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Evaluation of Medicines for Human Use

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ASSESSMENT REPORT FOR Zometa

International non-proprietary name/Common name:
zoledronic acid

Procedure No. EMEA/H/C/000336/II/0031

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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I SCIENTIFIC DISCUSSION

1.1 Introduction

Zometa (zoledronic acid 4 mg) is a nitrogen-containing, third generation bisphosphonate that inhibits osteoclastic bone resorption with very high potency. Zometa is resistant to hydrolysis by phosphatases because of the characteristic phosphorus–carbon–phosphorus bond. It binds tightly to calcified bone matrix and inhibits osteoclast-mediated bone resorption more effectively than earlier generation bisphosphonates, at doses that do not impair bone mineralization. As a bone resorption inhibitor, zoledronic acid has demonstrated therapeutic use in several diseases involving enhanced bone turnover.

Zometa was first registered in Canada on 21 August 2000 for the treatment of tumor-induced hypercalcemia (TIH). Zometa was authorized in the European Union for the treatment of TIH and for the prevention of skeletal related events (SRE) in patients with advanced malignancies involving bone on 20 March 2001 and 19 July 2002, respectively.
In general, Zometa is currently approved as a solution for infusions in a powder formulation in 96 countries and as a concentrate in 81 countries worldwide, including European Union, for the treatment of 2 conditions:

- Prevention of SREs (pathological fractures, spinal compression, radiation or surgery to bone, or TIH) in patients with advanced malignancies involving bone, and
- Treatment of TIH.

The Osteogenesis imperfecta (OI) comprises a group of inherited disorders that primarily (but not always) arise from mutations in the genes for type I collagen (COL1A and COLA2). These molecular defects result in impaired bone formation, increased bone fragility and low bone mass. These essential features lead to the common name “brittle bone disease” for the condition. The clinical classification system published by Sillence in 1979 is widely used and divides the condition into Types I-IV. More recently, additional OI types (V-VII) have been identified from within the Type IV phenotype, and have distinct clinical and molecular characteristics. The severity of the clinical characteristics increases as follows: type I < types IV, V, VI, VII < type III < type II.

Children with severe OI suffer recurrent fractures resulting in severe deformity and impaired growth (short stature), usually accompanied by chronic bone pain, and progressive loss of independent ambulation by the teenage years in over 50% of cases.

The cornerstone of treatment for OI includes physical therapy, rehabilitation, pain management, and orthopedic surgery to address deformities. Early trials with several different medical therapies were unsuccessful, including those involving fluoride, magnesium, calcitonin, and anabolic steroids.

The most promising long-term results have come from studies using intravenous pamidronate. An observational study of 30 children with severe type III or IV OI aged 3-16 years, treated with cyclic intravenous pamidronate 1.5-3.0 mg/kg q 4-6 months for 1.5 to 5 years, showed substantial increases in BMD and BMD Z-score, suppression of metabolic bone markers, reduction in fractures, increase in height, and in many patients improved mobility. Subsequently, smaller trials of i.v. pamidronate have shown similar efficacy.

With the exception of neridronate, which is nationally approved in Italy only, there are no approved pharmacologic therapies to address the frequent fractures, impaired growth, skeletal deformities, and impaired mobility that are characteristic of severe OI in affected children.

With this variation application the Marketing Authorisation Holder (MAH) sought approval for a new indication in the treatment of severe OI in paediatric patients aged 1 to 17 years to be added to section 4.1 of the Summary of Product Characteristics (SPC). Furthermore, the MAH proposed also revisions to SPC sections 4.2, 4.4, 5.1 and 5.2 related to the available data in paediatric patients. In addition, SPC section 4.4 was proposed to be amended with a warning regarding the concomitant use of Aclasta as well as changes to SPC sections 4.3, 4.6 and 4.8 were applied to align with the QRD template. Moreover, Annex II is to be updated with the RMP standard text reflecting the latest agreed version number. The package leaflet has been proposed to be revised based on the results of a Readability

Testing. The MAH took also the opportunity to introduce minor corrections to the PI of several languages.

Information on Paediatrics

The paediatric program in OI was agreed between Novartis and the FDA during 2002 and later amended in 2003. The data was submitted to and evaluated by the FDA and data with respect to available data for paediatric patients included in the US Prescribing Information.

In Europe, the MAH submitted to EMEA/PDCO on 26 July 2007 a proposal for a Zometa Paediatric Investigation Plan (PIP) (EMEA-000024-PIP01-07), in accordance with articles 13 and 16.1 of the Regulation (EC) No. 1901/2006. The MAH voluntarily proposed a paediatric program in severe OI and applied for paediatric waivers for all paediatric subsets in the currently approved Zometa adult indications. A modified version of the PIP was discussed with PDCO on 07 May 2008 and received a positive PDCO opinion and the corresponding EMEA Decision on 08 May 2008 and 24 June 2008, respectively.

In addition to the acceptance of paediatric waivers for all paediatric subsets for the Zometa adult indications by EMEA/PDCO, a clinical program in paediatric OI was agreed between EMEA/PDCO and the MAH so that this program formed the basis for the EMEA Zometa PIP Decision (EMEA/310261/2008).
The PIP is completed, the PDCO issued an opinion on compliance.

1.2 Nonclinical aspects

1.2.1 Pharmacology

The CHMP had initially concerns that prior to any further clinical studies in osteogenesis imperfecta every effort should be made to further study the disease and potential therapies in preclinical models.
The MAH summarised that some studies in OI pre-clinical models were conducted. The study by Camacho, et al (2001) was carried out in oim/oim mice, an established animal model of OI based on a naturally occurring mutation. In their study, alendronate was shown to reduce fracture risk and increase bone density in growing mice that serve as a model for the disease. Since the model used growing mice, that could be relevant to bone biology in children. Other positive outcomes from their study included increased bone diameter and decreased tibial bowing. In contrast to these findings, a decrease in femur length and a persistence of calcified cartilage were also found with treatment; both were considered indicators of potential negative outcomes. The same research later investigated the effect of alendronate on the material properties in these mice and concluded that the observable improvement to the oim/oim mouse bone was increased in cancellous bone volume and geometry but not material properties. This study suggested that in this mouse model of OI, the previously demonstrated bisphosphonate associated reduction in fractures was primarily attributable to increased metaphyseal bone mass and not changes in material properties (Misof, et al 2005).

The most recent publication related to alendronate and OI in mice was from Uveges, et al (2009). The authors used the Brtl mouse model, which had a glycine substitution in COL1A1 and was ideal for modeling the effects of bisphosphonate in classical OI (most closely mimicking the phenotype of type IV OI). The study demonstrated that alendronate treatment improved femoral areal BMD and cortical volumetric BMD without altering bone length (longitudinal bone growth). Alendronate improved diaphyseal cortical thickness and trabecular number, and cross-sectional shape, resulting in significantly increased load to fracture in femora after 12 weeks. However, predicted material strength and elastic modulus were negatively impacted at 12 weeks presumably due to the retention of metaphyseal remnants of mineralized cartilage. Femoral brittleness was unimproved by alendronate.

From the MAH's point of view, overall there is evidence in favor of treatment benefits (such as reduced number of fractures, and reduced bone deformation) in those pre-clinical models. The results from these studies seem to explore the association between bone mass improvement and therapeutic benefits for OI, including reductions in fracture and bone deformation. Although these studies used alendronate, not zoledronic acid, a similar effect is expected because of the same mechanism of alendronate and zoledronic acid. Novartis is not planning any further pre-clinical studies in OI.

The CHMP noted that no pre-clinical proof-of-concept studies have been conducted with zoledronic acid. However, published scientific data indicate that bisphosphonates may be beneficial for the treatment of osteogenesis imperfecta due to their effects on bone remodelling. The *in vivo* assessment of bone architecture and strength are known to be important for the initial efficacy assessment in other products used in somewhat related indications (e.g. treatment of primary osteoporosis). Nevertheless, the clinical efficacy of zoledronic acid in treatment of osteogenesis imperfecta has been compared to pamidronate, the most common standard of care. Furthermore, Zometa has been used in adults for several years. Thus, the CHMP considered that further non-clinical pharmacology studies are not warranted as the efficacy of zoledronic acid in non-clinical disease models would not significantly affect the risk-benefit balance.

1.2.2 Toxicology

Environmental Risk Assessment

The MAH has provided a phase I environmental risk assessment for the proposed new indication. The predicted environmental concentration (PEC) was calculated by the MAH based on the formula proposed in guideline EMEA/CHMP/4447/00. The MAH used a refined Fpen. For the refinement of the Fpen the MAH calculated consumption data for the active substance based on 4 treatments/ patient/ year and the prevalence of the disease (number of patients in Europe).

The outcome of MAH`s approach is a PEC below the trigger value of 10ng/L for a phase II assessment. It should be pointed out that the guideline EMEA/CHMP/4447/00 assumes in phase I that one percent of the population is treated with the product on a given day. Therefore an annual dose for one patient is not acceptable for PEC calculation. An Fpen refinement in phase I would only be possible on published prevalence data for the disease/indication. The MAH has provided data on number of patients with severe osteogenesis imperfecta.

Subsequently, the MAH provided a full Phase II-Tier A environmental risk assessment (EAR) for zoledronic acid. From the MAH's point of view, this ERA showed that there is no concern for the environmental compartments considered in this assessment, i.e. sewage treatment plants, surface waters, groundwaters, sediments and soils.

Due to the properties of the active pharmaceutical ingredient, zoledronic acid, analytical verification of test substance concentrations has not been possible for all concentrations tested. The available UV photometric detection at 209 nm for zoledronic acid enables the analysis of concentrations down to 1.97 mg/L. As effective concentrations of zoledronic acid in Daphnia magna and fish have been observed in the µg/L range, the development of a more sensitive LC-MS method was tackled.

The following problems have been identified impeding the development of a suitable analytical method for zoledronic acid:

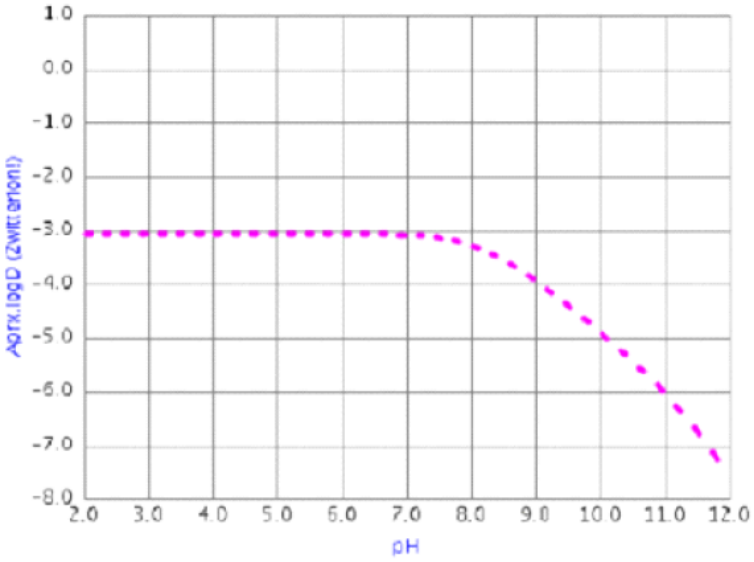
- The volatility is poor so no GC analysis is possible.
- The test item is a poor chromophor and thus HPLC-UV analysis can only be performed at very high concentrations.
- The test item is highly polar with acidic and alkaline groups making it difficult to concentrate the test item.
- Zoledronic acid forms complexes with the calcium ions present in test media used for aquatic toxicity tests.

Zoledronic acid belongs to the class of bisphosphonates, which is specifically mentioned in the OECD guidance document on aquatic toxicity testing of difficult substances and mixtures (OECD, 2000. OECD Series on Testing and Assessment Number 23). In Chapter 3.7 on 'Complexing substances', the authors of this document come to the conclusion that 'Analysis methods for quantifying exposure concentrations, which are capable of distinguishing between the complexed and non-complexed fraction of a test substance, may not always be available or economic. Where this is the case approval should be sought from the regulatory authority for expressing the test results in terms of nominal concentrations.' Following these recommendations, the environmental toxicity and fate testing has been conducted to the extent possible with zoledronic acid. The effective concentrations in the aquatic toxicity tests have been expressed as nominal concentrations calculated from the higher test

concentrations, which could be verified with the previously implemented UV spectrophotometric method.

Zoledronic acid contains 5 acidic groups and 1 basic group (imidazole ring) and is not present as a neutral substance over a wide pH range, including environmentally relevant pHs (see Figure 4-1).

Figure 4-1 **Calculated logD values for zoledronic acid range from -3.1 at pH 2 to 7.4 to -7.6 at pH 12.**



pH	logD
2	-3.1
3	-3.1
4	-3.1
5	-3.1
6	-3.1
6.8	-3.1
7	-3.1
7.4	-3.1
8	-3.3
9	-4.0
10	-4.9
11	-6.1
12	-7.6

Based on the properties of zoledronic acid as an ionisable substance, a significant potential to accumulate in aquatic organisms is therefore highly unlikely in the MAH's opinion. Moreover, an experimental determination of an octanol-water partition coefficient will also be impeded by the properties of zoledronic acid described above, hindering the development of a suitable HPLC method for the analytical determination of partitioned substance in water and octanol.

Therefore, the experimental determination of an octanol-water partition coefficient is neither technically feasible nor indicated based on the known physico-chemical properties of zoledronic acid.

As the predicted environmental concentration (PEC) is 0.02 µg/L, which exceeds the trigger value of 0.01 µg/L a Phase II – Tier A ERA assessment was needed. The Phase II – Tier A environmental risk assessment indicated no concern for surface water, ground water and microorganisms in sewage treatment plants.

With reference to the determination of transformation half-life in sediments and total systems the OECD 308 demonstrated significant shifting of Zoledronic acid and its transformation products to the sediment (>90% as well as bound residues and free substance in total). The CHMP requested a test on lumbriculus (OECD 225to be undertaken. The MAH agreed to conduct this test as a Follow-Up Measure.

1.3 Clinical aspects

The clinical development program to support the treatment of children with severe OI comprised two studies. The core randomized, active-controlled open-label Study H2202 was conducted to demonstrate both the efficacy and the safety of zoledronic acid in the target population over 12 months. The open-label extension Study H2202E1 provides an additional 12 months of treatment data with zoledronic acid in the patient population who completed the controlled study H2202 regardless of the treatment received in the original core study.

GCP compliance

According to the MAH all studies were conducted in accordance with the ethical requirements of Directive 2001/20/EC and with the ICH E6 guideline on Good Clinical Practice and the principles set forth in the Declaration of Helsinki.

All studies were closely monitored by Novartis personnel or a contract organization for compliance to the protocol and the procedures described in it.

No new pharmacokinetic or pharmacodynamic studies were performed for this submission.

1.3.1 Clinical Efficacy

1.3.1.1 Main study H2202

Study H2202 was an international, multicenter, randomized, open-label, parallel efficacy and safety trial of intravenous Zoledronic acid compared to intravenous pamidronate in children with severe osteogenesis imperfecta (OI).

Methods

Study Participants

Approximately 132 children 1 to 17 years of age with severe OI were to be randomized (66 patients per treatment group) in order to obtain 120 evaluable patients for the primary efficacy variable. The main inclusion criteria were:

- Children, male or female, between 1 and 17 years of age, all inclusive.
- Any child with phenotypic OI type III or IV.
- Any child with phenotypic OI type I who had≥3 minimal trauma fractures (including vertebral fractures) in the previous 2 years or with a history of limb deformity requiring surgery.

The washout period for other metabolic bone therapies, in particular for bisphosphonates, prior to study drug administration at visit 2 was:

- If used for >12 months, the washout period was 12 months.
- If used for 4 - ≤12 months, the washout period was 6 months.
- If used for ≤3 months, there was no washout period.

A “use” could be daily or weekly oral bisphosphonate or every 3 months intravenous injections, where one dose by i.v. injection = 3 months’ use if the patient received the complete dose over the 3 day period (e.g. pamidronate 3 mg/kg was given as 1 mg/kg/day over 3 consecutive days as 4 hour i.v. infusions; therefore, the total dose of three infusions over 3 days was considered equivalent to 3 months’ use).

All patients must have completed 2 weeks of treatment with an appropriate dose of vitamin D daily and elemental calcium (or equivalent described in the protocol) daily (prestudy and/or within the screening period) prior to the first administration of zoledronic acid or pamidronate.

Treatments

Patients were randomized to either zoledronic acid or pamidronate in a 1:1 ratio.

