normal at 24 U/L. Patient CZOL446H2202_0503_00001 in the pamidronate group had an elevated SGPT at baseline at 69 U/L. It continued to increase during the course of the study and was 179 U/L at the end of the study (4X>ULN, or 2.6X above the baseline value).

Only one patient, CZOL446H2202_0801_00015, already described in the previous paragraph had SGOT/AST values >3XULN during the course of the study.

Medical officer’s comments-

There were no clear liver-related safety concerns identified in this trial.

Renal Abnormalities-

Minor elevations in serum creatinine were slightly more common in the pamidronate subgroup and occurred most frequently during the initial two weeks following infusions. During the whole treatment period, 10/74=13.5% patients in the zoledronic acid group and 15/77=19.5% patients in the pamidronate group had significant creatinine increases, defined as $\geq 50\%$ increase from baseline when the midpoint of serum creatinine normal range is ≤ 0.6 mg/dL or a value that is greater than 2 times the baseline value when the midpoint of serum creatinine normal range is >0.6 mg/dL (see Table 14). Only 3/74=4.1% patients in the zoledronic group and 4/77=5.2% patients in the pamidronate group had significant creatinine increases observed from baseline at the last visit. No patients had creatinine levels greater than 0.70mg/dL and the patients with the largest % increases from baseline in each treatment group went from 0.21 to 0.44mg/dL in the zoledronic acid group and from 0.26 to 0.54mg/dL in the pamidronate group.

Urine protein >2+ was detected once in one patient in each treatment group at any time during the study and repeat urinalyses were normal (see sponsor’s Table 14.3.4-1.2 in Clinical Study Report for Urine Protein measurements at any time during the study, Table 14 only lists abnormalities at 9-11 days after an infusion.)

Table 14

Renal abnormalities in serum creatinine† and urine protein (>2+) in the safety population at 9-11 days after an infusion

Visit	Criterion	Zoledronic acid		Pamidronate	
		N	n (%)	N	n (%)
9-11 days post 1st infusion	Serum creatinine increase †	70	1 (1.4)	76	2 (2.6)
	Urine protein dipstick > 2+	67	0	76	0
9-11 days post 2nd infusion	Serum creatinine increase †	71	2 (2.8)	70	6 (8.6)
	Urine protein dipstick > 2+	67	1 (1.5)	68	0
9-11 days post 3rd infusion	Serum creatinine increase †	68	3 (4.4)	64	6 (9.4)
	Urine protein dipstick > 2+	64	0	64	0
9-11 days post 4th infusion	Serum creatinine increase †	67	2 (3.0)	68	6 (8.8)
	Urine protein dipstick > 2+	66	0	69	0
9-11 days post 5th infusion	Serum creatinine increase †	na	na	0	0
	Urine protein dipstick > 2+	na	na	1	0
9-11 days post 6th infusion	Serum creatinine increase †	na	na	0	0
	Urine protein dipstick > 2+	na	na	1	0

N = the number of patients with both baseline and at least one post-baseline evaluable value at the specified visit.
 n = number of patients meeting the criterion at the specified visit. Missing baseline values were excluded.

† A clinically significant increase in serum creatinine is defined as a $\geq 50\%$ increase from baseline when the midpoint of serum creatinine normal range is ≤ 0.6 mg/dl or a value that is greater than 2 times the baseline value when the midpoint of serum creatinine normal range is > 0.6 mg/dl.

na = not applicable

Source: (Table 14.3-3.3).

Medical officer's comments-

There were no clear renal-related safety concerns identified in this trial.

7.1.8 Vital Signs

Increases in body temperature and heart rate were seen as part of an acute phase reaction during the first few days following drug infusion and are a known side effect seen with intravenous bisphosphonate administration. 37/73=51% of zoledronic acid patients and 27/77=35% of pamidronate patients showed a significant increase of $\geq 1.1^\circ\text{C}$. Pyrexia was reported as an early onset AE in 38/74=51% of patients in the zoledronic acid group and in 38/78=49% of patients in the pamidronate group (see Table 10).

