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ASSESSMENT REPORT

Aclasta
International non-proprietary name: zoledronic acid

TYPE II VARIATION: EMEA/H/C/000595/II/0016

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

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SCIENTIFIC DISCUSSION

INTRODUCTION

Zoledronic acid is a "third-generation" nitrogen-containing bisphosphonate and as such, inhibits osteoclast mediated bone resorption. An intravenous formulation of zoledronic acid has been approved in over 96 countries worldwide, including Europe, under the trade name of Zometa for several indications, including tumour-induced hypercalcaemia, treatment of patients with multiple myeloma, and treatment of bone metastases from solid tumours.

For the indication Paget's disease of bone, zoledronic acid is approved worldwide under the trade name Aclasta as of 15 June 2007 in over 70 [A1]countries and as Reclast in the United States.

In July 2007, Aclasta received a positive CHMP opinion for the treatment of post-menopausal osteoporosis (PMO) in women at increased risk of fracture.

Aclasta is presented in vials of 5 mg in 5 ml of solution for dilution with 100 ml of isotonic saline or dextrose. The presentation intended for the market was also used in most of the clinical studies of PMO. It consists of 5 mg zoledronic acid in 100 ml of solution, containing mannitol as an isotonising agent.[A3]

Zoledronic acid in the treatment of PMO and in the indication proposed in this variation is administered once a year as a 5 mg i.v. infusion over at least 15 minutes.

The purpose of the current submission for a Type II variation for Aclasta was to seek approval for an extension of indication to include the prevention of clinical fractures after hip fracture in men and women. This indication however was not in line with the "Guideline on the evaluation of new medicinal products in the treatment of primary osteoporosis" and the indication wording was therefore changed during the procedure, also in view of the indication in the male population. Based on the provided safety data for the extension of indication, the MAH also proposed to change the recommendation not to treat patients with a creatinine clearance cut-off less than 40 ml/min to 35 ml/min.

The MAH has reanalysed data for the male subpopulation in the hip fracture study 2310 and has provided comparisons between the male and female subpopulations in this study as well as comparisons with the postmenopausal population in the larger study 2301. Study 2301 was the pivotal study for approval of the indication "Treatment of osteoporosis in post-menopausal women at increased risk of fracture" (variation H/C/595/II/10). Further data from the supportive study 2308, which compared the effects on BMD of Aclasta and alendronate treatment in male osteoporosis patients, have also been assessed.

Development programme/Compliance with CHMP Guidance/Scientific Advice
The MAH has previously received 3 Scientific Advices on the development program in PMO, in November 2001, in January 2003 and in June 2005. The first 2 advices were mainly concerned with the pre-clinical development but the 2001 advice also addressed the plan to perform a study in patients following a recent hip fracture. This plan was considered acceptable but it was recommended to study males and females separately. Furthermore, to support the indication "treatment of osteoporosis after acute hip fracture" it was considered a requirement to have available at least interim results from the large PMO trial.

General comments on compliance with GMP, GLP, GCP
All studies fully adhered to GCP guidelines of the CHMP and Directive 91/507/EEC of the European Union. All studies were closely monitored by the MAH or a contract organisation for compliance to the protocols and procedures described in them.

NON CLINICAL ASPECTS

In vitro data
Data on efficacy *in vitro* was included in the submission of the initial Marketing Authorisation for Aclasta and was demonstrated *in vitro* in cultures of murine calvaria. No further preclinical *in vitro* data was submitted for this variation.

In vivo data
The MAH submitted further data from four pre-clinical studies on fracture healing during the procedure.