Zometa dose selection for the core study was based on several sources available at the time of protocol development: adults with benign disease safely received up to 5 mg i.v. infusion over 15 minutes. Compared to pamidronate, Zometa 4 mg was more efficacious than 90 mg pamidronate in patients with TIH or metastatic cancers to the bone. These approved doses of zoledronic acid (4 mg) and pamidronate (90 mg) in adults for oncology indications are equal to an approximate dose of zoledronic acid of 0.07 mg/kg or pamidronate 1.5 mg/kg for a 60 kg adult. In a long-term paediatric pamidronate OI study, pamidronate 1.5 or 3.0 mg/kg was tested and the dose range was safe and efficacious. Age-specific dose range of zoledronic acid being administrated as an i.v. infusion in this paediatric trial is comparable to that of pamidronate. Therefore, the higher zoledronic acid dose selected in children 3 years of age or older, 0.05 mg/kg, was expected to provide similar safety and efficacy (demonstrated with BMD measurements) compared to that previously reported for pamidronate in OI patients. The

maximum allowable zoledronic acid dose of 4 mg (regardless of patient weight), does not exceed the 4 mg single dose that has been used in adults.

A dose of zoledronic acid equivalent to that administered to adults with other metabolic bone conditions is approximately 0.05 mg/kg (maximum of 4.0 mg). This is the zoledronic acid dose range comparable to pamidronate 90 mg which has been studied in patients with OI.

The doses of zoledronic acid to be administered as an i.v. infusion at a peripheral site, based on age and body weight are presented below.

Table 9-1 Zoledronic acid pediatric dosing schedule

Age	Dose of zoledronic acid	Frequency
1 to <3 years	0.025 mg/kg diluted in 50 mL of normal saline †	30 to 45 minute infusion every 3 months
3 to 17 years	0.05 mg/kg diluted in 100 mL of normal saline ‡	30 minute infusion every 3 months

Body weight was measured at each dose administration visit, for calculation of the dose. Patients aged 3 to 17 years were to receive 0.05 mg/kg of zoledronic acid up to a maximum of 4 mg. Patients aged 1 to <3 years were to receive a lower zoledronic acid dose of 0.025 mg/kg up to a maximum of 2 mg, until they reached their third birthday. If a 2 year old patient had a birthday during the study, the zoledronic acid dose was to be increased from 0.025 to 0.05 mg/kg at the next scheduled dose administration visit. To enable accurate dosing in the children aged <3 years, zoledronic acid was provided in 5 mg/100 mL vials.

The doses of pamidronate to be administered as an i.v. infusion at a peripheral site, based on age and body weight, are presented below.

Table 9-2 Pamidronate pediatric dosing schedule

Age	Dose of pamidronate †	Frequency
1 to <2 years	0.5 mg/kg/day	4 hour infusion on each of 3 successive days, every 2 months
2 years	0.75 mg/kg/day	4 hour infusion on each of 3 successive days, every 3 months
3 to 17 years	1.0 mg/kg/day	4 hour infusion on each of 3 successive days, every 3 months

Body weight was measured at each dose administration visit, for calculation of the dose. The pamidronate dose was not to exceed 60 mg per day for any patient (total of 180 mg over 3 days). The volume of the infusion was the same on each successive day except on the first day of the first infusion cycle for pamidronate (day 1 of visit 2), when only half of the patient's calculated daily dose was infused to mitigate initial post-dose symptoms. Pamidronate patients followed the same dosing schedule assigned to them at randomization throughout the study, regardless of age increases.

Objectives

The primary objective was to assess the percentage change in lumbar spine BMD at month 12 relative to baseline in zoledronic acid-treated paediatric patients with severe OI compared to pamidronate-treated paediatric patients who were ≥1 year to ≤17 years of age. The efficacy of zoledronic acid would be considered demonstrated, if it was shown to be noninferior to pamidronate (i.e. the percentage change from baseline in bone mineral density after 12 months is less than 13% inferior to pamidronate).

The secondary objectives were:

- To assess the change in Z-score of the lumbar spine at month 12 relative to baseline in zoledronic acid-treated patients with severe osteogenesis imperfecta compared to pamidronate in children ≥1 year to ≤17 years of age.

- To assess the effect of zoledronic acid on the change in femoral neck bone mineral content (BMC) after 6 and 12 months of treatment relative to baseline compared to pamidronate in children ≥1 year to ≤17 years of age.
- To assess the effect of zoledronic acid on the number of clinical fractures that occurred over a 1-year period compared to pamidronate in children ≥1 year to ≤17 years of age.
- To assess the effect of zoledronic acid on the change in bone resorption and bone formation markers after 6 and 12 months of treatment relative to baseline compared to pamidronate by measuring the following bone markers in serum: bone specific alkaline phosphatase (BSAP) (formation), N-terminal propeptide of type I collagen (P1NP) (formation), and C-telopeptide (CTx) (resorption) in children ≥3 years to ≤17 years of age.
- To assess the effect of zoledronic acid on the change in supine length (or height) after 6 and 12 months of treatment relative to baseline compared to pamidronate in children ≥1 year to ≤17 years of age.
- To assess the effect of zoledronic acid on the change in bone pain, using the Wong-Baker FACES pain rating scale, relative to baseline compared to pamidronate in children ≥1 year to ≤17 years of age.

Outcomes/endpoints

The primary efficacy variable was percentage change in lumbar spine BMD at month 12 relative to baseline. Secondary efficacy variables were the following:

- 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)

Sample size

The primary objective of this trial was to demonstrate that zoledronic acid (0.025 mg/kg or 0.05 mg/kg, dependent upon age) is not inferior to pamidronate (1.5 mg/kg, 2.25 mg/kg or 3.0 mg/kg – total dose over three days, dependent upon age) in children with severe osteogenesis imperfecta, with respect to the percentage change in lumbar spine bone mineral density (LS BMD) at month 12 relative to baseline. A previous study suggests that the annualized percentage change in LS BMD after treatment is as much as 42% (SD 29%).

μP and μZ were defined as the population means of annualized percentage change in LS BMD for the pamidronate and zoledronic acid patients, respectively, and $\Delta = \mu Z - \mu P$ the treatment difference. The null hypothesis that zoledronic acid is more than 13% inferior to pamidronate ($H0 : \Delta \leq -13\%$) was tested, or was rejected in favor of the alternative hypothesis that zoledronic acid is less than 13% inferior to pamidronate ($HA : \Delta > -13\%$). In testing this hypothesis, it was assumed that the standard deviations for two treatments were the same under H0 and HA and that zoledronic acid had approximately a 2% advantage with respect to the annualized percentage change in LS BMD under HA relative to pamidronate. Therefore, given a two-sample t-test with 80% power and a one-sided level of significance of 0.025 to detect a non-inferiority margin of 13%, approximately 60 evaluable patients per treatment group were necessary. Assuming a 5% adjustment for dropouts and missing data for LS BMD, the total sample size required in the study was approximately 132 patients (66 per group).

Statistical methods

The 2-sided 95% CI, based on t-distribution, for the difference of percentage change from baseline in LS BMD between the two treatment groups was calculated. The noninferiority and superiority of zoledronic acid relative to pamidronate were assessed by comparing the lower bound of the 95% CI to a pre-defined non-inferiority margin (-13%) in the ITT, per-protocol and completers populations.

An analysis of covariance (ANCOVA) model with baseline value as a covariate, treatment, region, gender and puberty stage as factors was fitted for all efficacy variables except fracture and Wong-Baker FACES score. Cox's proportional hazard model and Kaplan-Meier estimate with log-rank test

were used to compare the risk of fracture, and the t-test was used to compare the number of fractures per patient during treatment between the two treatment groups. Descriptive statistics was provided to summarize the Wong-Baker FACES pain scores.

In the ANCOVA model applied to changes in biomarkers, a loge transformation of the ratio of the on treatment value at a visit relative to baseline value (relative change) was used in the analysis to approximate normality. A non-parametric ANCOVA model based on rank scores was used as a confirmatory analysis for the percentage change from baseline in LS BMD at month 6 and 12 when the assumption of normality was not valid.
All hypothesis tests were evaluated at a 0.05 level of significance, and no adjustments for multiplicity were performed for any of secondary variables. No interim analysis was performed for any of the efficacy variables.

Results

Participant flow
A total of 155 patients were randomized out of the 205 patients screened. A screening log was maintained at each center but records of screen failures were not entered in the clinical database. Therefore frequency and reasons for screen failures were not summarized in the report. Patients were randomized at 20 centers in 9 countries (Belgium, Canada, France, South Africa, Hungary, Poland, Finland: 1 center each, Great Britain: 3 centers, USA: 10 centers). The first patient was enrolled on 26 June 2003 (first patient screened) and the last patient completed on 09 May 2007.

Patient Status	Zoledronic acid N=74 n (%)	Pamidronate N=76 n (%)	Total N=150 n (%)
Completed	68 (91.9)	69 (90.8)	137 (91.3)
Discontinued	6 (8.1)	7 (9.2)	13 (8.7)
Subject withdrew consent	3 (4.1)	3 (3.9)	6 (4.0)
Adverse Event(s)	2 (2.7)	2 (2.6)	4 (2.7)
Lost to follow-up	1 (1.4)	2 (2.6)	3 (2.0)

The majority of patients in both groups completed the study. Reasons for discontinuation were similar in each group, namely withdrawal of consent, AE or lost to follow up at comparable frequencies. Only 2 patients in each group discontinued because of AEs.

The proportions of patients with major protocol deviations were similar in the two treatment groups.

Table 10-2 Major protocol deviations (ITT)

	Zoledronic acid N=74 n (%)	Pamidronate N=76 n (%)	Total N=150 n (%)
Total number of ITT patients excluded from per-protocol population	21 (28.4)	16 (21.1)	37 (24.7)
Major protocol deviations:			
Bisphosphonate washout < 12 months	1 (1.4)	0	1 (0.7)
No valid baseline LS BMD	10 (13.5)	8 (10.5)	18 (12.0)
No valid LS BMD at month 12	19 (25.7)	15 (19.7)	34 (22.7)
Patient discontinued	6 (8.1)	7 (9.2)	13 (8.7)
Patient received non clinical trial medication for first infusion	0	1 (1.3)	1 (0.7)
Use of calcitonin as a prior/ concomitant medication	0	1 (1.3)	1 (0.7)

Lack of valid baseline or month 12 lumbar spine BMD assessments were the most frequent cause of major PDs.
All patients received randomized study medication, as assigned, except one pamidronate treated patient (GBR/0403/00007) who received hospital supply of drug for the first infusion due to issues

with delivery of study drug. Three randomized patients (1 zoledronic acid, 2 pamidronate) were not administered any study drug and were excluded from all analyses.

Baseline data

The characteristics matched the intended target, paediatric population including children aged 1 to 17 years: 51% were between 9 and 17 years of age, 41% were aged 3 to 8 years, 7% were 2 years old and one child in each group was just 1 year old. Most children were Caucasian (84%) and there was a slightly higher proportion of boys versus girls particularly in the pamidronate group (zoledronic acid boys vs. girls: 51% vs. 49%, pamidronate boys vs. girls: 59% vs. 41%). Otherwise the two groups were comparable.

		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/m^2)	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)

Children with OI type I accounted for 49% of the study subjects overall. Some imbalance was noted in terms of the distribution across the 3 OI types, in that a higher proportion of pamidronate patients had OI type IV (zoledronic acid 24%, pamidronate 34%).

Almost all the children (97%) had a history of fracture, approximately 45% had undergone surgical correction of deformities, 50% of zoledronic acid patients and 43.4% of pamidronate patients used a mobility aid at baseline, and 27% and 25% respectively were using a wheelchair.

Mean and median number of fractures per patient in the last 12 months prior to this study (mean 3.0 vs. 2.3) and in the children's lifetimes (mean 18.9 vs. 16.5) were slightly higher in the zoledronic acid group versus pamidronate. A similar proportion of children in each group had suffered at least one fracture in the 12 months before this study (zoledronic acid 77%, pamidronate 79%).

There were no notable differences between the two treatment groups with respect to baseline characteristics, except for serum calcium with a higher baseline mean value in the pamidronate group (p=0.0024).

		Zoledronic acid N=74	Pamidronate N=76	Total N=150
OI phenotype - n (%)	I	38 (50.7)	35 (46.1)	73 (48.7)
	III	18 (24.3)	15 (19.7)	33 (22.0)
	IV	18 (24.0)	26 (34.2)	44 (29.3)
Age at OI diagnosis	n	74	76	150
(years)	Mean (SD)	2.2 (2.99)	2.0 (3.28)	2.1 (3.13)
	Median	1.0	1.0	1.0
	Min - max	0 - 11	0 - 14	0 - 14
Lumbar spine BMD	n	64	68	132
(g/cm^2)	Mean (SD)	0.417 (0.137)	0.444 (0.174)	0.431 (0.157)
	Median	0.414	0.398	0.405
	Min - max	0.13 - 0.76	0.16 - 0.94	0.13 - 0.94
Lumbar spine Z-score†	n	44	49	93
	Mean (SD)	-2.80 (1.247)	-2.53 (1.517)	-2.66 (1.395)
	Median	-2.70	-2.70	-2.70
	Min - max	-5.9 - -0.1	-7.1 - 0.7	-7.1 - 0.7
Femoral neck BMC	n	43	49	92
(g)	Mean (SD)	1.358 (0.771)	2.127 (3.994)	1.767 (2.973)
	Median	1.115	1.390	1.322
	Min - max	0.27 - 3.31	0.19 - 28.74‡	0.19 - 28.74‡
History of fracture	Yes	73 (98.6)	73 (96.1)	146 (97.3)
n (%)	No	1 (1.4)	3 (3.9)	4 (2.7)
No. of patients with fractures in the last 12 months - prior to first infusion				
	n (%)	57 (77.0)	60 (78.9)	117 (78.0)
No. of fractures per patient in the last 12 months - prior to first infusion				
	n	74	74	148
	Mean (SD)	3.0 (3.28)	2.3 (1.74)	2.6 (2.64)
	Median	2.5	2.0	2.0
	Min - max	0 - 20	0 - 7	0 - 20
No. of fractures per patient in lifetime - prior to first infusion				
	n	74	76	150
	Mean (SD)	18.9 (24.25)	16.5 (26.54)	17.7 (25.38)
	Median	10.5	9.5	10.0
	Min - max	0 - 115	0 - 200	0 - 200

Numbers analysed

155 patients were randomized (zoledronic acid 75, pamidronate 80). The efficacy analysis comprised 150 patients in the ITT population (zoledronic acid 74,pamidronate 76); 152 patients were analyzed for safety (zoledronic acid 74, pamidronate 78) and 11 patients were analyzed for PK of zoledronic acid (4 aged 3-8 years, 7 aged 9-17 years).

	Zoledronic acid N=75 n (%)	Pamidronate N=80 n (%)	Total N=155 n (%)
Analysis population:			
Intent-to-treat	74 (98.7)	76 (95.0)	150 (96.8)
Per-protocol	53 (70.7)	60 (75.0)	113 (72.9)
Completers	68 (90.7)	69 (86.3)	137 (88.4)
Safety	74 (98.7)	78 (97.5)	152 (98.1)
Pharmacokinetic	11 (14.7)	0	11 (7.1)

Outcomes and estimation

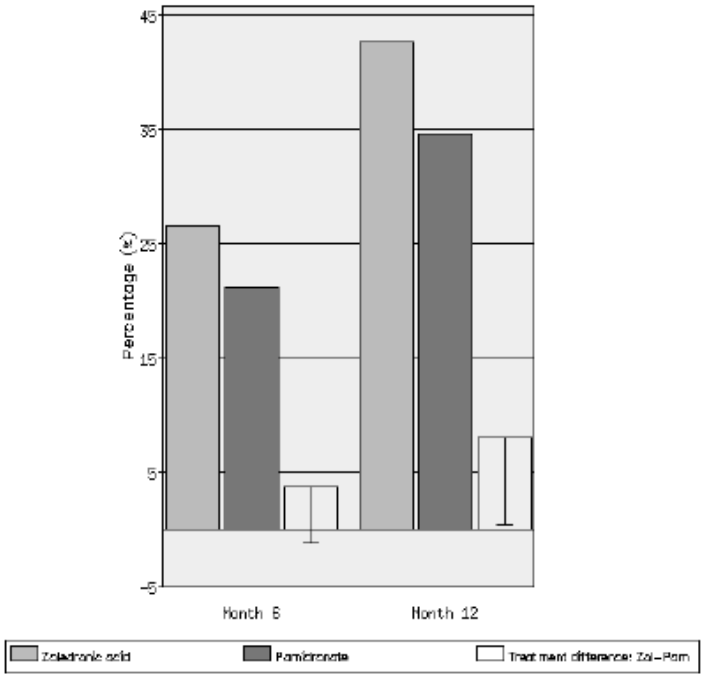
The primary analysis of the percentage change in lumbar spine (LS) BMD at month 12 relative to baseline in the ITT (LOCF) population demonstrated that the estimated effects on BMD were similar between zoledronic acid and pamidronate with an 8.06% greater increase in LS BMD and lower limit of the 95% confidence interval of 0.42%. This result was confirmed by analyses in the per-protocol and completers population and by a non-parametric ANCOVA model in the ITT (LOCF) population.