7.1.9 Electrocardiograms (ECGs)

ECGs were not routinely measured in this trial. Six patients in the zoledronic acid group and four in the pamidronate group had tachycardia AEs. All but one of these events occurred within 2 days of the start of a study drug infusion (zoledronic acid 6/6, pamidronate 3/4 patients), usually following the first infusion (zoledronic acid 5/6, pamidronate 2/4 patients), and at the same time as pyrexia, a common post-dose symptom (zoledronic acid 5/6, pamidronate 3/4 patients). All 6/6 cases of tachycardia AEs in the zoledronic acid-treated patients resolved within 2 days of onset, and 5/6 were considered mild in severity requiring no action.

There have been recent reports of serious cases of atrial fibrillation in elderly females treated with zoledronic acid for postmenopausal osteoporosis. No cases of atrial fibrillation were reported in this trial.

7.1.10 Immunogenicity

No immunogenicity testing was performed in this trial.

7.1.11 Human Carcinogenicity

No human carcinogenicity data was included in this submission.

7.1.12 Special Safety Studies

None

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Therapy with bisphosphonates has not been previously associated with withdrawal or abuse potential and no new relevant data was included in this submission.

7.1.14 Human Reproduction and Pregnancy Data

Female patients of child bearing potential were to be negative for pregnancy at enrollment and were to use a reliable method of birth control from 2 months prior to the start of the trial to at least 1 year after completing the trial. Despite these safe guards, one 16 y/o female (Hun/0801/00013) in the pamidronate group became pregnant one month after her second infusion, and was discontinued from the study. She gave birth to a healthy 37 wk old normal baby boy.

7.1.15 Assessment of Effect on Growth

Mean supine length increased at the 12 month visit compared to baseline by $6.0\text{cm} \pm 5.3\text{cm}$ in the zoledronic acid group and by $6.5\text{cm} \pm 7.0\text{cm}$ in the pamidronate group. Mean vertebral spine length increased at the 12 month visit compared to baseline by $1.9\text{cm} \pm 3.2\text{cm}$ in the zoledronic acid group and by $2.7\text{cm} \pm 5.8\text{cm}$ in the pamidronate group. Although the increases in both supine length and vertebral spine length were numerically greater in the pamidronate group the results were not statistically significant consistent with the large overlapping standard deviations in both groups. Height was not adjusted for age so it was not possible to tell from the data if there was an improvement in growth (Z-score) in patients on bisphosphonates.

7.1.16 Overdose Experience

No cases of overdosage were described in this submission.

7.1.17 Postmarketing Experience

No bisphosphonates are currently approved for the treatment of OI. See Literature Review Section 8.6 for a description of clinical trials using pamidronate to treat patients with OI.

As of 30-Apr-2007 the world-wide exposure based on the amount of zoledronic acid drug-substance sold and the defined doses is estimated at 11,373 patient-years. The majority of the patients were adults being treated for cancer related illnesses. In 2007 zoledronic acid was also approved to treat adults with Paget's disease and women with postmenopausal osteoporosis.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Study 1 was a single-dose PK study of intravenous zoledronic acid in pediatric patients with OI. The study enrolled 11 patients in the following age groups: 2 to <6 years (2), 6 to < 12 years (2) and 12 to 16 years (7). Ten patients (4 female, 6 male) completed the study and had blood and urine measurements. Post-dose fixed sampling was avoided in half of the patients. Urine samples were collected from patients 4 through 16 years of age. Zoledronic acid plasma concentration-time profiles, and zoledronic acid urinary excretion data, were characterized.

Study 2 was a randomized, parallel-group study to compare the safety and efficacy of intravenous zoledronic acid to intravenous pamidronate in the treatment of children with moderate-to-severe OI. At least 155 patients between 1 and 17 years of age, distributed among the following age groups: 1 year of age (2), 2 to <6 years (42), 6 to <12 years (67), 12 to 16 years (43) and 17 years of age (1), were randomized (1:1) to receive zoledronic acid or pamidronate. Zoledronic acid patients ≥ 1 to < 3 years of age were administered 0.025 mg/kg as a 30 to 45-minute intravenous infusion every 3 months for one year, whereas patients ≥ 3 years to ≤ 17 years of age were administered 0.05 mg/kg as a 30-minute intravenous infusion every 3 months for one year. Pamidronate patients were administered a 4-hour intravenous infusion. Patients ≥ 1 year to < 2 years of age were administered 0.5 mg/kg/day on each of three consecutive days every 2 months for one year. Patients ≥ 2 years to < 3 years of age were administered 0.75 mg/kg/day on each of three consecutive days every 3 months for one year. Patients ≥ 3 years to ≤ 17 years of age were administered 1 mg/kg/day on each of three consecutive days every 3 months for one year. Mandatory vitamin D and calcium supplementation before and during the study, and monitoring of calcium, phosphate, magnesium, albumin, post-dose symptoms and renal safety (BUN, Cr, urine protein, systolic BP) were performed. The primary endpoint was comparison of the percent change in LS BMD from baseline to month 12 in zoledronic acid-