The effect of zoledronic acid (zoledronic acid) on fracture healing in laboratory animals was studied using three different animal models:
- Distraction osteogenesis in the rabbit tibial diaphysis (*Little, et al 2003; Smith, et al 2004)*
- Critical size defect healing in the rat femoral diaphysis (*Little, et al 2005)*
- Closed fracture healing in the rat femoral diaphysis (*Amanat, et al 2007)*

Three studies published up to the end of 2005 were assessed within the type II variation to extend the indication to include osteoporosis in post-menopausal women (II-10). Subsequently new results from an additional study became available in 2007 (*Amanat, et al 2007).*

Overall, the results of the *Amanat, et al 2007* study in the rat closed fracture model indicated that administration of zoledronic acid at 0, 1 and 2 weeks post-fracture increases the size and strength of the callus without exerting any apparent deleterious effects on the fracture healing process. The timing of the zoledronic acid infusion, post-fracture, markedly affected the magnitude of these local effects in the callus as well as the relative distribution of drug between the callus and the rest of the skeleton.

Discussion on non-clinical aspects
Although the 1-2 week post-fracture timeframe from the rat study may not be directly applicable to the clinical situation, timing of the dose played an important role in the modulation of callus properties, and delaying the dose resulted in a stronger callus. The MAH pointed out that this short-term rat study revealed that the timing of bisphosphonate therapy following fracture affected callus size and strength as well as the distribution of drug between the fracture site and the rest of the skeleton. Although the fracture repair process in the rat closed fracture model closely resembles that occurring in human bone, it has to be taken into consideration that bone metabolism is more active in skeletally immature, young rats than in osteoporotic bone of adult humans.

For example, dosing immediately after fracture would be expected to produce a systemic exposure pattern similar to that in a patient without a fracture, with little drug binding to the fracture site. Consequently, the potential positive effect of zoledronic acid on callus strength would be suboptimal. In the alternative scenario, delayed dosing post-fracture should result in high drug binding to the callus and maximal mechanical benefit at the fracture site.

However, as the callus remodels, the bound zoledronic acid will be released and redistributed to new sites of active bone turnover where it will again be able to exert its anti-resorptive activity. (In the long-term distraction osteogenesis study in rabbits treated with zoledronic acid, the callus was fully remodelled by 44 weeks, presumably releasing the drug that had initially been bound to the callus (*Smith, et al 2004*). Whilst the rat experiments have demonstrated the potential of zoledronic acid to increase callus strength when administered during the initial weeks post-fracture, they were not designed to address the clinical observation that delayed dosing apparently enhances anti-fracture efficacy; thus they provide little pertinent information on this topic.

The CHMP noted that in the animal models, delayed dosing of the zoledronic acid clearly led to increased binding of the drug in the fracture area and increased BMC and callus volume as compared with dosing at the time of fracture. There is also a plausible mechanistic explanation to this that probably applies to both animals and humans. It therefore seems very likely that delayed dosing in humans would give better results than dosing immediately after fracture and information about the ideal timing after fracture repair was therefore included in the SPC as discussed in section clinical efficacy below.

CLINICAL ASPECTS

Introduction

Osteoporosis is a systemic skeletal disorder characterised by low bone mass and micro-architectural deterioration of bone tissue, with consequent increase in bone fragility and susceptibility to fractures. Age and menopause are the two main determinants of osteoporosis. Asian or white ethnic origin, underweight, dietary calcium deficiency, sedentary lifestyle, alcohol use, family history, and cigarette smoking appear to be independent risk factors for osteoporotic fractures.

Most osteoporotic fractures occur in women because they have lower peak bone mass than men. Additionally, the effect of menopause increases the risk of fracture at any given age, and women have a higher life expectancy. However, the life-time risk of fragility fractures in men is also considered as a significant public health issue. No WHO definition for osteoporosis exists for men. However, in clinical practice the same cut-off for the diagnosis of osteoporosis in men, i.e. BMD below -2.5 standard deviations of the female reference range, has been used. Epidemiological studies have shown a similar relationship between BMD and fracture risk in men and in postmenopausal women, i.e. the predictive value of BMD for the occurrence of fractures is similar in men and in women.

Prevalent fractures also predict the risk of future fractures to the same extent in both genders, and numerous studies have reported increased risks of hip, spine and other fractures among patients who had previously diagnosed fractures. It has also been demonstrated that patients with hip fractures lose bone and muscle mass in the year following the fracture.