Primary efficacy results: percent change from baseline in LS BMD at month 12

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.

Mean percentage change from baseline in lumbar spine BMD by treatment (ITT LOCF)



Secondary efficacy results

Analyses of LS Z-score at 6 and 12 months in femoral neck and total body BMC also demonstrated similarity between zoledronic acid and pamidronate.

Change from baseline in lumbar spine BMD, femoral neck and total body BMC, and lumbar spine Z-score by visit: treatment comparisons (ITT LOCF)

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)			
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

Subgroup analysis of LS BMD by OI type subgroups

Table 11-7 Percentage change from baseline in LS BMD by OI type (ITT LOCF)

OI type Visit	Zoledronic acid Mean (SE)	Pamidronate Mean (SE)	Mean Difference Zol - Pam
OI Type I	N=37	N=31	
Month 6	24.847 (2.289)	18.222 (2.289)	6.625
Month 12	40.675 (3.207)	30.060 (2.959)	10.615
OI Type III or IV	N=26	N=37	
Month 6	29.215 (3.088)	23.657 (3.299)	5.558
Month 12	45.614 (5.038)	38.495 (4.165)	7.119

BMD change from baseline was greater in OI type III or IV patients than in OI type I patients at Months. It seems that increase in LS BMD was higher with zoledronic acid than pamidronate in both subgroups although p values are not provided.

Serum biomarkers of bone turnover

Serum biomarkers of bone turnover were measured in patients aged ≥3 years from fasting blood samples.

For all three biomarkers of bone turnover, zoledronic acid had a greater effect than pamidronate on reducing resorption and formation from baseline. The relative change from baseline was statistically significantly greater at month 6 and month 12 for zoledronic acid compared to pamidronate.

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 inversing 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.

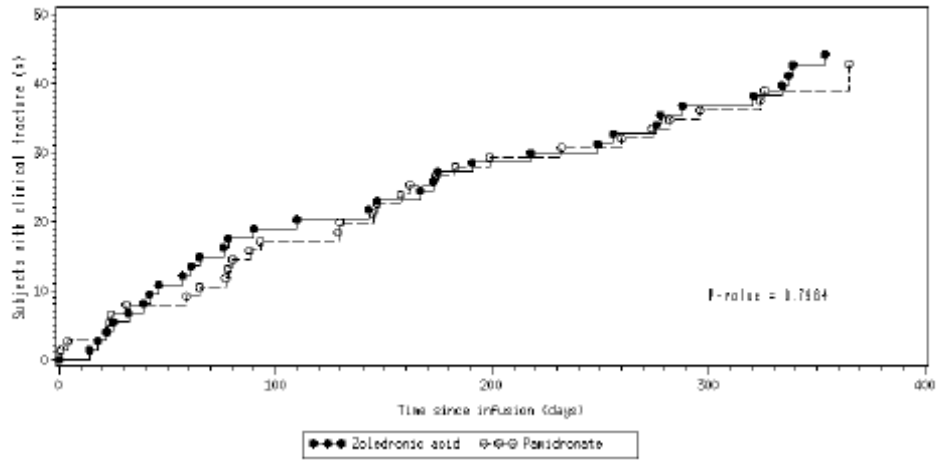
Clinical fractures

Incidence and time to first clinical fracture after first infusion, overall and by OI type (ITT)

	Zoledronic acid	Pamidronate	Hazard ratio	P-value
Number (%) of patients with any fracture in 12 months (1)				
Overall	N=74	N=76		
n (%)	32 (43.2)	31 (40.8)	1.05 (0.64, 1.72)	0.8687
OI Type I	N=38	N=35		
n (%)	19 (50.0)	10 (28.6)	2.12 (0.96, 4.69)	0.0934
OI Type III or IV	N=36	N=41		
n (%)	13 (36.1)	21 (51.2)	0.59 (0.29, 1.19)	0.2506
Time (days) to first clinical fracture after first infusion (2)				
Overall				
Median	NA	NA		0.7964
95% CI	(334, none)	(326, none)		
OI Type I				
Median	321	NA		0.0659
95% CI	(218, none)	(none, none)		
OI Type III or IV				
Median	NA	326		0.1446
95% CI	(354, none)	(199, none)		

(1) P-value is from Fisher's exact test; Hazard ratio and 95% CI of zoledronic acid vs. pamidronate is computed from a Cox proportional hazards regression model with treatment, region, gender and puberty stage as factors. A hazard ratio <1 implies that a zoledronic acid-treated patient has a lower risk of having a fracture than a pamidronate-treated patient.
(2) P-value is from Kaplan-Meier log-rank test.
NA = Not available due to ≤50% of the patients having experienced an event during this time period.

Figure 11-2 Kaplan-Meier estimate of time (days) to first clinical fracture after first infusion (all ITT patients)



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

Number of clinical fractures per patient within and between treatment, overall and by OI type (completers population)

	Overall		OI Type I		OI Type III or IV	
	Zoledronic acid	Pamidronate	Zoledronic acid	Pamidronate	Zoledronic acid	Pamidronate
Baseline: fractures per patient occurred in the last 12 months prior to first infusion						
n	68	67	33	31	35	36
Mean (SD)	3.00 (3.37)	2.22 (1.75)	2.88 (2.62)	2.61 (1.61)	3.11 (3.99)	1.89 (1.82)
Median	3	2	3	3	2	2
Min - max	0 - 20	0 - 7	0 - 11	0 - 7	0 - 20	0 - 7
P1	0.0963		0.6288		0.0989	
Post-baseline: fractures per patient occurred in 12 months after first infusion						
n	68	67	33	31	35	36
Mean (SD)	1.04 (3.00)	0.67 (1.21)	0.67 (0.74)	0.39 (0.72)	1.40 (4.12)	0.92 (1.48)
Median	0	0	1	0	0	0
Min - max	0 - 24	0 - 7	0 - 3	0 - 3	0 - 24	0 - 7
P1	0.3479		0.1288		0.5110	
Reduction of number of fractures per patient from baseline: baseline - post-baseline						
n	68	67	33	31	35	36
Mean (SD)	1.96 (3.84)	1.55 (2.08)	2.21 (2.77)	2.23 (1.69)	1.71 (4.66)	0.97 (2.22)
Median	1	1	2	2	1	1
Min - max	-14 - 19	-5 - 7	-1 - 10	0 - 7	-14 - 19	-5 - 6
P1	0.4495		0.9812		0.3924	
P2	<0.0001	<0.0001	<0.0001	<0.0001	0.0364	0.0128

Fractures are based on medical history at baseline, and radiograph or radiographic interpretation reports post-baseline.
n = number of patients with values at baseline. If a patient did not report any clinical fractures during the study, the number of fractures for this patient post-baseline is zero.
P1: p-value between treatment groups from two-sample t-test.
P2: p-value within treatment group by comparing the post-baseline with baseline values using paired t-test.

Fewer patients had clinical fractures in the 12 months of the study compared with the 12 months prior to randomization, with decreases in the proportions of patients with fractures from 77% to 43% in the zoledronic acid group and 79% to 41% in the pamidronate group (ITT population).

Overall, the incidence of fracture during treatment with zoledronic acid (43.2%) versus pamidronate (40.8%) was similar (p=0.8687, hazard ratio 1.05, 95% CI 0.64 - 1.72) and the Kaplan-Meier estimates of time to clinical fracture were comparable.

However, rates of clinical fracture by OI type subgroup, I / III or IV, showed a higher incidence with zoledronic acid relative to pamidronate in the OI type I patients (zoledronic acid 50.0%, pamidronate 28.6%, hazard ratio 2.12, 95% CI 0.96 - 4.69) and a lower incidence relative to pamidronate in the OI type III or IV patients (zoledronic acid 36.1%, pamidronate 51.2%, hazard ratio 0.59, 95% CI 0.29 - 1.19).

Within treatment groups, the overall mean reductions of 1.96 fractures/patient/year with zoledronic acid treatment and 1.55 fractures/patient/year with pamidronate treatment were statistically significant ($p<0.0001$ in both groups). Similarly, reductions in fracture rates were observed in each of the OI type subgroups. The highest mean reductions in fractures/patient/year were seen in the OI type I subgroup (reductions: zoledronic acid 2.21 fractures/patient/year $p<0.0001$, pamidronate 2.23 $p<0.0001$), while those in the OI type III or IV subgroups were lower (reductions: zoledronic acid 1.71 $p<0.05$, pamidronate 0.97 $p<0.05$).
The comparison of treatments regarding fracture rates showed no statistically significant differences between zoledronic acid and pamidronate.

Bone pain
Summaries of bone pain scores using Wong-Baker FACES, for all patients and by OI type subgroups, did not show any marked, consistent differences between zoledronic acid and pamidronate treatments at any time during the study versus the baseline pain assessment.
At baseline and post-baseline assessments the majority of patients or their legal guardian reported "no hurt" or "hurts little bit". Some imbalance at baseline was observed in the OI type I subgroup where 30 (79%) of patients in the zoledronic acid group compared to 21 (60%) of patients in the pamidronate group reported "no hurt". With high proportions of patients having none or very little pain at baseline, improvements in pain status post-baseline relative to baseline were difficult to detect.

	Zoledronic acid			Pamidronate		
Visit Wong-Baker FACES	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)

1.3.1.2 Study H2202E1

This was a one-year, international, multicenter, randomized, open-label, parallel-group, safety and efficacy study extending treatment to paediatric patients with severe OI who completed the first year of treatment in core Study H2202, stratifying extension zoledronic acid regimens (once or twice yearly) by core treatment (zoledronic acid or pamidronate). The first visit of the extension study coincided with the final visit of study H2202.

The once yearly treatment group had 1 dosing visit (extension visit 1 at month 12 relative to the core baseline) when patients received a zoledronic acid infusion (0.025 mg/kg in children 1 to < 3 years of age and 0.05 mg/kg in children 3 to 17 years of age).

The twice yearly treatment group had two dosing visits (extension visit 1 and extension visit 4 at month 18 relative to the core baseline).

The study was conducted according to Good Clinical Practice, randomizing 103 patients into zoledronic acid once a year or twice a year treatment group. With previous treatment assignment in the core study, the treatment assignment over the 2-year core-extension are displayed as the following 4 study groups: 25 zol-zol 1x/yr, 27 zol-zol 2x/yr, 24 pam-zol 1x/yr, 27 pam-zol 2x/yr.

The primary objective of Study H2202E1 was to examine the long-term general and renal safety of once yearly or twice yearly zoledronic acid over a 12 month extension treatment period in patients aged who had completed one year of treatment with either zoledronic acid or pamidronate in the core study. Continued efficacy of zoledronic acid was a secondary objective of the extension study.

Baseline demographics

	Zoledronic acid		Pamidronate		Total
	Zol 1x/yr N = 25	Zol 2x/yr N = 27	Zol 1x/yr N = 24	Zol 2x/yr N = 27	Zol 1x/yr or 2x/yr N = 103
Sex – n (%)					
Male	14 (56.0)	13 (48.1)	13 (54.2)	18 (66.7)	58 (56.3)
Female	11 (44.0)	14 (51.9)	11 (45.8)	9 (33.3)	45 (43.7)
Race – n (%)					
Caucasian	20 (80.0)	25 (92.6)	21 (87.5)	21 (77.8)	87 (84.5)
Black	3 (12.0)	1 (3.7)	2 (8.3)	3 (11.1)	9 (8.7)
Oriental	1 (4.0)	1 (3.7)	0	0	2 (1.9)
Other	1 (4.0)	0	1 (4.2)	3 (11.1)	5 (4.9)
Age group – n (%)					
2- < 3 years	1 (4.0)	0	0	1 (3.7)	2 (1.9)
3- < 9 years	13 (52.0)	12 (44.4)	9 (37.5)	8 (29.6)	42 (40.8)
≥ 9 years	11 (44.0)	15 (55.6)	15 (62.5)	18 (66.7)	59 (57.3)
Age (year)					
Mean (SD)	8.9 (4.98)	9.9 (4.29)	10.0 (4.81)	10.0 (3.97)	9.7 (4.47)
Median	8.0	10.0	12.0	11.0	10.0
Min - max	2 - 17	3 - 17	3 - 16	2 - 15	2 - 17
Weight (kg)					
Mean (SD)	21.76 (12.835)	26.41 (17.681)	32.03 (21.436)	28.36 (12.659)	27.10 (16.617)
Median	18.50	20.60	27.05	30.00	23.20
Min - max	7.4 - 63.1	7.6 - 90.0	9.2 - 97.0	6.3 - 53.6	6.3 - 97.0
Height/supine length (cm)					
n	24	27	24	27	102
Mean (SD)	109.5 (25.03)	109.0 (26.36)	118.0 (26.91)	116.9 (23.23)	113.3 (25.35)
Median	108.0	107.0	120.5	115.0	113.5
Min - max	70 - 170	63 - 174	72 - 164	54 - 158	54 - 174
BMI (kg/m^2)					
n	24	27	24	27	102
Mean (SD)	17.47 (3.248)	20.78 (8.043)	20.60 (6.266)	20.07 (6.340)	19.77 (6.329)
Median	17.30	17.30	19.25	18.00	17.80
Min - max	12.6 - 25.1	13.0 - 44.2	14.6 - 40.8	10.9 - 37.0	10.9 - 44.2

Baseline values for height, weight and BMI are from the core study.
Age is calculated at the baseline of the extension study.

Baseline disease characteristics

	Zoledronic acid		Pamidronate		Total
	Zol 1x/yr N = 25	Zol 2x/yr N = 27	Zol 1x/yr N = 24	Zol 2x/yr N = 27	Zol 1x/yr or 2x/yr N = 103
OI phenotype – n (%)					
I	14 (56.0)	11 (40.7)	12 (50.0)	13 (48.1)	50 (48.5)
III	7 (28.0)	8 (29.6)	7 (29.2)	5 (18.5)	27 (26.2)
IV	4 (16.0)	8 (29.6)	5 (20.8)	9 (33.3)	26 (25.2)
Age at OI diagnosis (year)					
n	25	27	24	27	103
Mean (SD)	1.9 (2.81)	2.4 (3.11)	2.1 (3.97)	2.6 (3.42)	2.3 (3.31)
Median	1.0	1.0	1.0	1.0	1.0
Min - max	0 - 10	0 - 11	0 - 14	0 - 13	0 - 14
Lumbar spine BMD (g/cm^2)					
n	22	21	22	22	87
Mean (SD)	0.35 (0.140)	0.43 (0.122)	0.50 (0.222)	0.43 (0.154)	0.43 (0.171)
Median	0.333	0.405	0.437	0.409	0.382
Min - max	0.13 - 0.64	0.17 - 0.64	0.19 - 0.94	0.24 - 0.80	0.13 - 0.94
Lumbar spine Z-score †					
n	13	12	12	18	55
Mean (SD)	-3.19 (1.624)	-2.70 (0.902)	-1.64 (1.357)	-2.91 (1.714)	-2.65 (1.540)
Median	-3.50	-2.51	-2.08	-3.10	-2.70
Min - max	-5.9 - -0.1	-4.2 - -1.5	-3.5 - 0.7	-7.1 - -0.4	-7.1 - 0.7
Total body BMC (g)					
n	24	27	23	25	99
Mean (SD)	617.14 (428.826)	696.43 (466.720)	906.91 (594.619)	782.79 (420.323)	747.91 (484.511)
Median	584.66	589.62	655.36	580.22	589.62
Min - max	131.91 - 1775.61	187.40 - 2153.48	193.37 - 2252.56	275.77 - 1750.44	131.91 - 2252.56
History of fracture – n (%)					
Yes	25 (100)	26 (96.3)	23 (95.8)	26 (96.3)	100 (97.1)
No	0	1 (3.7)	1 (4.2)	1 (3.7)	3 (2.9)
Number (%) of patients with fracture in the last 12 months prior to first infusion of the core study					
n (%)	21 (84.0)	20 (74.1)	19 (79.2)	22 (81.5)	82 (79.6)
Number of fractures per patient in the last 12 months prior to first infusion of core study					
n	25	27	24	27	103
Mean (SD)	3.6 (3.39)	3.0 (4.01)	2.1 (1.69)	2.1 (1.96)	2.7 (2.97)
Median	3.0	2.0	2.0	2.0	2.0
Min - max	0 - 11	0 - 20	0 - 7	0 - 7	0 - 20

Baseline values for lumbar spine BMD and Z-score and total body BMC are from the core study.
† Lumbar spine Z-score data includes only patients aged ≥3 years imaged on the Hologic equipment and patients aged ≥5 years imaged on the Lunar equipment which have manufacturer validated normative ranges.