treated patients versus pamidronate-treated patients. Growth was measured as supine length (or height) at months 6 and 12. Additional bone changes that were measured were LS Z-score at 12 months, femoral neck bone mineral content, number of clinical fractures, bone pain, and bone biomarker measurements. Biochemical marker data was not be collected in patients < 3 years of age.

7.2.1.2 Demographics

The baseline demographics were comparable between pamidronate and zoledronic acid groups by mean age (8.6yrs vs. 8.5yrs), race (85% vs. 83% Caucasian, 8% vs. 9% Black), and BMI (19 vs. 20). There was, however, a slightly greater percentage of males in the pamidronate group compared to the zoledronic acid group (59% vs. 51%).

Table 15

Baseline Demographics in study ZOL446H2202

		Zoledronic acid N=74	Pamidronate N=76	Total N=150
Age (years)	n	74	76	150
	Mean (SD)	8.6 (4.25)	8.5 (4.20)	8.5 (4.21)
	Median	8.5	9.0	9.0
	Min - max	1 - 16	1 - 17	1 - 17
Age group – n (%)	1 - <2 years	1 (1.4)	1 (1.3)	2 (1.3)
	2 - <3 years	6 (8.1)	5 (6.6)	11 (7.3)
	3 - <9 years	30 (40.5)	31 (40.8)	61 (40.7)
	≥9 years	37 (50.0)	39 (51.3)	76 (50.7)
Sex – n (%)	Female	36 (48.6)	31 (40.8)	67 (44.7)
	Male	38 (51.4)	45 (59.2)	83 (55.3)
Race – n (%)	Caucasian	63 (85.1)	63 (82.9)	126 (84.0)
	Black	6 (8.1)	7 (9.2)	13 (8.7)
	Oriental	3 (4.1)	1 (1.3)	4 (2.7)
	Other	2 (2.7)	5 (6.6)	7 (4.7)
Weight (kgs)	n	74	76	150
	Mean (SD)	25.58 (14.889)	28.32 (16.008)	26.97 (15.476)
	Median	20.65	24.35	23.50
	Min - max	7.4 - 90.0	6.3 - 97.0	6.3 - 97.0
Height/supine length (cm)	n	73	74	147
	Mean (SD)	112.82 (24.104)	116.74 (24.925)	114.80 (24.516)
	Median	114.00	117.00	116.00
	Min - max	63.0 - 174.0	51.0 - 164.0	51.0 - 174.0
BMI (kg/m²)	n	73	74	147
	Mean (SD)	19.04 (5.912)	19.94 (6.876)	19.49 (6.410)
	Median	17.40	17.95	17.70
	Min - max	12.6 - 44.2	10.9 - 53.8	10.9 - 53.8
Pubertal stage - n(%)	Pre-adolescence	22 (29.7)	20 (26.3)	42 (28.0)
	Early adolescence	38 (51.4)	44 (57.9)	82 (54.7)
	Middle adolescence	6 (8.1)	7 (9.2)	13 (8.7)
	Late adolescence	8 (10.8)	5 (6.6)	13 (8.7)

Source: [Table 14.1-3.1](#), [Table 14.1-3.2](#)

Background characteristics of OI subgroups were slightly different between treatment groups with more type IV patients in the pamidronate group (34 vs. 24%) and fewer type I (46 vs. 51%) and type III patients (20 vs. 24%). But this did not lead to a substantive difference in risk of

fracture as the mean LS Z-scores were similar between treatment groups e.g. -2.80 ± 1.25 for zoledronic acid and -2.53 ± 1.52 for pamidronate, and the mean number of patients with fractures in the 12 months prior to the first infusion was also similar between treatment groups (e.g. 77% for zoledronic acid vs. 79% for pamidronate).