Other independent risk factors (e.g. family history of hip fracture, alcohol or tobacco use) have not, however, been validated to the same extent in men as in women. Clinical trials of pharmacological intervention in osteoporotic men have shown BMD increases and changes in biochemical markers of bone turnover similar to those observed in postmenopausal women. The limited available fracture data in men show that, when observed, the degree of reduction in vertebral fractures and height loss in men was consistent with that observed in postmenopausal women.

The goal of osteoporosis therapy is prevention of fractures in susceptible patients. The appropriate timing and proper use of agents such as calcium, vitamin D, estrogen, bisphosphonates, calcitonin, PTH, and raloxifene and the role of exercise have generated major research efforts and considerable controversy. Intake of adequate amounts of calcium and vitamin D and continuing moderate weight-bearing exercise, are basic preventive measures for persons of all ages. Orally administered bisphosphonates have low bioavailability but are widely used to prevent fractures in the osteoporotic population.

In July 2007, Aclasta was approved for the treatment of post-menopausal osteoporosis with once yearly i.v. administration. Currently, no i.v. bisphosphonate has been approved for the treatment of osteoporosis in men.

According to the EMEA guideline on the evaluation of new medicinal products in the treatment of primary osteoporosis, “the clinical significance of osteoporosis lies in the fractures that occur”. This statement seems to be true also for other forms of osteoporosis (resulting from immobilisation, from diseases such as hyperthyroidism, hyperparathyroidism, rheumatoid arthritis or from the use of drugs such as glucocorticoids or from hormonal ablation therapy).

In most studies on osteoporosis, DXA measurements of lumbar spine BMD and often also of total hip BMD and femoral neck BMD, have been important study parameters.

Pharmacokinetics

Key PK/PD studies, were conducted in patients with bone metastases, receiving single or multiple infusions of 2 – 16 mg zoledronic acid, and presented in earlier submissions for the Marketing Authorisation of zoledronic acid in the oncologic indication, and 1 subsequent PK/PD study. Additional pharmacokinetic studies have not been performed in either patients with Paget's disease or in patients with osteoporosis.

Clinical efficacy

Results from a Phase III, randomised, double-blind, placebo-controlled clinical trial intended to demonstrate efficacy for the use of zoledronic acid in the prevention of clinical fractures after hip fracture (study 2310) were submitted. This study was considered pivotal for this extension of indication procedure.

The MAH presented during the procedure also further supportive analyses from study 2308, which was a double-blind double-dummy randomised active-controlled 2-arm trial comparing the efficacy and safety of i.v. zoledronic acid with oral alendronate in osteoporotic men.

Study 2310

This was a randomised, double-blind, placebo-controlled, event-driven study to assess the efficacy of intravenous zoledronic acid in preventing subsequent clinical fractures after a hip fracture with surgery. Recruitment was from 148 sites around the world. The population included both men and women who had surgical repair of a low-trauma hip fracture within 90 days of study entry. Patients were randomised in a 1:1 ratio to receive either zoledronic acid or placebo.

The trial was event-driven. It was planned to enrol approximately 2038 patients to yield 211 patients with confirmed clinical fracture events. There were two planned interim analyses after approximately 70 and 140 patients, respectively, had experienced confirmed clinical fracture events. Following the 2nd interim analysis, a 3rd interim analysis was requested by the drug safety monitoring board (DSMB). After review of this interim analysis based on 185 patients with confirmed clinical fracture events in November of 2006, the DSMB recommended study close-out over a 90-day period.

Participants
Males and females who were 50 years old or older and who had had surgical repair of an acute hip fracture caused by low - energy -trauma within 90 days of randomisation (according to the inclusion criteria before amendment 3 in April 2003, patients should be included within 42 days after hip fracture surgery) [A5]and who were ambulatory prior to the fracture were included in this study. Important exclusion criteria were: calculated creatinine clearance ≤ 30 ml/min, history of iritis or uveitis, serum calcium > 2.75 mmol/l, serum alkaline phosphatase > 2.5 x upper normal limit, serum corrected calcium < 2.0 mmol/l and prior use of oral bisphosphonates during the last 2 years. Concurrent treatment with other bisphosphonates, sodium fluoride, PTH and PTH analogs, strontium and anabolic steroids (except for testosterone substitution in hypogonadal men) was not allowed, and specific washout periods for each treatment were required.