The population and baseline characteristics of patients in the open-label extension were similar to those of the initial study. Mean LS BMD, LS Z-score and total body BMC were lowest at baseline for patients who were in the extension zoledronic acid once-yearly group of the core zoledronic acid stratum (zol-zol 1x/yr) and highest in the pam-zol 1x/yr group.

Patients were grouped by core treatment stratum (zoledronic acid or pamidronate) and extension study zoledronic acid regimen (1x/yr or 2x/yr). The majority of patients in each treatment group completed the extension study. Seven patients discontinued for administrative problems, namely the termination of the study as per the recommendation of the Data Safety Monitoring Board. They were brought in for their final visit earlier than intended and therefore did not complete the study as originally planned. All 7 of these patients received the first study drug infusion and one patient in the zol-zol 2x/yr group

also had the second infusion at 6 months. Two of these 7 patients completed 3 months, one 4 months, two 6 months and two 9 months of the planned 12 month extension study period.

The extension study was terminated early at the recommendation of the DSMB who in their review of unblinded interim safety and efficacy data had observed an "excess fracture risk" that "had not changed from the core" study (see discussion in safety section below). The changes in study conduct necessary to terminate the extension study were communicated to the investigators.

Patient disposition

	Zoledronic acid		Pamidronate		Total
Patient status	Zol 1x/yr n (%)	Zol 2x/yr n (%)	Zol 1x/yr n (%)	Zol 2x/yr n (%)	Zol 1x/yr or 2x/yr n (%)
Randomized, ITT and safety patients	25 (100)	27 (100)	24 (100)	27 (100)	103 (100)
Completed	23 (92.0)	24 (88.9)	21 (87.5)	24 (88.9)	92 (89.3)
Discontinued	2 (8.0)	3 (11.1)	3 (12.5)	3 (11.1)	11 (10.7)
Primary reason for discontinuation:					
Subject withdrew consent	2 (8.0)	1 (3.7)	0	0	3 (2.9)
Lost to follow-up	0	0	0	1 (3.7)	1 (1.0)
Administrative problems	0	2 (7.4)	3 (12.5)	2 (7.4)	7 (6.8)

Baseline demographic and disease characteristics in the open-label extension were similar to those of the initial study and the completion rates were acceptable.

Results

Long term efficacy outcome

A summary of clinical fractures by core treatment stratum is presented in the table below.

	Zoledronic acid N = 52	Pamidronate N = 51
During 12 month extension study:		
Number (%) of patients with any clinical fracture	16 (30.8)	21 (41.2)
Number of clinical fractures per patient:		
Mean (SD)	2.1 (1.57)	1.7 (1.15)
Median	1.5	1.0
Min - max	1 - 7	1 - 4
Time (days) to first clinical fracture after the first infusion in the extension study		
Median	not applicable	not applicable
During 24 month combined core and extension studies:		
Number (%) of patients with any clinical fracture	29 (55.8)	34 (66.7)
Number of clinical fractures/patient:		
Mean (SD)	3.3 (4.61)	2.1 (2.19)
Median	2.0	1.0
Min - max	1 - 24	1 - 11
Time (days) to first clinical fracture after the first infusion in the core study		
Median	537.5	462.0
95% CI	256.0 - none	326.0 - 652.0

Source: [Study H2202E1-Table 14.2-3.1 (M.5, 5.3.5.1)], [Study H2202E1-Table 14.2-3.2

As noted assessment of continued efficacy and disease control over an additional 12 months in paediatric patients with severe OI who completed the core study was a secondary objective in extension.

Median percentage increases in LS BMD from core baseline to month 24 (LOCF) were 56.7%, 50.7%, 43.4% and 44.3% in the zol-zol 1x/yr (n=22), zol-zol 2x/yr (n=21), pam-zol 1x/yr (n=22) and pam-zol

2x/yr (n=22) groups, respectively. There is no apparent efficacy advantage in LS BMD of the twice a year zoledronic acid regimen over the once yearly regimen.

Sustained decreases in median values of serum biomarkers of bone resorption β-CTx and bone formation P1NP and BSAP were observed in all treatment groups over 24 months, however, both bone resorption and formation remained active at month 24.

The majority of patients reported “no hurt” in the Wong-Baker FACES pain scores throughout the 24 month treatment period with no clinically relevant changes in the distribution of scores within or between treatment groups.

The proportion of patients who had clinical fractures in the 24 months of treatment was higher in the core pamidronate stratum (34/51 patients, 66.7%) compared to the core zoledronic acid stratum (29/52 patients, 55.8%). All treatment regimens reduced the proportion of patients with clinical fractures during the extension phase compared to the 12 months before the study when 41/51 (80.4%) and 41/52 (78.8%) patients reported fractures in the pamidronate and zoledronic acid strata, respectively.

Over the combined 24 months of treatment, patients who sustained a clinical fracture in the zoledronic acid stratum had a higher mean (3.3) and median (2.0) number of clinical fractures per patient compared to those in the pamidronate stratum (mean 2.1, median 1.0). However, due to the small sample sizes these analyses should be interpreted with caution.

1.3.1.3 Overall conclusion on clinical efficacy

The clinical development program to support the treatment of children with severe OI comprised two studies. The core randomized, active-controlled open-label Study H2202 was conducted to demonstrate both the efficacy and the safety of zoledronic acid in the target population over 12 months. The open-label extension Study H2202E1 provides an additional 12 months of treatment data with zoledronic acid in the patient population who completed the controlled study H2202 regardless of the treatment received in the original core study.
Zometa dose selection was based on several sources: adults with benign disease safely received up to 5 mg i.v. infusion over 15 minutes. Compared to pamidronate, Zometa 4 mg was more efficacious than 90 mg pamidronate in patients with TIH or metastatic cancers to the bone. Doses in adults for oncology indications are equal to an approximate dose of zoledronic acid of 0.07 mg/kg or pamidronate 1.5 mg/kg for a 60 kg adult. In a long-term paediatric pamidronate OI study, pamidronate 1.5 or 3.0 mg/kg was tested and the dose range was safe and efficacious. Age-specific dose range of zoledronic acid being administrated as an i.v. infusion in this paediatric trial is comparable to that of pamidronate. The maximum allowable zoledronic acid dose of 4 mg (regardless of patient weight), does not exceed the 4 mg single dose that has been used in adults. A dose of zoledronic acid equivalent to that administered to adults with other metabolic bone conditions is approximately 0.05 mg/kg (maximum of 4.0 mg). This is the zoledronic acid dose range comparable to pamidronate 90 mg which has been studied in patients with OI.

Notwithstanding the more recently identified subtypes of OI (type VII and VIII), where a recessive inheritance was found and mutations of additional genes involved in the cellular machinery responsible for synthesis and output of type I collagen were noticed, it is held that OI diagnosed according to the Sillence classification is a heterogeneous condition, both clinically and pathogenetically. Silence types III and IV are deforming variants that are associated with variable severity of growth retardation and limb deformity. The phenotype is a consequence of a genetic mutation affecting the structure of the type 1 collagen molecule. The qualitative defects of the extracellular matrix account for distinctly low mineral bone mass at an early age, impaired bone growth and severe deformities. In contrast, a number of cases of less deforming or even non-deforming OI type I are the result of mutations affecting the production and/or the output from osteoblasts of otherwise normal type 1 collagen. Bone cell biology, bone mineral content, frequency and location of fractures, and the response to antiresorptive medication in the paediatric age from 1 to 17 years, are conceivably different among OI types.

Clinical consequences of the differences involve the phenotype, which is usually milder in type I than in the two other types and, on the other hand, is usually most severe in type III. The majority of

individuals affected with this type do not walk without assistance, and a number of them use a wheelchair because of marked bone fragility and deformities. It is reasonable to think that also bone resorption and bone turnover rate be different among types, the excess being more apparent in cases of recognized structural abnormalities of the collagen triple helix. Accordingly, the response to antiresorptive bisphosphonates, when studied as changes of BMD from baseline is conceivably greater in such cases, as indeed was noticed in the MAH's studies (post-hoc analyses).

Children with type I accounted for half of the study subjects overall. Moreover, the pamidronate arm had a higher percentage of cases with the more severe types. A number of cases had received metabolic bone therapies prior to study. Due to long-term skeletal accumulation of bisphosphonates, the chosen washout periods were questionable. Dietary calcium, parathyroid hormone (PTH) and sex hormone levels were not systematically assessed. 25-OH Vitamin D was measured at screening before study H2202 after supplementation if necessary (distribution of patients in classes of hypovitaminosis is not provided). Measurements of levels of 25-OHD were made for safety purposes (and not efficacy), as a precaution to minimize the risk of developing clinically apparent hypocalcemia upon first administration of study drug. Briefly, heterogeneity of the study population for pathogenesis and endocrine signals to bone at the time of starting therapy was inadequately addressed; as a consequence, overall interpretation of results – either efficacy or safety – has important limitations.
Official positions of qualified scientific societies state that in children fracture prediction should primarily take into account fracture of long bones in the lower extremities, together with vertebral compression fractures, or two or more long-bone fractures of the upper extremities. DXA measurements should be part of a comprehensive skeletal health assessment, and therapeutic interventions should not be based on a single DXA measurement. Pertinently, DXA measures an "areal" bone density (BMC/projection area). The areal BMD (g/cm2) is particularly deceptive when measured in growing patients. The influence of body (and bone) size must always be considered, not only for the initial assessment but also in the follow-up of growing patients; otherwise, for example, a subject might appear to have an increased BMD while this could be an artefact due to an increased bone size. Correction methods are used to attenuate difficulties in BMD assessment when children with osteoporosis are studied longitudinally.

Although the PDCO recommended a randomization of patients among the different subtypes of OI, to allow proper assessment of the benefit/risk per subtype of OI, randomisation was carried out by sites and not by OI type. The MAH has provided a posthoc analysis on efficacy among the different subtypes of OI. However, this did not provide additional, convincing information on the benefit/risk for subtype of OI. The chosen criteria for clinically assessing the efficacy "within-treatment" and "after-treatment" are based mostly on BMD changes and are therefore questionable.

The primary efficacy variable in study H2202 was percentage change in lumbar spine BMD at month 12 relative to baseline and secondary endpoints were change from baseline in lumbar spine Z-score at month 12, change from baseline in femoral neck BMC at month 6 and 12 and number of clinical fractures over a year. A total of 155 patients were randomized out of the 205 patients screened.

Discontinuation rates and major protocol deviations were similar in the two groups. At baseline some imbalances were noted with respect to gender, the 3 OI subtypes and number of fractures between the two treatment groups. The study showed that estimated effects on the primary endpoint were similar between zoledronic acid and pamidronate in terms of the primary endpoint of increase in LS-BMD after 12 months of treatment. This was also supported regarding sustained reductions in serum markers of bone resorption and bone formation. With respect to fractures, the proportion of patients who had clinical fractures during the 12 months of treatment was similar between the zoledronic acid and pamidronate treatment groups. Similarly no significant differences were observed regarding LS-BMD Z-score at 6 and 12 months and femoral neck and total body BMC. No changes from baseline or differences between the two treatments in Wong-Baker FACES pain assessments were detected.

The open-label extension study H2202E1, designed as a safety study with secondary efficacy parameters including small sample sizes, did not demonstrate any antifracture effect of zoledronic acid over pamidronate and median LS Z-score and total body BMC. During the extension period sustained

decreases in median values of serum biomarkers of bone resorption and bone formation were observed in all treatments.

Although the estimated effects on BMD were similar, the trial design was not sufficiently robust to conclusively establish non-inferior efficacy for Zometa. In particular there was no conclusive evidence of efficacy on incidence of fracture or on pain. The hallmark of OI is the occurrence of fractures. It is not clear that the key efficacy parameter "improvement in BMD at 12 months from baseline" translated into clinical benefit for patients with osteogenesis imperfecta in terms of less fractures, less disability and less chronic bone pain. The pivotal study H2202 was neither designed nor powered to estimate the efficacy of zoledronic acid on fractures or other clinically relevant outcome measures. This lack of a clear relationship between surrogate and clinical efficacy parameter was also reflected by a high rate of new fractures after start of the two bisphosphonates.

Furthermore, the CHMP questioned the choice of comparator. Regarding the use of pamidronate as the active control the applicant argued that this selection was an acknowledgement of the product's ability to alter the natural disease course, improve the clinical status and quality of life in children and are referring to two studies. The study by Glorieux 1998 showed that Cyclical i.v. treatment with pamidronate was associated with a marked increase in BMD and physical activity increased markedly in these patients and decreased fracture rate. This study was an observational and uncontrolled study. In the study by Plotkin children younger than 3 years old pamidronate infusion every 2-4 months over a increased BMD, and decreased the rate of fracture. This was also an observational study using a group of "historical controls". Despite the use of bisphosponates in clinical practice (off-label), the scientific evidence for pamidronate in this indication is quite weak with regards to placebo-controlled studies:

- the lack of a placebo-controlled clinical study in an indication without a well-established pharmacological therapy was not sufficiently justified.

- in the absence of a well quantified effect of pamidronate versus placebo the choice of non-inferiority margin required further justification (see CPMP/EWP/2158/99).

- it has not been established that the study has adequate assay sensitivity, so that any important differences between active agents could be detected.

Therefore, the CHMP emphasized the weakness of the study design and considered this to be not sufficient in support of the proposed new indication.

1.3.2 Clinical safety

Patient Exposure

Table 1-3 Exposure to study drug by number of infusions (Study H2202, safety population)

Number of infusions	Zoledronic acid N=74 n (%)	Pamidronate N=78 n (%)	Total N=152 n (%)
1	74 (100)	78 (100)	152 (100)
2	73 (98.6)	76 (97.4)	149 (98.0)
3	72 (97.3)	73 (93.6)	145 (95.4)
4	67 (90.5)	71 (91.0)	138 (90.8)
5	na	1 (1.3)	1 (0.7)
6	na	1 (1.3)	1 (0.7)

Note: During the study, zoledronic acid was infused every 3 months (up to 4 doses); pamidronate was infused every 3 months (up to 4 doses) for patients ≥2 years of age and every 2 months (up to 6 doses) for patients <2 years of age. na = not applicable

All patients in the extension study received at least one infusion of zoledronic acid, and 49/54 patients randomized to twice yearly zoledronic acid received two infusions, per protocol. Three patients did not receive the second infusion because of the early termination of the study when they were required to

discontinue for "administrative problems" (defined as incorrect early terminations of study due to administrative errors). For the other 2 patients in the pam-zol 2x/yr group who did not receive the second infusion, one was lost to follow up and the other had only one infusion but was reported to have completed the study.

Another 3 patients were considered to be protocol deviators due to dosing errors or failure to follow protocol procedures in the event of additional infusions: 1 patient in the zol-zol 2x/yr group and 1 patient in the pam-zol 1x/yr group had dosing errors when too little zoledronic acid was administered at the first infusion, however this was corrected within 2 weeks in both cases. One other patient in the zol-zol 2x/yr group received 2 additional infusions of zoledronic acid due to increased fatigue secondary to severe OI but did not discontinue from the extension study as required per protocol.