7.2.1.3 Extent of exposure (dose/duration)

Over 90% of patients in each treatment group completed all scheduled infusions.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

None

7.2.2.2 Postmarketing experience

See Section 7.1.17

7.2.2.3 Literature

See Section 8.6.

7.2.3 Adequacy of Overall Clinical Experience

There was adequate data to show that both intravenous bisphosphonates reduced fracture incidence during the 12 months of treatment compared to the 12 months prior to the first infusion. There was insufficient data to conclude if one therapy was superior to the other even though, there appeared to be more fractures in the zoledronic acid group in the type I patients and in the pamidronate group in the type III & IV patients. Also there was inadequate data to tell how long the treatment effect would last after discontinuation following one year of therapy, and if there would be additional benefit or novel safety concerns with longer durations of therapy.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No special animal and/or in vitro testing data were included in this submission.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing of study subjects, including efforts to monitor laboratory parameters, vital signs and efforts to elicit adverse event data were considered adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Zoledronic acid does not inhibit human P450 enzymes *in vitro* and does not undergo biotransformation *in vivo*. Drug that is not bound up in bone is excreted unmetabolized in the urine. No new information about metabolism, clearance or drug interactions was included in this submission.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Adverse events associated with the use of bisphosphonates have been well characterized with this and previous bisphosphonates. Bisphosphonates are associated with small but increased risks of: hypocalcemia (especially in patients with Paget's Disease) usually following the initial infusion, ocular inflammation and ONJ.

Oral bisphosphonates are specifically associated with esophagitis and esophageal erosions.

Intravenous bisphosphonates like zoledronic acid and pamidronate can result in acute phase reactions (pyrexia, influenza-like illness, bone and muscle pains) usually following the initial infusion, hypersensitivity has been seen with repeat dosing and dose-related transient renal toxicity can be worsened if the infusion rate is too rapid.

It was not possible to study children under one year of age in this study because their baseline renal function did not meet predetermined eligibility criteria set up by the DSMB.

It is recommended that clinical studies be designed to establish guidelines for long term therapy in patients with OI. It would be helpful to identify which bone markers correlate best with BMD, bone pain, and fracture incidence, and as such could be used as surrogates to aide with chronic dosing.

7.2.8 Assessment of Quality and Completeness of Data

The data submitted and reviewed was complete and of good quality.

7.2.9 Additional Submissions, Including Safety Update

The 4-month Safety Update included results from the open-label, extension study ZOL446H2202E1, in which patients, who had completed the first year of the core study ZOL446H 2202 on pamidronate or zoledronic acid, were re-randomized to once or twice yearly zoledronic acid for an additional year of therapy. The study was terminated early, when 89% of patients had completed all 12 months of the per-protocol assessments, due to an interim assessment of increased fracture risk from the original study. However, the initial estimate of excess risk was not confirmed in the final data analysis. Fewer patients treated with zoledronic acid for 24 months had fractures in the 12 months of the extension study (31%) compared to the

12 months of the core study (43%), and compared to the 12 months prior to the first infusion (82%). There was no advantage to twice yearly dosing compared to yearly dosing with zoledronic acid with respect to increase in BMD, or change in any of the bone biomarkers (β -CTX, P1PNP and BSAP).

There were fewer SAEs in the 12 month extension trial (18%) than in the 12 months of the original core study (32% with zoledronic acid given every 3 months, 19% with pamidronate given every two to three months). There were a similar proportion of SAEs and total AEs in the once yearly and twice yearly dosing groups in the extension trial consistent with the safety of repeat dosing with zoledronic acid.