Treatments
Zoledronic acid 5 mg or placebo were administered to study patients every 12 months until the study was completed. With a study amendment, the number of doses was limited to three but by the time of this amendment, a number of patients had already received four doses and one patient had received five doses of study drug. The study drug was given as a slow intravenous infusion during over at least 15 minutes. All study patients received a loading dose of 75.000 – 125.000 units of vitamin D2 i.m. or orally once or 50.000 – 75.000 units of vitamin D3 i.m. or orally once prior to randomisation. All

patients thereafter received a maintenance dose of 800 – 1200 units of oral vitamin D daily. All patients received elemental calcium 1000 – 1500 mg orally daily in a divided dose.
Patients received their study drug infusion at any time from day 14 (amended from Day 7) following vitamin D2 or D3 administration up to 90 days after surgical repair of their hip fracture.

All patients without contraindication to paracetamol were provided with a standard dose of paracetamol for 72 hours following each dose of study drug, to treat post-dose symptoms of fever, myalgia, arthralgia and bone pain.

These "usual care medications" excluded other bisphosphonates but included hormone replacement therapy (HRT), selective estrogen receptor modulators (SERMs), calcitonin, tibolone, tamoxifen, dehydroepiandrosterone (DHEA) or its sulfated form (DHEAs), ipraflavone, and medroxyprogesterone. Patients were randomly assigned to receive either zoledronic acid or placebo. An intravenous formulation of the study drug was administered annually at randomisation, at Year 1, and at Year 2.

Study Objectives
The primary efficacy variable was the time to first clinical fracture. Only the fractures confirmed by a Clinical Endpoint Committee were counted as clinical fractures in the time-to-event analysis.
Differences between treatments were compared using a log-rank test and Kaplan-Meier estimates of the survival functions for each treatment were also calculated. The superiority of zoledronic acid relative to placebo was concluded if the statistical significance was achieved at the 3.51% level with respect to the time to first clinical fracture being longer for zoledronic acid-treated patients than for placebo-treated patients. The significance level was adjusted to account for 3 interim analyses previously conducted.

The following key secondary efficacy variables were evaluated.

1. Other clinical fracture endpoints including time to first clinical vertebral fracture, time to first hip fracture, time to first non-vertebral fracture.
2. BMD: Percent change from baseline at each analysis visit was assessed at the total hip and femoral neck, using dual X-ray absorptiometry (DXA), of the non-fracture hip.
3. Hospitalisation: Between-treatment difference in the number of patients being hospitalised at least once at any time post-randomisation was evaluated using Fisher's exact test.

Sample size
A total of 2127 patients were randomised to treatment and of these, 2111 patients received at least one study drug infusion.

ITT population: All randomised patients (n = 2127)
PP population: ITT patients who did not have a major protocol violation (n = 1909)
Safety population: All randomised patients who were exposed to study drug (n = 2111)

All efficacy endpoints were analysed using the ITT population, which included all randomised patients. A total of 2127 patients were randomised to treatment, 1065 patients to zoledronic acid and 1062 patients to placebo. In total, 508 men (24%) were randomised and 1619 women (76%). The safety population included 2111 patients who were exposed to at least one study drug infusion.

Results – Study 2310

Demographic data
Demographic characteristics of patients were comparable for the two treatment groups. The majority of patients were Caucasian (91.11%) and female (76.12%). The median age was 76 years (range: 50 to 98); 27.08% of patients were between 65 and 74 years old and 55.81% were more than 75 years of age. Overall, the two treatment groups were similar with respect to all baseline disease and background characteristics. More than half of all patients were from Western and Eastern Europe (58.34%). Baseline mean standardised femoral neck and hip BMD values were similar for the two treatment groups. Nearly 42% of all patients had a femoral neck T-score of ≤ -2.5.