Table 1-4 Long-term exposure to study drug by number of infusions (Study H2202E1, safety population)

Arm in Core	Zoledronic acid		Pamidronate		Total
Arm in Extension	Zol 1x/yr	Zol 2x/yr	Zol 1x/yr	Zol 2x/yr	Zol 1x/yr or 2x/yr
	N = 25	N = 27	N = 24	N = 27	N = 103
Number of infusions	n (%)	n (%)	n (%)	n (%)	n (%)
1	25 (100)	27 (100)	24 (100)	27 (100)	103 (100)
2	-	26 (96.3)	1 (4.2)	23 (85.2)	50 (48.5)
3	-	2 (7.4)	-	-	2 (1.9)
4	-	1 (3.7)	-	-	1 (1.0)

Adverse events

Adverse events by primary system organ class (Study H2202)

	Zoledronic acid	Pamidrona
	N=74	N=78
Primary system organ class	n (%)	n (%)
Patients with any AE	71 (95.9)	76 (97.4)
General disorders and administration site conditions	51 (68.9)	55 (70.5)
Musculoskeletal and connective tissue disorders	49 (66.2)	40 (51.3)
Injury, poisoning and procedural complications	42 (56.8)	48 (61.5)
Gastrointestinal disorders	37 (50.0)	28 (35.9)
Infections and infestations	36 (48.6)	34 (43.6)
Metabolism and nutrition disorders	24 (32.4)	21 (26.9)
Nervous system disorders	22 (29.7)	21 (26.9)
Respiratory, thoracic and mediastinal disorders	17 (23.0)	21 (26.9)
Investigations	16 (21.6)	13 (16.7)
Skin and subcutaneous tissue disorders	13 (17.6)	13 (16.7)
Cardiac Disorders	6 (8.1)	4 (5.1)
Ear and labyrinth disorders	6 (8.1)	4 (5.1)
Eye disorders	6 (8.1)	3 (3.8)
Vascular disorders	3 (4.1)	2 (2.6)
Blood and lymphatic system disorders	2 (2.7)	3 (3.8)
Psychiatric disorders	2 (2.7)	6 (7.7)
Reproductive system and breast disorders	2 (2.7)	1 (1.3)
Congenital, familial and genetic disorders	1 (1.4)	2 (2.6)
Hepatobiliary disorders	1 (1.4)	0
Immune system disorders	1 (1.4)	3 (3.8)
Renal and urinary disorders	1 (1.4)	1 (1.3)
Pregnancy	0	1(1.3)
Social circumstances	0	1 (1.3)

Frequent adverse events (at least 10% in either group) by preferred term (Study H2202)

	Zoledronic acid N=74	Pamidronate N=78
Preferred term	**n (%)**	**n (%)**
Patients with any AE	71 (95.9)	76 (97.4)
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)

Frequent early vs. later onset adverse events (at least 5% in either group) by preferred term and infusion (Study 2202)

	Early onset †		Later onset ‡	
	Zoledronic acid	Pamidronate	Zoledronic acid	Pamidronate
	N=74	N=78	N=74	N=78
Preferred term	n (%)	n (%)	n (%)	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, ≤ 3 days after infusion. For pamidronate, ≤ 6 days after infusion start.
‡ For zoledronic acid, > 3 days after infusion. For pamidronate, > 6 days after infusion start.

Frequent adverse events (at least 5% in either group) occurring between infusions by preferred term (Study 2202)

Preferred term	Zoledronic acid N=74 n (%)	Pamidronate N=78 n (%)
After 1st and before 2nd infusion:		
Any AE	69 (93.2)	66 (84.6)
Pyrexia	43 (58.1)	39 (50.0)
Vomiting	18 (24.3)	9 (11.5)
Hypocalcemia	16 (21.6)	6 (7.7)
Headache	12 (16.2)	10 (12.8)
Pain in extremity	10 (13.5)	10 (12.8)
Femur fracture	9 (12.2)	3 (3.8)
Nausea	7 (9.5)	8 (10.3)
Fatigue	7 (9.5)	3 (3.8)
Arthralgia	6 (8.1)	9 (11.5)
Back pain	6 (8.1)	8 (10.3)
Abdominal pain upper	6 (8.1)	3 (3.8)
Tachycardia	5 (6.8)	3 (3.8)
Bone pain	5 (6.8)	3 (3.8)
Musculoskeletal pain	5 (6.8)	2 (2.6)
Diarrhea	5 (6.8)	2 (2.6)
Pain	4 (5.4)	6 (7.7)
Acute phase reaction	4 (5.4)	5 (6.4)
Nasopharyngitis	4 (5.4)	5 (6.4)
Dizziness	4 (5.4)	3 (3.8)
Hand fracture	4 (5.4)	2 (2.6)
Hypophosphatemia	4 (5.4)	1 (1.3)
Blood calcium decreased	3 (4.1)	5 (6.4)
Anorexia	3 (4.1)	7 (9.0)
Chills	2 (2.7)	4 (5.1)
Influenza like illness	1 (1.4)	4 (5.1)
After 2nd and before 3rd infusion:		
Any AE	49 (66.2)	50 (64.1)
Pain in extremity	10 (13.5)	5 (6.4)
Arthralgia	9 (12.2)	3 (3.8)
Femur fracture	6 (8.1)	3 (3.8)
Pyrexia	4 (5.4)	7 (9.0)
Back pain	4 (5.4)	4 (5.1)
Influenza	4 (5.4)	1 (1.3)
Fall	1 (1.4)	4 (5.1)
Infusion site pain	0	5 (6.4)

Preferred term	Zoledronic acid N=74 n (%)	Pamidronate N=78 n (%)
After 3rd and before 4th infusion:		
Any AE	48 (64.9)	47 (60.3)
Arthralgia	8 (10.8)	6 (7.7)
Tibia fracture	6 (8.1)	1 (1.3)
Bone pain	6 (8.1)	0
Pain in extremity	5 (6.8)	4 (5.1)
Nasopharyngitis	5 (6.8)	3 (3.8)
Femur fracture	4 (5.4)	4 (5.1)
Pyrexia	4 (5.4)	3 (3.8)
Musculoskeletal pain	4 (5.4)	1 (1.3)
Headache	3 (4.1)	4 (5.1)
Upper limb fracture	2 (2.7)	4 (5.1)
After 4th infusion to end of study:		
Any AE	43 (58.1)	44 (56.4)
Femur fracture	5 (6.8)	2 (2.6)
Arthralgia	4 (5.4)	2 (2.6)
Bone pain	4 (5.4)	0
Pain in extremity	3 (4.1)	8 (10.3)
Headache	2 (2.7)	4 (5.1)

AEs included are those starting or continuing in the relevant treatment period between infusions

Almost all patients in both groups experienced at least one AE during the study (zoledronic acid 95.9%, pamidronate 97.4%). The proportion of patients with AEs in the most frequently affected primary SOCs were similar between zoledronic acid and pamidronate. More patients in the zoledronic acid treatment group experienced musculoskeletal and connective tissue disorders (zoledronic acid 66% vs. pamidronate 51%) and GI disorders (zoledronic acid 50% vs. pamidronate 36%) than those treated with pamidronate.

Pyrexia was the most frequent early onset AE, affecting approximately 50% of patients in both treatment groups. Hypocalcemia and vomiting occurred more frequently in the zoledronic acid group and with early onset relative to the first infusion in the great majority of cases. No hypocalcemia AEs were reported as late onset.

For patients receiving pamidronate, the protocol-specified procedure to infuse only half of the patient's calculated daily dose on the first day of the first infusion cycle (day 1 of visit 2). This was intended to reduce the risk of acute-phase reactions. This infusion procedure was not applicable for the first zoledronic acid infusion because it required 30 to 45 minutes infusion to be completed in a single dose. Hence early onset adverse events related to acute-phase reactions in the pamidronate group may have been fewer than could have been expected without the dose reduction on day 1.

Over the whole 12 month treatment period, pain in extremity, arthralgia and headache were the most frequent AEs and affected similar proportions of patients in both treatment groups.

Vomiting, femur fracture, hypocalcemia and bone pain were 10% or more (absolute proportion) among zoledronic acid-treated patients than pamidronate-treated patients.

Common AEs contributing to the higher rates of musculoskeletal disorders with zoledronic acid versus pamidronate included bone pain and musculoskeletal pain, and for GI disorders vomiting and upper abdominal pain.

Acute-phase reactions were mainly observed after the first infusion and were much less frequent after subsequent infusions of either study drug. While more zoledronic acid-treated patients than pamidronate-treated patients presented AEs after the first infusion, this difference was much less marked after subsequent infusions.

Adverse events by primary system organ class (Study H2202E1)

Arm in Core	Zoledronic acid		Pamidronate	
Arm in Extension	Zol 1x/yr	Zol 2x/yr	Zol 1x/yr	Zol 2x/yr
	N = 25	N = 27	N = 24	N = 27
Primary system organ class	n (%)	n (%)	n (%)	n (%)
Patients with any AE(s)	24 (96.0)	24 (88.9)	17 (70.8)	20 (74.1)
Injury, poisoning and procedural complications	14 (56.0)	15 (55.6)	14 (58.3)	16 (59.3)
Infections and infestations	13 (52.0)	16 (59.3)	8 (33.3)	9 (33.3)
Musculoskeletal and connective tissue disorders	11 (44.0)	13 (48.1)	8 (33.3)	13 (48.1)
General disorders and administration site conditions	6 (24.0)	2 (7.4)	4 (16.7)	2 (7.4)
Gastrointestinal disorders	5 (20.0)	3 (11.1)	3 (12.5)	3 (11.1)
Nervous system disorders	5 (20.0)	2 (7.4)	4 (16.7)	3 (11.1)
Respiratory, thoracic and mediastinal disorders	2 (8.0)	6 (22.2)	5 (20.8)	5 (18.5)
Skin and subcutaneous tissue disorders	2 (8.0)	2 (7.4)	0	3 (11.1)
Cardiac disorders	1 (4.0)	0	0	0
Congenital, familial and genetic disorders	1 (4.0)	1 (3.7)	0	0
Eye disorders	1 (4.0)	0	1 (4.2)	1 (3.7)
Renal and urinary disorders	1 (4.0)	0	0	0
Immune system disorders	0	3 (11.1)	0	1 (3.7)
Metabolism and nutrition disorders	0	2 (7.4)	0	2 (7.4)
Psychiatric disorders	0	0	1 (4.2)	2 (7.4)
Blood and lymphatic system disorder	0	1 (3.7)	1 (4.2)	0
Ear and labyrinth disorders	0	1 (3.7)	0	0
Reproductive system and breast disorders	0	1 (3.7)	0	0
Investigations	0	1(3.7)	0	0

Frequent adverse events (at least 5% in either group) by preferred term (Study H2202E1)

Arm in Core	Zoledronic acid		Pamidronate	
Arm in Extension	Zol 1x/yr	Zol 2x/yr	Zol 1x/yr	Zol 2x/yr
	N = 25	N = 27	N = 24	N = 27
Preferred term	n (%)	n (%)	n (%)	n (%)
Patients with any AE(s)	24 (96.0)	24 (88.9)	17 (70.8)	20 (74.1)
Femur fracture	5 (20.0)	3 (11.1)	3 (12.5)	4 (14.8)
Muscle spasms	5 (20.0)	0	0	0
Nasopharyngitis	5 (20.0)	5 (18.5)	0	2 (7.4)
Headache	4 (16.0)	1 (3.7)	2 (8.3)	3 (11.1)
Pain in extremity	4 (16.0)	5 (18.5)	0	3 (11.1)
Tibia fracture	4 (16.0)	5 (18.5)	1 (4.2)	4 (14.8)
Arthralgia	3 (12.0)	2 (7.4)	2 (8.3)	4 (14.8)
Back pain	3 (12.0)	4 (14.8)	3 (12.5)	1 (3.7)
Fatigue	3 (12.0)	1 (3.7)	1 (4.2)	0
Nausea	3 (12.0)	0	1 (4.2)	0
Sinusitis	3 (12.0)	0	0	0
Upper respiratory tract infection	3 (12.0)	2 (7.4)	1 (4.2)	3 (11.1)
Influenza	2 (8.0)	4 (14.8)	2 (8.3)	1 (3.7)
Musculoskeletal chest pain	2 (8.0)	4 (14.8)	0	1 (3.7)
Vomiting	2 (8.0)	1 (3.7)	2 (8.3)	1 (3.7)
Bone pain	1 (4.0)	2 (7.4)	2 (8.3)	4 (14.8)
Clavicle fracture	1 (4.0)	2 (7.4)	0	0
Diarrhea	1 (4.0)	2 (7.4)	0	0
Fall	1 (4.0)	2 (7.4)	1 (4.2)	2 (7.4)
Fibula fracture	1 (4.0)	2 (7.4)	0	1 (3.7)
Hand fracture	1 (4.0)	1 (3.7)	2 (8.3)	1 (3.7)
Pyrexia	1 (4.0)	2 (7.4)	3 (12.5)	2 (7.4)
Ulna fracture	1 (4.0)	1 (3.7)	1 (4.2)	2 (7.4)
Cough	0	2 (7.4)	2 (8.3)	1 (3.7)
Ear infection	0	1 (3.7)	2 (8.3)	0
Epistaxis	0	0	0	2 (7.4)
Forearm fracture	0	0	0	2 (7.4)
Humerus fracture	0	3 (11.1)	1 (4.2)	0
Hypercalcemia	0	1 (3.7)	0	2 (7.4)
Migraine	0	0	2 (8.3)	0
Pharyngitis	0	0	0	2 (7.4)
Pharyngitis streptococcal	0	0	2 (8.3)	0
Radius fracture	0	0	0	2 (7.4)
Scoliosis	0	2 (7.4)	0	1 (3.7)
Seasonal allergy	0	2 (7.4)	0	0
Sunburn	0	0	2 (8.3)	0

In the extension study, the overall AE incidence was higher in the core zoledronic acid stratum than in the core pamidronate stratum (48 patients, 92.3% vs. 37 patients, 72.6%). The most noticeable difference was a higher frequency of core zoledronic acid patients with AEs in the infections and infestations SOC.

For AEs affecting at least 10% of patients in any group, there were twice as many patients in the core zoledronic acid stratum versus the core pamidronate stratum who experienced muscle spasms, nasopharyngitis, pain in extremity, fatigue, nausea, sinusitis, influenza, musculoskeletal chest pain and humerus fracture. Bone pain was the only AE affecting at least 10% of patients in any group and twice as many patients in the core pamidronate stratum versus the core zoledronic acid stratum.

AEs related to acute-phase reactions were the most frequent overall in the core study, as expected on first administration of bisphosphonate infusions, and such acute-phase reactions were infrequent in the extension. The most frequent AEs overall in the extension were fractures. However, the proportions of patients with fractures in core zoledronic acid and pamidronate strata during the extension phase were similar to those reported in the core study.

Frequent suspected drug related adverse events (at least 5% in either group) by preferred term

Preferred term	Zoledronic acid N=74 n (%)	Pamidronate N=78 n (%)
Patients with suspected drug related AE(s)	56 (75.7)	54 (69.2)
Pyrexia	40 (54.1)	39 (50.0)
Hypocalcemia	16 (21.6)	6 (7.7)
Vomiting	13 (17.6)	6 (7.7)
Fatigue	9 (12.2)	3 (3.8)
Nausea	8 (10.8)	6 (7.7)
Headache	7 (9.5)	7 (9.0)
Pain in extremity	7 (9.5)	5 (6.4)
Tachycardia	5 (6.8)	0
Acute phase reaction	4 (5.4)	5 (6.4)
Pain	4 (5.4)	4 (5.1)
Arthralgia	4 (5.4)	4 (5.1)
Musculoskeletal pain	4 (5.4)	1 (1.3)
Body temperature increased	4 (5.4)	1 (1.3)
Hypophosphatemia	4 (5.4)	1 (1.3)
Blood calcium decreased	3 (4.1)	5 (6.4)
Anorexia	3 (4.1)	5 (6.4)
Chills	2 (2.7)	4 (5.1)
Back pain	2 (2.7)	4 (5.1)
Influenza like illness	1 (1.4)	4 (5.1)

The incidence of suspected study drug related AEs reflected the pattern of early onset AEs after the first infusion. Pyrexia was the most frequent AE suspected to be study drug related in both groups and numerically higher in the zoledronic acid group. Hypocalcemia, vomiting and fatigue were by far more frequent with zoledronic acid than pamidronate. Tachycardia was reported by the investigators as a suspected study drug related event in 5 (6.8%) zoledronic acid-treated patients and none in the pamidronate group. However, 6 patients (8.1%) in the zoledronic acid group and 4 (5.1%) pamidronate-treated patients experienced tachycardia, regardless of study drug relationship.

Tachycardia was the only suspected cardiac disorder occurring in at least 5% of a treatment group in this study.

AEs suspected to be study drug-related by the investigator were more frequent in the zol-zol 1x/yr group compared with the pam-zol 1x/yr group, 4 (16.0%) patients vs. none, respectively, but there was little difference between the twice yearly groups, 3 (11.1%) patients vs. 4 (14.8%). Suspected study drug-related AEs reported by 2 patients over all extension treatments were pyrexia, hypercalcemia and pain in extremity; other study drugrelated AEs affected only single patients.

Serious adverse events and deaths

No patient died during the core or extension study.