There were no deaths, and no patients discontinued the extension study due to AEs. There were 3 cases of eye disorders, but no reports of uveitis or episcleritis. There were no reports of tachycardia AEs or atrial fibrillation, and there were no relevant differences between treatment groups with respect to vital sign changes including blood pressure, heart rate, height or weight. The number of renal abnormalities, defined as a specific increase in creatinine relative to the normal midpoint value based on age and gender, was lower in the 12 month extension trial than in the initial 12 months during the core part of the trial. However, all renal changes were still within the age adjusted normal upper limit for the central laboratory. So there were no clear renal-related concerns identified in the extension part of the trial which included only patients with normal serum creatinine values and no pathological proteinuria at baseline.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Acute phase reactions are common drug related events seen in pediatric OI patients treated with intravenous bisphosphonates (e.g. zoledronic acid and pamidronate). Acute phase related-AEs seen in study ZOL446H2202 included pyrexia, vomiting, headache, nausea, malaise, tachycardia, chills and influenza like-illness. These AEs were typically seen in the first 3 to 6 days after the infusion and were much less common with repeat dosing.

Adverse events of hypocalcemia were reported in this study despite supplementation with calcium and vitamin D for 2 weeks prior to randomization and during the trial. More AEs of hypocalcemia were reported in the zoledronic acid treatment group (22%) than in the pamidronate group (9%). At least four of seven zoledronic acid patients, with SAEs of hypocalcemia or blood calcium decreased, reported symptoms of hypocalcemia, and received treatment for the hypocalcemia during hospitalizations. The lowest total calcium level reported after zoledronic acid infusions was 6.8 mg/dL and after pamidronate infusions was 7.7mg/dL. Hypocalcemia was typically seen in the first 3 days after the first infusion and was much less common with repeat dosing. In contrast to hypocalcemia, hypercalcemia was much more common with about half the patients having a lab value above the ULN of 10.28mg/dL and was seen throughout the entire length of the trial. However, no patients had serum calcium levels above 12mg/dL and none of these events was considered SAEs or required discontinuation of the study drug.

Minor elevations in serum creatinine were seen at 9-11 days after infusion with intravenous bisphosphonates, as had been previously reported in adult patients. No pediatric patients had increases in serum creatinine values to levels above 0.7mg/dL or required specific intervention because of these minor transient elevations. Only patients with normal renal function were included in this study so no information is available about the risk for renal deterioration in pediatric patients with abnormal baseline renal function or in children under 1 year of age.

AEs that had been rarely reported in adult patients taking intravenous bisphosphonates such as ONJ and eye inflammatory changes (e.g. uveitis and episcleritis) were not seen in this trial in pediatric OI patients. But the number of patients in this trial was too small to draw any conclusions about the risk for these AEs in this patient population.

In conclusion, the safety profile in pediatric OI patients, over 1 year of age, treated with zoledronic acid on a mg/kg basis was similar to what had been previously observed in adult patients receiving infusions of up to 5mg/day, but there is data to suggest that the rate of certain adverse events may be somewhat higher in the pediatric population [e.g. pyrexia (61%), hypocalcemia (22%) and headache (22%)] compared to what was seen in adults.

7.4 General Methodology

The primary endpoint was a percent change from baseline in LS BMD at month 12 in the ITT, LOCF population using a non inferiority margin of <13%. Once non-inferiority was observed the data were also analyzed to look for superiority between treatment groups. Data was also analyzed at 6 months and in the per-protocol and completer populations to look for consistency in the results. Time to first clinical fracture and total number of patients with fractures in each treatment group were analyzed as secondary endpoints, as the study was not originally powered to see a difference in fracture incidence. The incidence of fractures in each treatment group was similar for the 12 month duration of the core study, but there was a discrepancy with respect to the different OI types and the incidence of fracture, favoring pamidronate in the type I patients and favoring zoledronic acid in the type III & IV patients. The secondary endpoints of BMD, bone biomarkers and bone pain were analyzed to see if there was any correlation with these fracture findings in the OI subtypes, and none was found. This was interpreted by this reviewer to suggest that these OI type specific fracture rates probably represent a chance finding, and should not be used as evidence to recommend use of either bisphosphonate over the other in specific OI types.

The safety review focused on the known AEs associated with the use of intravenous bisphosphonates e.g. acute-phase related AEs, hypocalcemia, renal and eye disorders, ONJ and musculoskeletal pain.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The sponsor is not seeking an indication for the treatment of patients with severe OI with this submission.