Approximately 46% of patients received their first infusion of study drug within 6 weeks after hip fracture surgery and 54% received their first infusion of study drug more than 6 weeks following hip surgery. The median number of days from hip surgery to the time of the first infusion was 47.0 for zoledronic acid and 44.5 for placebo.

Baseline creatinine clearance values were comparable for the two treatment groups. Approximately 40% of all patients had mild to moderate renal impairment at baseline (baseline creatinine clearance ≥ 30 ml/min and < 60 ml/min).

Participant flow
The discontinuation rates were very variable between different centres, however the discontinuation rates in the zoledronic acid group were lying in the same magnitude as in the placebo group with a slightly higher discontinuation rate in the patients that received zoledronic acid when death was excluded as a reason for discontinuation [A6](see table 1).

Table 1: Patient disposition, ITT population, study 2310.

	Zoledronic acid N=1065 n (%)	Placebo N=1062 n (%)	Total N=2127 n (%)
Total no. of patients			
Completed	770 (72.30)	746 (70.24)	1516 (71.27)
Death	102 (9.58)	142 (13.37)	244 (11.47)
	Zoledronic acid N=1065 n (%)	**Placebo N=1062 n (%)**	**Total N=2127 n (%)**
Discontinued [1]	193 (18.12)	174 (16.38)	367 (17.25)
Reason for discontinuation			
Subject withdrew consent	120 (11.27)	109 (10.26)	229 (10.77)
Lost to follow-up	35 (3.29)	28 (2.64)	63 (2.96)
Adverse event(s)	21 (1.97)	18 (1.69)	39 (1.83)
Administrative problems	9 (0.85)	8 (0.75)	17 (0.80)
Protocol violation	4 (0.38)	7 (0.66)	11 (0.52)
Abnormal laboratory value(s)	4 (0.38)	3 (0.28)	7 (0.33)
Unsatisfactory therapeutic effect	0 (0.00)	1 (0.09)	1 (0.05)

The treatment groups were well balanced with regard to demographic and other baseline factors. The patients were elderly, mainly females. About 40% had osteoporosis as defined by a T-score of ≤–2.5 and about 60% had osteoporosis based on the criteria of previous radiographic fracture with femoral neck T-score > -2.5.

Comorbidities
Active medical conditions at randomisation were representative of an elderly population with typical chronic comorbidities. The most commonly reported active medical conditions (i.e., ≥ 10.0% of all patients) were the following: hypertension (49.86% zoledronic acid vs. 50.56% placebo), osteoarthritis (19.15% zoledronic acid vs. 17.89% placebo), depression (15.59% zoledronic acid vs. 16.85% placebo), osteoporosis (13.99% zoledronic acid vs. 13.84% placebo), insomnia (13.99% zoledronic acid vs. 11.68% placebo), constipation (12.21% zoledronic acid vs. 13.18% placebo), and diabetes mellitus (10.89% zoledronic acid vs. 9.98% placebo).

Concomitant medication
Overall, the distribution of concomitant medication use (which may have been started prior to first study drug administration or at anytime during the conduct of the study) was similar between the treatment groups. The three most commonly used concomitant medications (apart from vitamin D and calcium) prior to and after start of study drug infusion were over-the-counter pain relievers including paracetamol, acetylsalicylic acid, and furosemide, all of which were used comparably in the two treatment groups

According to the protocol, all patients received a loading dose of 75,000–125,000 units of vitamin D2 or 50,000–75,000 units of vitamin D3 i.m. or orally. All patients immediately thereafter began a daily maintenance dose of oral vitamin D (800–1200 IU) and oral elemental calcium (1000–1500 mg in a divided dose).

The comparably high proportion of patients receiving paracetamol after start of study drug reflects the recommended use of paracetamol to reduce post-dose symptoms as per study protocol.

Concomitant use of other bisphosphonates was not permitted during the study. Nevertheless, a number of patients in both study arms (more patients in the placebo group) had other bisphosphonates during the study. The difference between groups in this aspect could be explained with the higher incidence of fractures in the placebo group.