Serious adverse events by preferred term (Study H2202)

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
Tibia fracture	1 (1.4)	1 (1.3)
Femoral neck fracture	1 (1.4)	1 (1.3)
Head injury	1 (1.4)	1 (1.3)
Medical device complication	1 (1.4)	1 (1.3)
Chills	1 (1.4)	0
Bacteremia	1 (1.4)	0
Tooth abscess	1 (1.4)	0
Incision site hematoma	1 (1.4)	0
Radius fracture	1 (1.4)	0
Subdural hematoma	1 (1.4)	0
Ulna fracture	1 (1.4)	0
Upper limb fracture	1 (1.4)	0
Blood calcium decreased	1 (1.4)	0
Hypokalemia	1 (1.4)	0
Hypophosphatemia	1 (1.4)	0
Arthralgia	1 (1.4)	0
Bone pain	1 (1.4)	0
Lower limb deformity	1 (1.4)	0
Musculoskeletal chest pain	1 (1.4)	0
Pseudarthrosis	1 (1.4)	0
Upper limb deformity	1 (1.4)	0
Cough	1 (1.4)	0
Dyspnea	1 (1.4)	0
Clavicle fracture	0	1 (1.3)
Fracture displacement	0	1 (1.3)
Joint dislocation	0	1 (1.3)
Lower limb fracture	0	1 (1.3)
Muscle strain	0	1 (1.3)
Joint instability	0	1 (1.3)
Joint range of motion decreased	0	1 (1.3)
Joint swelling	0	1 (1.3)
Cerebral disorder	0	1 (1.3)
Hemorrhage intracranial	0	1 (1.3)
Hypoesthesia	0	1 (1.3)
Vasculitis	0	1 (1.3)

Serious adverse events suspected to be related to study drug by preferred term (Study H2202)

	Zoledronic acid	Pamidronate
	N=74	N=78
Preferred terms	n (%)	n (%)
Patients with any suspected SAE	8 (10.8)	1 (1.3)
Hypocalcemia	6 (8.1)	0
Pyrexia	2 (2.7)	0
Blood calcium decreased	1 (1.4)	0
Chills	1 (1.4)	0
Cough	1 (1.4)	0
Dyspnea	1 (1.4)	0
Hypophosphatemia	1 (1.4)	0
Musculoskeletal chest pain	1 (1.4)	0
Vasculitis	0	1 (1.3)

Serious adverse events by preferred term (Study H2202E1)

Arm in Core	Zoledronic acid		Pamidronate	
Arm in Extension	Zol 1x/yr	Zol 2x/yr	Zol 1x/yr	Zol 2x/yr
	N = 25	N = 27	N = 24	N = 27
Preferred term	n (%)	n (%)	n (%)	n (%)
Patients with any SAE(s)	5 (20.0)	6 (22.2)	3 (12.5)	5 (18.5)
Femur fracture	3 (12.0)	1 (3.7)	2 (8.3)	3 (11.1)
Tibia fracture	1 (4.0)	2 (7.4)	0	0
Femoral neck fracture	1 (4.0)	0	0	0
Arthralgia	1 (4.0)	0	0	0
Fracture malunion	1 (4.0)	0	0	0
Clavicle fracture	0	1 (3.7)	0	0
Fibula fracture	0	1 (3.7)	0	0
Medical device complication	0	0	0	1 (3.7)
Medical device discomfort	0	1 (3.7)	0	0
Multiple fractures	0	1 (3.7)	0	0
Post-traumatic pain	0	1 (3.7)	0	0
Radius fracture	0	0	0	1 (3.7)
Ulna fracture	0	0	0	1 (3.7)
Scoliosis	0	1 (3.7)	0	0
Type 2 diabetes mellitus	0	1 (3.7)	0	0
Atrial septal defect	0	1 (3.7)	0	0
Adenoidal hypertrophy	0	0	1 (4.2)	0
Tonsillar hypertrophy	0	0	1 (4.2)	0

Serious adverse events suspected to be related to study drug by preferred term (Study H2202E1)

Arm in Core	Zoledronic acid		Pamidronate	
Arm in Extension	Zol 1x/yr	Zol 2x/yr	Zol 1x/yr	Zol 2x/yr
	N = 25	N = 27	N = 24	N = 27
Preferred terms	n (%)	n (%)	n (%)	n (%)
Patients with any suspected SAE	1 (4.0)	0	0	0
Tibia Fracture	1 (4.0)	0	0	0
Fracture malunion	1 (4.0)	0	0	0

SAEs were more frequent with zoledronic acid than with pamidronate (32.4% versus 19.2%) mainly due to the higher rates of femur fracture, hypocalcemia and pyrexia observed with zoledronic acid. In fact in the core study hypocalcemia and pyrexia as suspected as drug related were not observed in the pamidronat group at all.

Hypocalcemia (6 patients) and blood calcium decreased (1 patient), reported as SAEs in 7 zoledronic acid-treated patients, occurred in the 3 days after the first zoledronic acid infusion and did not recur after subsequent infusions. Four of the 7 zoledronic acid patients reported symptoms of hypocalcemia, and 4 required either supplemental calcium or vitamin D. Two of these 7 patients had multiple early onset SAEs: one patient had cough with sternal pain, dyspnea, pyrexia, chills and hypocalcemia, whereas another patient had hypophosphatemia, hypokalemia and hypocalcemia - events consistent with the clinical picture of hypocalcemia (Study H2202).

Two patients in the zoledronic acid group and none on pamidronate had SAEs leading to discontinuation: one patient had bone pain in the right tibia one patient had a left arm fracture.

Thirteen zoledronic acid patients had SAEs involving fractures, 5 of whom had more than one fracture during the study. One patient sustained multiple fractures of the axial and appendicular skeleton after being struck by an automobile, and in another case skull fractures were due to a fall. Both patients had type III OI, a history of 100 fractures in their lifetimes and 10 - 20 fractures in the 12 months before randomization into this study. Only nine pamidronate patients had fracture SAEs, 4 of whom had more than one fracture during the study.

With respect to the patients who had fracture SAEs relative to the most recent study drug infusion, 6 out of 13 patients in the zoledronic acid group had fractures that occurred between the 1st and 2nd dose and 5 of these were femur fractures. In the pamidronate group, 2 out of 9 patients had SAE fractures between the 1st and 2nd cycles of pamidronate infusions, one femur fracture and the other lower limb fracture.

The overall incidence of SAEs in the extension study was lower than in the core study (19/103 patients, 18.4% vs. 39/152 patients, 25.7%). The number and percentage of patients with any SAE in the core zoledronic acid stratum versus the core pamidronate stratum were 5 (20.0%) in zol-zol 1x/yr vs. 3 (12.5%) in pam-zol 1x/yr and 6 (22.2%) in zol-zol 2x/yr vs. 5 (18.5%) in pam-zol 2x/yr. The majority of SAEs were attributed to the injury, poisoning and procedural complications SOC and primarily comprised the preferred terms of femur and tibia fractures.

Fracture AEs

Fracture AEs by preferred term (Study H2202)

Preferred terms	Zoledronic acid N=74 n (%)	Pamidronate N=78 n (%)
Patients with any fracture	37 (50.0)	36 (46.2)
Femur fracture	18 (24.3)	9 (11.5)
Tibia fracture	10 (13.5)	4 (5.1)
Hand fracture	6 (8.1)	2 (2.6)
Fibula fracture	4 (5.4)	1 (1.3)
Humerus fracture	3 (4.1)	7 (9.0)
Rib fracture	3 (4.1)	1 (1.3)
Clavicle fracture	2 (2.7)	4 (5.1)
Facial bones fracture	2 (2.7)	0
Foot fracture	2 (2.7)	5 (6.4)
Forearm fracture	2 (2.7)	3 (3.8)
Radius fracture	2 (2.7)	1 (1.3)
Skull fracture	2 (2.7)	0
Upper limb fracture	2 (2.7)	5 (6.4)
Femoral neck fracture	1 (1.4)	1 (1.3)
Lower limb fracture	1 (1.4)	2 (2.6)
Multiple fractures	1 (1.4)	0
Scapula fracture	1 (1.4)	0
Skull fractured base	1 (1.4)	0
Spinal fracture	1 (1.4)	0
Ulna fracture	1 (1.4)	1 (1.3)
Wrist fracture	1 (1.4)	1 (1.3)
Epiphyseal fracture	0	1 (1.3)
Spinal compression fracture	0	1 (1.3)
Thoracic vertebral fracture	0	1 (1.3)
Fracture displacement	0	1 (1.3)
Fracture delayed union	2 (2.7)	0

Includes all AEs where "fracture" is found in preferred term text.

Fracture AEs by OI type and preferred term (Study H2202)

	OI Type I		OI Type III/IV	
	Zoledronic acid	Pamidronate	Zoledronic acid	Pamidronate
	N=38	N=36	N=36	N=42
Preferred term	n (%)	n (%)	n (%)	n (%)
Patients with Fracture AE(s)	19 (50.0)	11 (30.6)	18 (50.0)	25 (59.5)
Femur fracture	9 (23.7)	0	9 (25.0)	9 (21.4)
Tibia fracture	4 (10.5)	1 (2.8)	6 (16.7)	3 (7.1)
Hand fracture	3 (7.9)	1 (2.8)	3 (8.3)	1 (2.4)
Fibula fracture	1 (2.6)	0	3 (8.3)	1 (2.4)
Clavicle fracture	1 (2.6)	1 (2.8)	1 (2.8)	3 (7.1)
Fracture delayed union	1 (2.6)	0	1 (2.8)	0
Forearm fracture	1 (2.6)	1 (2.8)	1 (2.8)	2 (4.8)
Upper limb fracture	1 (2.6)	0	1 (2.8)	5 (11.9)
Wrist fracture	1 (2.6)	1 (2.8)	0	0
Femoral neck fracture	1 (2.6)	0	0	1 (2.4)
Humerus fracture	0	3 (8.3)	3 (8.3)	4 (9.5)
Rib fracture	0	0	3 (8.3)	1 (2.4)
Foot fracture	0	1 (2.8)	2 (5.6)	4 (9.5)
Facial bones fracture	0	0	2 (5.6)	0
Radius fracture	0	0	2 (5.6)	1 (2.4)
Skull fracture	0	0	2 (5.6)	0
Lower limb fracture	0	1 (2.8)	1 (2.8)	1 (2.4)
Multiple fractures	0	0	1 (2.8)	0
Scapula fracture	0	0	1 (2.8)	0
Skull fractured base	0	0	1 (2.8)	0
Spinal fracture	0	0	1 (2.8)	0
Ulna fracture	0	0	1 (2.8)	0
Epiphyseal fracture	0	1 (2.8)	0	0
Thoracic vertebral fracture	0	1 (2.8)	0	0
Ulna fracture	0	1 (2.8)	0	0
Fracture displacement	0	0	0	1 (2.4)
Spinal compression fracture	0	0	0	1 (2.4)

The total number and proportion of patients who had any fracture reported as an AE during the study were comparable with both treatments.

Whereas the total number of fractures was similar in the treatment groups the frequency of fractures in lower extremity long bones were higher among zoledronic acid patients than pamidronate patients and contrastingly in upper extremity fractures were observed with higher frequency among pamidronate patients than zoledronic acid patients.

Other imbalances by type of fracture were less marked, and, in some cases, the non-specific nature of the reports and hence preferred terms make between-treatment comparison by fracture type not clinically meaningful.

Fracture AEs by OI type and preferred term (Study H2202E1)

Arm in Core	Zoledronic acid				Pamidronate			
Arm in Extension	Zol 1x/yr		Zol 2x/yr		Zol 1x/yr		Zol 2x/yr	
	Type I N=14 n (%)	Type III/IV N=11 n (%)	Type I N=11 n (%)	Type III/IV N=16 n (%)	Type I N=12 n (%)	Type III/IV N=12 n (%)	Type I N=13 n (%)	Type III/IV N=14 n (%)
Total	6 (42.9)	5 (45.5)	6 (54.5)	5 (31.3)	7 (58.3)	2 (16.7)	5 (38.5)	8 (57.1)
Femur fracture	2 (14.3)	3 (27.3)	1 (9.1)	2 (12.5)	2 (16.7)	1 (8.3)	1 (7.7)	3 (21.4)
Tibia fracture	2 (14.3)	2 (18.2)	2 (18.2)	3 (18.8)	1 (8.3)	0	1 (7.7)	3 (21.4)
Clavicle fracture	0	1 (9.1)	0	2 (12.5)	0	0	0	0
Fracture malunion	0	1 (9.1)	0	0	0	0	0	0
Femoral neck fracture	1 (7.1)	0	0	0	0	0	0	0
Fibula fracture	1 (7.1)	0	0	2 (12.5)	0	0	0	1 (7.1)
Hand fracture	1 (7.1)	0	1 (9.1)	0	1 (8.3)	1 (8.3)	0	1 (7.1)
Forearm fracture	0	0	0	0	0	0	0	2 (14.3)
Spinal compression fracture	1 (7.1)	0	0	0	0	0	0	0
Ankle fracture	0	0	0	0	0	0	1 (7.7)	0
Foot fracture	0	0	0	0	1 (8.3)		1 (7.7)	0
Humerus fracture	0	0	1 (9.1)	2 (12.5)	0	1 (8.3)	0	0
Radius fracture	0	0	0	0	0	0	2 (15.4)	0
Stress fracture	0	0	0	0	1 (8.3)	0	0	0
Ulna fracture	0	1 (9.1)	0	1 (6.3)	1 (8.3)	0	1 (7.7)	1 (7.1)
Upper limb fracture	0	0	1 (9.1)	0	0	0	0	1 (7.1)
Wrist fracture	0	0	0	0	1 (8.3)	0	1 (7.7)	0
Rib fracture	0	1 (9.1)	0	0	0	0	0	0
Lower limb fracture	0	0	0	0	0	1 (8.3)	0	0
Multiple fractures	0	0	0	1 (6.3)	0	0	0	0

The number and percentage of patients with fracture AEs was similar in the zoledronic and pamidronate strata, and femur or tibia fractures were most frequent. The pam-zol 1x/yr group had fewer patients with fracture AEs than the pam-zol 2x/yr group: 9 (37.5%) patients vs. 13 (48.1%), respectively. Whereas in the zol-zol 1x/yr and 2x/yr groups there was no relevant difference between the fracture rates: 11 (44.0%) patients vs. 11 (40.7%).

In the extension study, the cumulative incidence of total lower extremity long bone fracture (defined as femur, tibia, femoral neck or lower limb fracture) was 10 vs. 8 vs. 5 vs. 8 affecting 10 vs. 6 vs. 4 vs. 7 patients treated with zol-zol 1x/yr vs. zol-zol 2x/yr vs. pam-zol 1x/yr vs. pam-zol 2x/yr treatment group, respectively (some patients had more than one of these fracture types). The lowest incidence was found in the pam-zol 1x/yr group, the group with the lowest cumulative exposure to zoledronic acid, but having the highest baseline mean and median lumbar spine BMD compared to the other treatment groups.

For femur fracture AEs (not including femoral neck fracture), the incidence of fracture both by core treatment stratum (8 [15.4%] vs. 7 [13.7%] patients for core zoledronic acid vs. core pamidronate, respectively), and by extension treatment group (5 [20.0%] vs. 3 [11.1%] vs. 3 [12.5%] vs. 4 [14.8%] patients for zol-zol 1x/yr vs. zol-zol 2x/yr vs. pam-zol 1x/yr vs. pam-zol 2x/yr, respectively) was similar. During the extension study, the distribution of OI type I patients with femur fracture between core treatment strata was similar (3 in both strata) and also for OI type III and IV patients (5 vs. 4 in core zoledronic acid vs. core pamidronate, respectively). During the extension study, four of the 8 patients with femur fracture in the core zoledronic acid stratum and 2 of the 7 in the core pamidronate stratum also had a femur fracture during the core study.

Although there were 7 patients who were not observed for the planned length of the study due to early study termination, overall, the incidence of femur fracture events did not increase in frequency over time. Similarly, there was no apparent relationship between the timing of the tibia fractures and the last dose of zoledronic acid either. It appeared that there was a similar distribution of femur fractures in the first and second six months of the extension study, regardless of the number of infusions administered.