The core study, ZOL446H2202, used the following zoledronic acid dosing scheme based on age at time of the infusion for the first year of therapy:

Patients ≥ 1 to < 3 years of age were administered 0.025 mg/kg as a 30 to 45-minute intravenous infusion every 3 months.

Patients ≥ 3 years to ≤ 17 years of age were administered 0.05 mg/kg as a 30-minute intravenous infusion every 3 months.

The extension study, ZOL446H2202E1, compared once yearly to twice yearly dosing with zoledronic acid:

Patients ≥ 1 to < 3 years of age were administered 0.025 mg/kg as a 30 to 45-minute intravenous infusion every year vs. every 6 months.

Patients ≥ 3 years to ≤ 17 years of age were administered 0.05 mg/kg as a 30-minute intravenous infusion every year vs. every 6 months.

No information is available to describe the durability of the effect with yearly or biyearly dosing beyond one year of follow up.

8.2 Drug-Drug Interactions

No new drug-drug interaction studies were included in this submission.

8.3 Special Populations

All studies were performed in pediatric OI patients (see section 8.4 Pediatric). Patients with hepatic or renal insufficiency were excluded from these studies.

8.4 Pediatrics

The PK (Study 1) and pivotal efficacy studies (Study 2) were performed in pediatric OI patients as a response to a Written Request for pediatric data. The sponsor is not seeking an indication in pediatric patients but is using this submission to seek an additional 6 months of Drug Exclusivity for zoledronic acid.

8.5 Advisory Committee Meeting

None

8.6 Literature Review

OI is a genetic disorder resulting in increased bone fragility and low bone mass making patients at risk for recurrent fracture. Most patients have a dominant mutation in one of two genes that code for type I procollagen, the major structural protein in bone, skin and tendon extracellular matrix. Originally, 4 classic types related to a mutation in the procollagen gene were identified although more recently an additional three subtypes have been proposed for which the gene defect have not yet been determined³. Bone fragility is least severe in type I, the mildest form of the disorder, in which patients have the potential to reach normal adult height. This is followed by types (IV, V, VI and VII), and then type III which can have a progressive course with increasing bone deformities, short stature and chronic pain. And finally the most severe form of OI is type II, in which patients develop fractures in utero leading to prenatal death. Intensive rehabilitation programs can help to prevent some of the bone deformities. While there are currently no clinically approved medications to treat OI, bisphosphonates, are used off label for the treatment of patients with OI at high risk of fracture, and are currently the best treatment option for these patients. Clinical studies first with oral and later with intravenous pamidronate have shown an improvement in BMD, chronic pain, and fracture incidence⁴. More recently clinical trials have looked to see if the benefits obtained with intravenous pamidronate can be sustained with oral alendronate. Clinical trials are also underway to attempt to increase growth and stimulate bone metabolism with human growth hormone⁵.

Before a bisphosphonate could be approved for this indication clinical trials will be needed to identify effective treatment regimens describing both the duration of treatment and interval between doses needed to maintain a clinically relevant benefit. Attempts have been made to try to adjust dosing intervals using inadequate clinical surrogates, such as bone biomarkers and bone pain. Fracture incidence, while arguably the most relevant clinical outcome, has been difficult to correlate with treatment efficacy because it is affected by multiple external factors including age, mobility, capacity for ambulation and degree of limb immobilization. The most common side effects associated with the use of pamidronate in OI patients have been (1) an acute phase reaction, during the days immediately following the infusion, which responds well to acetaminophen and occurs much less frequently with repeat cycles, and (2) small decreases in serum calcium, also seen mainly after the first infusion, which largely have been asymptomatic and responded well to calcium and vitamin D supplementation. Renal function was unaffected in

3 [Rauch F, Glorieux FH](#). Osteogenesis imperfecta. *Lancet*. 2004 Apr 24;363(9418):1377-85.

4 [Plotkin H, Rauch F, Bishop NJ, Montpetit K, Ruck-Gibis J, Travers R, Glorieux FH](#). Pamidronate treatment of severe osteogenesis imperfecta in children under 3 years of age. *J Clin Endocrinol Metab*. 2000 May;85(5):1846-50.