Efficacy results:
In the ITT population, 231 patients had at least one adjudicated clinical fracture (92 in the zoledronic acid and 139 in the placebo group). A between-treatment comparison of the incidence of first clinical fracture is presented in Table 3-7. For the primary analysis in the ITT population, the hazard ratio of 0.65 (95% CI: 0.50 to 0.84) for the zoledronic acid group versus the placebo group represents a 35% reduction in the risk of clinical fractures over time (p = 0.0012).

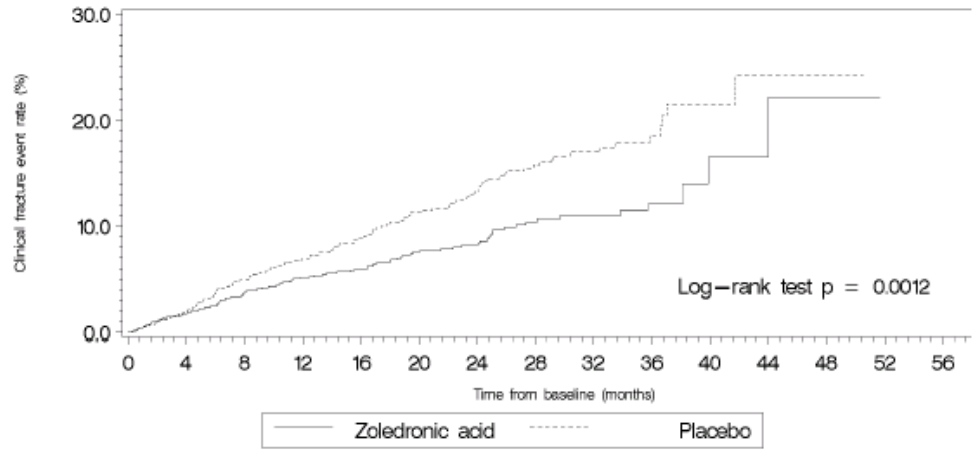
Table 3-7 Between-treatment comparison of the incidence of first clinical fracture over time – placebo-controlled study, Study 2310 (ITT and PP populations)

Location	Treatment	N	n [1]	Event rate [2] (%)	Hazard ratio (95% CI) [3]	p-value [4]
ITT population						
Clinical fracture	Zoledronic acid	1065	92	8.59	0.65 (0.50, 0.84)	0.0012
	Placebo	1062	139	13.88		
PP population						
Clinical fracture	Zoledronic acid	968	74	7.30	0.65 (0.48, 0.87)	0.0041
	Placebo	941	107	12.21		

1) n is the number of patients with a fracture.
2) The event rate is from Kaplan-Meier estimate at Month 24.
3) The hazard ratio and 95% CI of zoledronic acid vs. placebo are computed from a Cox proportional hazards regression model with treatment as a factor. A hazard ratio < 1 implies that zoledronic acid-treated patients have a lower risk of having a fracture than placebo-treated patients.
4) The p-value is calculated from a log-rank test. Note: Facial, skull, digital fractures, fracture due to metastatic cancer or osteomyelitis, or high energy trauma were not considered as endpoints in the analysis.

Kaplan-Meier curves for the cumulative clinical fracture rate are presented in Figure 3-1. After Month 36 the number of patients who were at risk of clinical fracture was 129 on zoledronic acid and 119 on placebo.

Figure 3-1 Kaplan-Meier curve of time to first clinical fracture – placebo-controlled study, Study 2310 (ITT population)



Primary efficacy variable

Zoledronic acid-treated patients experienced at least a 33% reduction in the risk of clinical fractures over time relative to placebo-treated patients in the following demographic subgroups: age < 65 and age ≥ 75 years; female gender; Caucasian and "Other" ethnicity. The ≥ 33% reductions were statistically significant for Caucasians, females, and patients aged ≥ 75 years (all three categories, $p < 0.005$). For all subgroups, the 24-month event rate was numerically lower in the zoledronic acid group compared to the placebo group. In addition, there was no evidence of any treatment-by-factor interactions for any of the demographic subgroups (all interaction p-values > 0.10),

Disease factors evaluated for the primary efficacy variable, time to first clinical fracture, were baseline femoral neck T-score (≤ -2.5, > -2.5) and baseline BMI (kg/m^2).