Tachycardia AEs

Patients with tachycardia AE (Study H2202)

Patient ID	Age/sex/race	Last dose study drug	Onset	Duration	Severity	Related to study drug	Action taken	Concurrent AEs
Zoledronic acid								
850/18	7/F/Ca	day 1	day 1	2 days	mild	suspected	none	pyrexia
502/3	13/M/As	day 1	day 2	1 day	mild	suspected	none	pyrexia, anorexia, na congestion
502/7	7/M/Ot	day 1	day 2	1 day	mild	suspected	none	pyrexia, vomiting, abdominal discomfort anorexia
502/11	12/F/As	day 1	day 2	2 days	mild	suspected	none	headache, pyrexia, vomiting, dehydration, Ca↓, K↓, Mg↓, PO_4↓, epistaxis, abdominal pain, asthenia, decreased appetite
504/3 †	10/M/Ca	day 271	day 271	1 day	mild	not suspect	none	deafness
506/6	13/M/Ca	day 1	day 2	1 day	moderate	suspected	conmed	pyrexia, musculoskel pain
Pamidronate								
850/11	10/F/Ca	day 1	day 19	9 days	moderate	not suspect	none	pyrexia
504/5	3/M/Ca	day 1	day 1	3 days	mild	not suspect	none	tachypnea, nausea, pyrexia
506/2	10/M/Ca	day 91	day 93	1 day	mild	not suspect	non-drug therapy	none
506/5 †	5/M/Ot	day 1	day 2	2 days	mild	not suspect	conmed	pyrexia

† AE reported as intermittent tachycardia

Tachycardia was the only cardiac disorder reported during this study.

Six patients in the zoledronic acid group and 4 in the pamidronate group had tachycardia AEs, 2 of which were intermittent tachycardia (1 in each group). 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 the first infusion (zoledronic acid 5/6, pamidronate 2/4 patients), and at the same time as pyrexia, a common symptom of an acute-phase reaction (zoledronic acid 5/6, pamidronate 3/4 patients). The protocol-specified procedure to infuse pamidronate at half of the patient's calculated daily dose on the first day of the first infusion cycle (day 1 of visit 2) reduced the risk of acute-phase reaction in this treatment arm.

All 6 cases of tachycardia AEs in the zoledronic acid-treated patients resolved within 2 days of onset, and 5 were considered mild in severity requiring no action.

Eye disorder AEs

All eye disorders affected 6 (8.1%) patients in the zoledronic acid group and 3 (3.8%) in the pamidronate group. The most frequently occurring eye disorders were eye irritation experienced by 3 patients in the zoledronic acid group and blurred vision in 2 pamidronate patients. Other unique reports of eye disorders were conjunctivitis, eye pruritus, lacrimation increased, ocular hyperemia, retinal dystrophy and visual disturbance in the zoledronic acid group and eye pain in a pamidronate-treated patient. Four of these eye disorders occurred in one zoledronic acid-treated patient. In the extension study eye disorders affected 1 (4.0%) patient with conjunctivitis in the zol-zol 1x/yr group, 1 (4.2%) patient with chalazion in the pam-zol 1x/yr group and 1 (3.7%) patient with conjunctivitis in the pam-zol 2x/yr group. There were no reported cases of uveitis or episcleritis.
No severe cases of eye disorders were observed and no obvious imbalances between groups were noted.

Osteonecrosis of the jaw (ONJ) AEs

In the core study, one patient presented to the study with "dental caries, peri-apical abscess, bacteremia" and was further evaluated to confirm that no ONJ occurred. This case was followed up for more detail of the events and was evaluated by the independent ONJ adjudication committee. The evaluation did not confirm that the events were consistent with ONJ. However, ONJ can not be excluded in paediatric population treated for this indication and it needs to be considered that in fact the sample size was too small to detect this adverse reaction.

Laboratory findings
Hypocalcemia AEs

Eighteen zoledronic acid patients (24.3%) and 12 pamidronate patients (15.4%) had hypocalcemia AEs. All such events occurred as early onset AEs and usually after the first infusion only (zoledronic acid 17/18 patients, pamidronate 9/12 patients). For 3 patients, hypocalcemia AEs recurred after subsequent infusions: one zoledronic acid patient after the 1st and 3rd infusions; one pamidronate patient after 1st and 2nd infusions; another pamidronate patient after 1st, 2nd and 3rd infusions. For one pamidronate patient, the hypocalcemia AE occurred after the third infusion only. In a few patients, concomitant hypophosphatemia (zoledronic acid: 2 patients) was also reported as an AE.

Hematology notable values

Increased lymphocytes, platelets and eosinophils, and decreased hematocrit, mean cell volume and neutrophils were common in both treatment groups during the study treatment period. It should be noted that high lymphocytes, high platelets, low mean cell volume and low neutrophils were also common at baseline.

The incidence of hematology values outside the normal range any time during treatment with study drug showed some differences between treatments in terms of low hemoglobin, low hematocrit, high neutrophils and high WBCs all of which were more frequent with zoledronic acid, whereas eosinophilia was more frequent with pamidronate treatment.

The most frequent (> 20% of patients in any group) hematology values outside the normal ranges at any time post-extension baseline were hemoglobin < LLN, hematocrit < LLN, mean cell volume < LLN, neutrophils < LLN, eosinophils > ULN and lymphocytes > ULN, with no consistent differences between treatments for any parameter.

Mean and median decreases from baseline in total calcium and phosphate were found in both groups, slightly more with zoledronic acid than pamidronate. The decreases were most evident at the 9-11 days post-infusion visit after the first infusion (e.g. mean decrease in total calcium 9-11 days post-first infusion: zoledronic acid -0.186 mmol/L, pamidronate - 0.159 mmol/L). Mean decreases from baseline at each subsequent dosing visit were lesser in magnitude.

Creatinine mean and median increases from baseline in both groups were highest at month 12 or the last visit (e.g. mean change in creatinine at last visit: zoledronic acid 0.037 mg/dL, pamidronate 0.046 mg/dL). Small mean decreases in blood urea nitrogen in the zoledronic acid group versus small mean increases in the pamidronate group were noted (e.g. mean change in BUN at last visit: zoledronic acid -0.18 mmol/L, pamidronate 0.23 mmol/L).

No clinically meaningful changes were observed in glucose, magnesium alkaline phosphatase or parathyroid hormone values.

The most frequent biochemistry values outside the normal ranges were those for calcium, phosphate, magnesium and albumin. High magnesium was found in about half the patients in both groups. High total calcium was more prevalent than low calcium, probably due to intake of calcium and vitamin D supplements as required in this study. Low total calcium and low phosphate were more frequent in the zoledronic acid group.

Increased ALT was seen in a higher proportion of zoledronic acid patients but there was no relevant difference between treatments in the incidence of AST values >ULN. One patient in the zoledronic acid group had very high ALT (1682 U/L, ULN 40 U/L) and AST (1944 U/L, ULN 34 U/L) on day 275 due to mild hepatopathy reported as an AE not suspected to be related to study drug which was last received on day 192. All other ALT and AST values for this patient were within the normal range.

Renal abnormalities

Renal abnormalities of creatinine and urine protein (safety population)

		Zoledronic acid		Pamidronate	
Visit	Criterion[†]	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 ≥ 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.

There was no evidence of an adverse effect of zoledronic acid on renal function during the treatment period. Renal abnormalities (defined by a significant creatinine increase dependent on the midpoint of age and gender specific normal range) were more frequent after pamidronate infusions.

During the whole treatment period, 10/74 patients (13.5%) in the zoledronic acid group and 15/77 patients (19.5%) in the pamidronate group had significant creatinine increases, compared to 3/62 patients (4.8%) and 4/64 patients (6.3%), respectively at the month 12 visit.

Only two events (one in each treatment arm) were reported by the investigators as AEs. Urine protein > 2+ was detected in only one patient in each group, but these two events were not associated with the two reported renal AE cases. It should be noted that although these events met the definition of renal abnormalities the changes that occurred were generally within the normal range of the centrallaboratory.

Vital signs data analysis in core study

There were no relevant differences between treatments in vital signs.

		Zoledronic acid		Pamidronate	
Parameter	Criterion	N	n (%)	N	n (%)
Systolic blood pressure	> ULN and increase > 20 mmHg	65	2 (3.1)	65	9 (13.8)
	< LLN and decrease > 20 mmHg		1 (1.5)		1 (1.5)
	≥ 20% increase from baseline		13 (20.0)		13 (20.0)
Diastolic blood pressure	> ULN and increase > 15 mmHg	60	1 (1.7)	70	7 (10.0)
	< LLN and decrease > 15 mmHg		3 (5.0)		2 (2.9)
Pulse	> ULN and increase > 15 bpm	68	6 (8.8)	70	4 (5.7)
	< LLN and decrease > 15 bpm		2 (2.9)		4 (5.7)
Body weight (kg)	Notable increase	74	60 (81.1)	76	51 (67.1)
	Notable decrease		1 (1.4)		3 (3.9)

N = the number of patients with non-clinically notable baseline value and at least one post-baseline value.
n = number of patients who reported the event at least once during the study, regardless of safety window.
Upper and lower limits of pulse and blood pressure and notable increase/decrease of body weight are based on age-sex specific normal ranges

1.3.2.2 Overall discussion on clinical safety

All patients in the extension study received at least one infusion of zoledronic acid, and 49/54 patients randomized to twice yearly zoledronic acid received two infusions, per protocol. Three patients did not receive the second infusion because of the early termination of the study when they were required to discontinue for "administrative problems" (defined as incorrect early terminations of study due to administrative errors). For the other 2 patients in the pam-zol 2x/yr group who did not receive the second infusion, one was lost to follow up and the other had only one infusion but was reported to have completed the study.

Another 3 patients were considered to be protocol deviators due to dosing errors or failure to follow protocol procedures in the event of additional infusions: 1 patient in the zol-zol 2x/yr group and 1 patient in the pam-zol 1x/yr group had dosing errors when too little zoledronic acid was administered at the first infusion, however this was corrected within 2 weeks in both cases. One other patient in the zol-zol 2x/yr group received 2 additional infusions of zoledronic acid due to increased fatigue secondary to severe OI but did not discontinue from the extension study as required per protocol.

In the core study more patients in the zoledronic acid treatment group experienced musculoskeletal and connective tissue disorders (zoledronic acid 66% vs. pamidronate 51%) and GI disorders (zoledronic acid 50% vs. pamidronate 36%) than in the pamidronate group. Similarly hypocalcemia and vomiting occurred more frequently in the zoledronic acid group. In the extension study the overall AE incidence was higher in the core zoledronic acid stratum than in the core pamidronate stratum. This was especially pronounced in terms of infections and infestations. For AEs affecting at least 10% of patients in any group, there were twice as many patients in the core zoledronic acid stratum versus the core pamidronate stratum who experienced muscle spasms, nasopharyngitis, pain in extremity, fatigue, nausea, sinusitis, influenza, musculoskeletal chest pain and humerus fracture. Pyrexia was the most frequent AE suspected to be study drug related in both groups and numerically higher in the zoledronic group. Furthermore hypocalcemia, vomiting and fatigue were by far more frequent with zoledronic acid than pamidronate. Similarly, tachycardia was reported as a suspected study drug related event in 6.8% zoledronic acid-treated patients and none in the pamidronate group.

SAEs were more frequent with zoledronic acid than with pamidronate, mainly due to a higher incidence of femur fractures, hypocalcemia and pyrexia observed with zoledronic acid. In fact in the core study hypocalcemia and pyrexia as suspected as drug related were not observed in the pamidronate group at all. Thirteen zoledronic acid patients had SAEs involving fractures whereas only nine pamidronate patients had fracture SAEs. Whereas the total number of fractures was similar in the treatment groups the frequency of fractures in lower extremity long bones was higher among zoledronic acid patients than pamidronate patients and contrastingly in upper extremity fractures were observed with higher frequency among pamidronate patients than zoledronic acid patients. In the extension study the lowest incidence of lower extremity fractures was found in the pam-zol 1x/yr group, the group with the lowest cumulative exposure to zoledronic acid. In terms of femur fracture AEs (not including femoral neck fracture), the incidence of fracture was similar in the groups. More patients in the zoledronic acid group experienced tachycardia compared to the pamidronate treated group. Most cases were considered mild in severity requiring no action. The nature of the tachycardia is not described. There was an overweight of hypocalcemia in the zoledronic acid group compared to the pamidronate treated patients. There was no evidence of an adverse effect of zoledronic acid on renal function during the treatment period. Actually, significant creatinine increases were observed in 13.5% of patients in the zoledronic acid group and 19.5% of patients in the pamidronate group, although within normal thresholds.

The significant creatinine increase is a matter of concern in this young patient population. It is not clear if this renal impairment is reversible or not. A decline in glomerular filtration rate is present before serum creatinine starts to rise.

In the study H2202E1 patients treated with four infusions (3-month apart) of zoledronic acid in the core study experienced a higher incidence of lower extremity long bone (femur, tibia) fractures than patients treated with pamidronate infusions, as outlined by DSMB during the interim unblinded safety analysis. Increasing BMD does not necessarily mean to avoid further fractures if the quality of the

bone does not improve accordingly. Moreover, some imbalances were noted with respect to gender, the 3 OI subtypes and number of fractures between to two treatment groups.

Bone quality was not addressed in the studies. The imbalances were not sufficiently explained. Orthopaedic care was not considered as a source of additional information and a follow-up beyond the two-year duration of the study was not planned by the MAH. Therefore, there would be a need to further evaluate the long term safety of Zometa in OI.

Recent focus on skeletal accumulation of highly active bisphosphonates such as zoledronic acid and pamidronate has led to the concept that prolonged suppression of bone modeling/remodeling affects bone health and mechanical properties especially at sites with greater metabolic demands.

Delayed osteotomy healing has been reported in children with OI treated with intravenous pamidronate. Anecdotal surgical reports describe the rock-hard, shatter-prone quality of OI bone after prolonged treatment with bisphosphonates. Additional concern comes from the prolonged half-life and bone accumulation of active nitrogen-containing bisphosphonates; the significance of giant osteoclast formation recently described in bone specimens form patients given long-term bisphosphonate therapy, including children with OI, is not clear.

In the last decade, accumulating reports on animal models of OI and on OI children treated with bisphosphonates as well, are compatible with a dichotomic response to treatment of vertebral and limb long bone, respectively. While controlled studies have found increased lumbar bone density by DEXA, improved vertebral shape, decreased central vertebral compression and fracture rate, effects on cortical mineralization and long bone strength and quality are possibly disadvantageous. Interestingly enough, in the study H2202E1 patients treated with four infusions (3-month apart) of zoledronic acid in the core study experienced a higher incidence of low extremity long bone (femur, tibia) fractures than patients treated with pamidronate infusions. Given the long life in the body of administered bisphosphonates (several years after discontinuation of treatment), it seems of clinical relevance to continue monitoring of fractures in this study population.
Overall, the safety profile of zoledronic acid in the present trials of a paediatric population is comparable to the known safety profile established with Zometa in the adult population. No new or unexpected safety findings were disclosed. It is however important to note that the dosing and dosing schedule differs and that the present study was not blinded or placebo controlled. Furthermore, in comparison with pamidronate, zoledronic acid seems to be associated with more pronounced risks for acute phase reactions (which however were less frequent and milder after subsequent infusions), hypocalcemia (most cases were typically asymptomatic and transient, although 4 patients had symptoms, and one patient required intravenous calcium treatment) and unexplained tachycardia. Also zoledronic acid-treated patients experienced a higher incidence of lower extremity long bone (femur, tibia) fractures than pamidronate-treated patients. Although the reason for this excess fracture risk is of uncertain clinical significance, this is a point of concern. No evidence of a long-term adverse effect of zoledronic acid on renal function and no cases of ONJ were reported.

1.3.3 Risk Management Plan

An updated Risk Management plan has been submitted with this application focusing on the update of the safety profile of the drug coming from the new studies. The MAH proposed routine pharmacovigilance activities in order to monitor the newly identified risks resulting from the OI population, which is considered acceptable. Characterization of the potential risks has been adequately addressed in the pharmacovigilance plan.

In conclusion, the RMP for Zometa is adequate, and the updates are relevant. No new additional risk minimization activities were proposed. This was also considered acceptable by the CHMP.

Below, a list of all ongoing safety concerns is presented.