5 [Devogelaer JP](#). New uses of bisphosphonates *Curr Opin Pharmacol*. 2002 Dec;2(6):748-53.

children with normal baseline renal function treated with pamidronate for OI⁶. These adverse effects are similar to findings already described in the current PI for pamidronate.

8.7 Postmarketing Risk Management Plan

None

8.8 Other Relevant Materials

None

9 OVERALL ASSESSMENT

9.1 Conclusions

Zoledronic acid was not only non-inferior, but also superior, to pamidronate with respect to the primary endpoint in study ZOL446H2202 (e.g. percent change in LS BMD at month 12 relative to baseline, ITT, LOCF.)

The safety profile seen in pediatric OI patients, over 1 year of age, treated with zoledronic acid on a mg/kg basis was similar to what had been previously observed in adult patients receiving infusions of up to 5mg/day, but there is some data to suggest that the rate of adverse events may be somewhat higher in the pediatric population compared to the adult population.

The efficacy and safety data was insufficient to support a new clinical indication for the treatment of pediatric OI patients, and additional studies would be recommended prior to approval of this indication.

9.2 Recommendation on Regulatory Action

AP-the labeling changes proposed by the sponsor are acceptable.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

None

⁶ [Glorieux FH, Bishop NJ, Plotkin H, Chabot G, Lanoue G, Travers R.](#) Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. N Engl J Med. 1998 Oct 1;339(14):947-52.

9.3.2 Required Phase 4 Commitments

None

9.3.3 Other Phase 4 Requests

None

9.4 Labeling Review

The sponsor proposed the following labeling changes to the “Pediatric Use” section”:
Zometa is not indicated for use in children.

And to the “Special Populations-Pediatric” section”:



Medical Officer’s comments:

Clinical Pharmacology recommended the following changes to the description of the PK data:

Plasma zoledronic acid concentration data was obtained from 10 patients with severe osteogenesis imperfecta (4 in the age group of 3-8 years and 6 in the age group of 9-17 years) infused with 0.05 mg/kg dose over 30 min. Mean Cmax and AUC(0-last) was 167 ng/mL and 220 ng.h/mL respectively. The plasma concentration time profile

_____ of zoledronic acid _____ in pediatric patients _____ imperfecta represent a multi-exponential decline, as _____ observed in adult cancer patients at an approximately equivalent mg/kg dose.

And that this information be moved to section 8.4 Pediatric Use. This medical officer agrees with the Clinical Pharmacology recommendations.

Before a bisphosphonate could be approved for this indication clinical trials would be needed to identify safe and effective treatment regimens describing dose, duration of initial treatment and interval between chronic dosing needed to maintain a clinically relevant benefit. Whereas the data from clinical trial ZOL446H2202 showed evidence for a decrease in fracture rate with both bisphosphonates compared to the 12 months prior to treatment, the study was not designed to look at fracture as a primary endpoint and it is hard to explain why there appeared to be more fractures in type I patients in the zoledronic acid group and type III & IV patients in the pamidronate group. Especially, since this differential fracture data did not correlate to the observed changes in BMD and bone biomarkers. Since the efficacy data is not sufficient for a clinical indication and there were unexplained inconsistencies between the BMD, bone biomarker and fracture data, it is not recommended that this efficacy information be included in the PI.

While the pediatric OI safety data showed a similar pattern of adverse events to those seen in adult patients, drug-related AEs such as, hypocalcemia, pyrexia, and headache were more common in the pediatric population than observed in adult populations treated with intravenous bisphosphonates (e.g. PMO or Paget's Disease pts). Such a finding is consistent with the observation in the PMO population that acute phase reactions were less common in elderly patients > 75 years of age, also suggesting younger patients with a greater baseline rate of bone turnover maybe at higher risk of AEs from intravenous bisphosphonates. It is this medical officer's opinion that since the pattern of adverse events in pediatric patients is similar to what is seen in adults but that certain adverse events were seen more commonly in children that the following statement be included in the Pediatrics subsection:

Pediatrics

ZOMETA is not indicated for use in children.



9.5 Comments to Applicant

None

10 APPENDICES

10.1 Review of Individual Study Reports

See Section 5.1 for the PK study and Section 6 for the pivotal efficacy study.

10.2 Line-by-Line Labeling Review

See Section 9.4 Labeling review

REFERENCES

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