Summary of activities for each safety concern

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Important identified risks		
Renal function impairment	Routine pharmacovigilance Targeted follow-up of all serious post-marketing and clinical trial reports using a questionnaire/checklist	**CDS Section 4.2 Posology and Method of Administration:** Infusion time ≥ 15 minutes. Hypercalcemia: evaluate benefit/risk in severe renal impairment. Prevention of SREs: dose reduction guidance by baseline CrCl. Monitor prior to each dose. Withhold treatment until resolution if pre-defined Serum Creatinine increases occur. **CDS Section 4.4 Special Warnings and Precautions for Use:** Renal function impairment and failure have been seen after one dose. Use of Zometa is not recommended in severe renal impairment (CrCl < 30 mL/min) **CDS Section 4.5 Interactions:** Caution advised when Zometa is administered with aminoglycosides, nephrotoxic drugs. Increased risk of renal dysfunction in myeloma patients treated with thalidomide. **CDS Section 4.8 Undesirable effects:** Acute renal failure, renal impairment, Serum Creatinine and BUN increased.
Osteonecrosis of the jaw	Routine pharmacovigilance Targeted follow-up of all serious post-marketing and clinical trial reports using a questionnaire/checklist Periodic reviews for the EMEA ONJ class-review of bisphosphonates Special 15-day expedited reporting of ONJ regardless of seriousness, listedness and causality will be provided to FDA. Adjudication of selected clinical trials reports of ONJ (confirmation of diagnosis by an expert's panel, based on pre-defined criteria) Ongoing clinical study on ONJ: SWOG	**Routine risk minimization activities:** **CDS Section 4.4 Special Warnings and Precautions for Use:** General information on ONJ. Dental examination and if necessary preventive dentistry recommended prior to treatment. Dental procedures to be avoided during treatment. Unknown effect of treatment discontinuation if ONJ occurs: in such case assess individual benefit/risk. **CDS Section 4.8 Undesirable effects:** ONJ and risk factors described in post-marketing experience **Enhanced risk minimization activities** An ONJ educational program is in place, and it delivers on a country by country bases key messages on ONJ prevention and management
Acute phase reaction	Routine pharmacovigilance Ongoing study on post-dose symptoms: ZOL446HUS136	**CDS Section 4.8 Undesirable effects:** Intravenous administration has been most commonly associated with a flu-like syndrome in about 9% of patients, including bone pain (9.1%), fever (7.2%), fatigue (4.1%) and rigors (2.9%).

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Hypocalcemia	Routine pharmacovigilance	**CDS Section 4.2 Posology and Method of Administration:** Prevention of SREs: Patients should also be administered 500 mg oral calcium supplement and 400 IU vitamin D daily. **CDS Section 4.4 Special Warnings and Precautions for Use:** Standard hypercalcemia-related metabolic parameters, such as serum levels of calcium, phosphate and magnesium, should be carefully monitored after initiating Zometa therapy. If hypocalcemia, hypophosphatemia, or hypomagnesaemia occurs, short-term supplemental therapy may be necessary. **CDS Section 4.8 Undesirable effects:** Hypocalcemia is included in the ADRs.
Ocular adverse events	Routine pharmacovigilance Targeted follow-up of all serious post-marketing and clinical trial reports using a questionnaire/checklist	**CDS Section 4.8 Undesirable effects:** Conjunctivitis, Uveitis, Episcleritis. Scleritis and Orbital inflammation are included in the ADRs.
Atrial fibrillation	Routine pharmacovigilance Targeted follow-up of all serious post-marketing and clinical trial reports using a questionnaire/checklist	**CDS Section 4.8 Undesirable effects:** Atrial fibrillation is listed in the post-marketing experience section.
Anaphylaxis	Routine pharmacovigilance	**CDS Section 4.8 Undesirable effects:** Anaphylactic reaction/shock is listed in the post-marketing experience section.
GI disorders in paediatric OI patients	Routine pharmacovigilance	**CDS Section 4.8 Undesirable effects:** Nausea, Vomiting, Anorexia, Diarrhea, Constipation, Abdominal pain, Dyspepsia, Stomatitis, Dry Mouth are included in the ADRs.
Important potential risks		
Cardiac arrhythmias	Routine pharmacovigilance Targeted follow-up of all serious post-marketing and clinical trial reports using a questionnaire/checklist	**CDS Section 4.8 Undesirable effects:** Atrial fibrillation is listed in the post-marketing experience section.
Cerebrovascular AEs	Routine pharmacovigilance Targeted follow-up of all serious post-marketing and clinical trial reports using a questionnaire/checklist	Currently available data do not support the need for risk minimization.
Focal Segmental Glomerulo-sclerosis	Routine pharmacovigilance	Currently available data do not support the need for risk minimization.
Fracture healing impairment	Routine pharmacovigilance	Currently available data do not support the need for risk minimization.
Interstitial lung disease	Routine pharmacovigilance	Currently available data do not support the need for risk minimization.
Bone growth impairment in paediatric OI patients	Routine pharmacovigilance	Currently available data do not support the need for risk minimization.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Progressive hearing loss in paediatric OI patients	Routine pharmacovigilance	Currently available data do not support the need for risk minimization.
Increased risk of fractures in paediatric type I OI patients	Routine pharmacovigilance	Currently available data do not support the need for risk minimization.
Potential Interactions		
Products that can significantly affect renal function	Routine pharmacovigilance Drug interactions monitored through case-specific content review for suspected interactions with targeted follow-up as appropriate	**CDS Section 4.4 Special Warnings and Precautions for Use:** Use of nephrotoxic drugs may increase the potential for deterioration in renal function. **CDS Section 4.5 Interaction with other medicinal products and other forms of interaction:** Caution is indicated when Zometa is used with other potentially nephrotoxic drugs.
Important missing information		
Paediatric OI patients < 1 year	Routine pharmacovigilance	**CDS Section 4.4 Special Warnings and Precautions for Use:** The safety and efficacy of Zometa in paediatric patients with severe OI under the age of 1 year have not been established.
Races other than Caucasian	Routine pharmacovigilance	Currently available data do not support the need for risk minimization.
Pregnancy and lactation	Routine pharmacovigilance	**CDS Section 4.3 Contraindications:** Zometa concentrate is contraindicated in pregnancy and in breast-feeding women. **CDS Section 4.6 Pregnancy and lactation:** Zometa should not be used during pregnancy. It is not known whether zoledronic acid is excreted into human milk. Zometa should not be used by breast-feeding women.
Patients with severe renal impairment	Routine pharmacovigilance	Detailed information in CDS Sections 4.2, 4.4, 4.5, 4.8 (See Renal function impairment above).
Paediatric patients with renal impairment	Routine pharmacovigilance	**CDS Section 4.4 Special Warnings and Precautions for Use:** The safety of Zometa in paediatric patients with renal impairment has not been established.
Patients with hepatic Insufficiency	Routine pharmacovigilance	**CDS Section 4.4 Special Warnings and Precautions for Use:** As only limited clinical data are available in patients with severe hepatic insufficiency, no specific recommendations can be given for this patient population.

1.4 Benefit Risk Assessment

BENEFITS

- The present controlled open label efficacy study demonstrated that infusions of zoledronic acid showed similar effects compared to pamidronate in terms of the primary endpoint of increase in LS-BMD after 12 months of treatment.
- Similarity between zoledronic acid and pamidronate was also shown regarding sustained reductions in serum markers of bone resorption and bone formation.
- The proportion of patients who had clinical fractures during the 12 months of treatment was similar between the zoledronic acid and pamidronate treatment groups.
- No significant differences were observed regarding LS-BMD Z-score at 6 and 12 months and femoral neck and total body BMC.
- No changes from baseline or differences between the two treatments in Wong-Baker FACES pain assessments were detected.
- The open-label extension study, designed as a safety study with secondary efficacy parameters did not demonstrate any antifracture effect of zoledronic acid over pamidronate and median LS Z-score and total body BMC.
- During the extension period sustained decreases in median values of serum biomarkers of bone resorption and bone formation were observed in all treatments.

RISKS

- In comparison with pamidronate, zoledronic acid seems to be associated with more pronounced risks for acute phase reactions (which however were less frequent and milder after subsequent infusions).
- In comparison with pamidronate, zoledronic acid was associated with risk of hypocalcemia (most cases were typically asymptomatic and transient, although 4 patients had symptoms, and one patient required intravenous calcium treatment) and unexplained tachycardia.
- Zoledronic acid-treated patients experienced a higher incidence of lower extremity long bone (femur, tibia) fractures than pamidronate-treated patients. Although the reason for this excess fracture risk is of uncertain clinical significance, this is a point of concern.

BALANCE

The MAH has supported its application with two randomized controlled clinical trials investigating zoledronic acid treatment of children 1 to 17 years of age with severe osteogenesis imperfecta (OI) (Protocol study H2202 and H2202E1, respectively).
The estimated effect on BMD zoledronic acid as well as regarding sustained reductions in serum markers of bone resorption and bone formation was similar to pamidronate. However, the hallmark of OI is the occurrence of fractures and the present studies were neither designed nor powered to estimate the efficacy of Zometa on fractures. BMD has not been demonstrated to be a meaningful surrogate marker for clinical efficacy in osteogenesis imperfecta. In this study, no meaningful positive effects were demonstrated on the clinically relevant parameters pain and new fractures.

It is not clear that the key efficacy parameter “improvement in BMD at 12 months from baseline” translated into clinical benefit for patients with osteogenesis imperfecta in terms of less fractures, less disability and less chronic bone pain. The pivotal study H2202 was neither designed nor powered to estimate the efficacy of zoledronic acid on fractures or other clinically relevant outcome measures. This lack of a clear relationship between surrogate and clinical efficacy parameter was also reflected by a high rate of new fractures after start of the two bisphosphonates.

Furthermore, the CHMP questioned the choice of comparator. Regarding the use of pamidronate as the active control the applicant argued that this selection was an acknowledgement of the product’s ability to alter the natural disease course, improve the clinical status and quality of life in children and are referring to two studies. The study by Glorieux 1998 showed that Cyclical i.v. treatment with pamidronate was associated with a marked increase in BMD and physical activity increased markedly in these patients and decreased fracture rate. This study was an observational and uncontrolled study. In the study by Plotkin children younger than 3 years old pamidronate infusion every 2-4 months over a increased BMD, and decreased the rate of fracture. This was also an observational study using a group of “historical controls”. Despite the use of bisphosponates in clinical practice (off-label), the

scientific evidence for pamidronate in this indication is quite weak with regards to placebo-controlled studies:

- the lack of a placebo-controlled clinical study in an indication without a well-established pharmacological therapy was not sufficiently justified.

- in the absence of a well quantified effect of pamidronate versus placebo the choice of non-inferiority margin required further justification (see CPMP/EWP/2158/99).

- it has not been established that the study has adequate assay sensitivity, so that any important differences between active agents could be detected.

Therefore, the CHMP emphasized the weakness of the study design and considered this to be a major limitation of the application having a major impact on the benefit risk assessment of the proposed new indication. Recent reviews are pertinent to the above stated comments in that they focus on the effects of bisphosphonates in children with OI and osteoporosis. These publications underline the fact that despite a large body of published observations, only very few studies have a sufficiently high level of internal validity to be truly informative. These studies confirm improvement in BMD. There is, on the other hand, limited evaluation of broader treatment impacts on clinical features such as deformities, need for orthopaedic surgery, pain, functioning, quality of life. More studies evaluating drug choices, optimal dosing, duration of treatment, post-treatment morbidities and long-term side effects are necessary.

The safety profile of zoledronic acid in the present trials of a paediatric population is comparable to the known safety profile established with Zometa in the adult population. No new or unexpected safety findings were disclosed. It is however important to noted that the dosing and dosing schedule differs and that the present study was not blinded or placebo controlled. Furthermore in comparison with pamidronate, zoledronic acid seems to be associated with more pronounced risks for acute phase reactions, hypocalcemia and unexplained tachycardia. Also zoledronic acid-treated patients experienced a higher incidence of lower extremity long bone (femur, tibia) fractures than pamidronate-treated patients.

From a clinical point of view a number of drawbacks with regard to the study population, choice of comparator drug, randomization and primary objective (Lumbar spine BMD) as well as safety concerns are present. The application to extend the indication of intravenous zoledronic acid (Zometa) for the treatment of children with severe OI was found not approvable since a clearly positive benefit/risk balance in patients with severe OI in the paediatric age is not sufficiently corroborated by the submitted data and discussion provided by the MAH.

Thus, the CHMP considered that the overall Benefit-Risk Ratio of Zometa in the applied extension of indications is negative.

In acknowledgment of the objections and concerns raised by the CHMP, the MAH proposed during the procedure to modify the scope of this application to request approval of paediatric information on the paediatric studies in SPC section 5.1 together with changes in other relevant sections of the PI (4.2, 4.4 and 5.2 and package leaflet) to reflect the available paediatric study data. Further, the MAH informed the Committee that the company no longer seeks approval for the initially requested severe osteogenesis imperfecta indication.

In conclusion, the extension of indication in SPC section 4.1 for the “treatment of severe OI in paediatric patients aged 1 to 17 years” was not acceptable. However, the CHMP considered that information on the clinical studies performed could be added to SPC section 5.1. Therefore, the changes to SPC section 5.1 as well as the related sections 4.2, 4.4 and 5.2 of the SPC and in the PL were accepted by the CHMP to be included in accordance with the Regulation (EC) No 1901/2006 of the European parliament and of the Council of 12 December 2006.

1.5 Significance of Paediatric Studies

The CHMP noted that the PDCO adopted on 12 December 2008 a positive Opinion on Compliance (EMEA-C-024-PIP01-07) with the agreed Paediatric Investigational Plan (PIP) (Decision P/32/2008) adopted on 24 June 2008) under Article 23 of Regulation (EC) No 1901/2006 as amended for Zometa (zoledronic acid).

The CHMP is of the opinion that studies H2202 and H2202E1, which are contained in the agreed Paediatric Investigation Plan and have been completed after 26 January 2007, are considered as significant. The assessment criteria of the significance of studies, as defined in Section 3 - Title 4.2 of the European Commission Communication "Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of compliance check and on criteria for assessing significant studies" (2008/C 243/01) has been fulfilled, taken into account the study type of clinical studies H2202 and H2202E1:

(1) Comparative efficacy studies (randomized/ active control or placebo)
Study H2202 was a randomized, active-controlled openlabel, multi-center phase III clinical trial that evaluated the safety and efficacy of intravenous zoledronic acid compared to intravenous pamidronate in paediatric patients (1-17 years) with severe osteogenesis imperfecta.
Study H2202E1 was one-year randomized, openlabel, parallel-group multi-center safety and efficacy study extending the treatment to paediatric patients with severe osteogenesis imperfecta who completed first year of treatment in study H2202.

(2) Prospective clinical safety studies
Studies H2202 and H2202E1 are prospective studies that collected key clinical safety information (tolerability, general safety and renal safety) which makes a major contribution to the safe use on the use of zoledronic acid and pamidronate in the study population."

1.6 Changes to the Product Information - User Testing

An update of SPC section 5.1 has been performed to include clinical trial results in the treatment of severe osteogenesis imperfecta in paediatric patients aged 1 to 17 years. SPC sections 4.2, 4.4, 4.8 and 5.2 have been revised as well considering the available data in paediatric patients. Furthermore, SPC section 4.4 has been amended with a warning regarding the concomitant use of Aclasta.

In addition, changes to SPC section 4.3, 4.6, 4.8 have been performed to align with the QRD template.

Annex II has been updated with the RMP standard text reflecting the latest agreed version number.

User Testing

The package leaflet has been revised based on the results of a Readability Testing. The MAH submitted with this application the final report comprising the results of consultations with target patient groups, dated 2007. The basis for this Zometa user testing was the package leaflet as submitted in the Type II variation application EMEA/H/C/336/II/021 with which the MAH applied for the new indication “Prevention of fracture and bone loss in postmenopausal women with early-stage breast cancer treated with aromatase inhibitors”. This application was subsequently withdrawn by the MAH.

The package leaflet for Zometa has been through a pilot and two rounds of user tests. Out of the 20 respondents that were recruited for the user test, 9 were cancer patients or their caretakers and 11 were healthy volunteers. The participant’s age range was between 19 and 68 years.

The questionnaire used in the test procedure was composed of 12 key points of information relating to specific safety and compliance issues in connection with the use of Zometa. Question selection ensured that points of information were asked for sections 1 to 4 of the PL.

The user testing and readability of the Zometa package leaflet (PL) was considered satisfactory. The methodology met the requirements of the Readability Guideline and the data were well recorded. The weaknesses of the PL identified by the interviewed population were addressed appropriately and led to amendments of some parts of the PL in order to improve readability. Furthermore, rephrasing of some passages of the PL were performed in order to facilitate patient friendly language.

II. CONCLUSION

On 17 December 2009 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.

Furthermore, the CHMP takes note that the agreed Paediatric Investigation Plan is fully completed and that the PDCO issued an Opinion on compliance. The CHMP reviewed the paediatric data of studies subject to this plan and the results of these studies are reflected in the Summary of Product Characteristics and, as appropriate, the Package Leaflet.
In accordance with Article 45(3) of Regulation EC (No) 1901/2006, significant studies in the agreed paediatric investigation plan have been completed after the entry into force of that Regulation.

Follow-up measures undertaken by the Marketing Authorisation Holder

As requested by the CHMP, the MAH agreed to submit the follow-up measures as listed below and to submit any variation application which would be necessary in the light of compliance with these commitments (see Letter of Undertaking attached to this report):

Area	Description	Due date
Nonclinical	The MAH commits to conduct a test on *lumbriculus* (OECD 225) and submit the results as follow-up to the ERA.	31/08/2010