Zoledronic acid-treated patients experienced at least a 30% reduction in the risk of clinical fractures over time relative to placebo-treated patients for baseline BMI ≤ 22.6 kg/ m^2, 22.6 < baseline BMI ≤ 26.3, and both baseline femoral neck T-scores (≤ -2.5, > -2.5). The ≥ 30% reductions were statistically significant at the 0.05 level for baseline BMI ≤ 22.6 kg/ m^2, and both femoral neck T-score categories.

The time of receiving the first study infusion after hip fracture surgery (≤ 6 weeks, > 6 weeks) was evaluated for all clinical fracture endpoints.

The sub-group analysis with regard to the timing of administration after hip surgery, suggested better efficacy when zoledronic acid is given more than 6 weeks after surgery. At all sites there was a trend for better protection against fractures. In contrast, when the infusion was less than 6 weeks from surgery, for subsequent hip fracture, there was an increased risk of fracture in the zoledronic acid group (p=0.44). However, when patients treated in the first 2 weeks after the hip fracture surgery are excluded, a significant reduction in hip fractures was observed in zoledronic acid treated patients.

Secondary efficacy variables

The percent changes from baseline in femoral neck BMD were significantly greater for zoledronic acid-treated patients relative to placebo-treated patients at Months 12, 24, and 36 (all $p < 0.005$). Treatment with zoledronic acid resulted in an increase of 0.76%, 2.21%, and 3.62% (least squares mean) at Months 12, 24, and 36, while treatment with placebo resulted in a decrease of 1.73%, 2.08%, and 0.73% respectively.

In both males and females, there were statistically significant differences in percentage change in BMD for total hip when comparing zoledronic acid with placebo, and at all timepoints. In the zoledronic acid group, the increase in BMD was less pronounced in males at 12 and 24 months compared with females and in the placebo group, the decrease in BMD was less pronounced at all timepoints in males compared with females. Results for between treatment differences in femoral neck BMD changes were statistically significant for males at 24 and 36 months.

Time to first non-vertebral, hip and clinical vertebral fractures

Analyses on the PP population showed findings very similar to those presented for the ITT population. Subgroup analyses were performed for the incidence of non-vertebral, hip and clinical vertebral fractures by the time of first infusion following hip fracture surgery (≤ 6 weeks or > 6 weeks). The risk reductions observed for the early infusion as well as for the late infusion groups were not statistically significant ($p > 0.05$).

The incidence of new hip fractures was low. The 2-year event rates for hip fracture, based on Kaplan-Meier estimates were 2.02 and 3.46 % for the zoledronic acid and placebo groups, respectively. The estimated hazard ratio was 0.70 (95 % CI: 0.41 – 1.19, $p = 0.1815$).

A 61 % risk reduction in hip fractures was seen in zoledronic acid-treated patients who got their first infusion more than 6 weeks after surgery. For patients who received their first infusion within 6 weeks after surgery, there was a greater risk of hip fractures in the zoledronic acid group, with an estimated hazard ratio of 1.37 (95 % CI: 0.62 – 3.01, $p = 0.4376$). However, as shown in further analyses provided by the applicant, exclusion of the patients who received their first infusion within 2 weeks after surgery resulted in greater significant anti-fracture efficacy for all fracture subgroups (including hip fractures) (see also p18).

Closed testing procedure

The following fracture endpoints were evaluated as part of the closed testing procedure: time to first clinical vertebral fracture (6th endpoint), time to first hip fracture (7th endpoint), and time to first non-vertebral fracture (8th endpoint). The incidence of clinical vertebral fractures was significantly reduced by zoledronic acid relative to placebo. An estimated hazard ratio of 0.54 [95% CI: 0.32 to 0.92, $p = 0.0210$] corresponds to a 46% reduction in the risk of a clinical vertebral fracture over time. Although the number of new hip fractures was low since surgical repair of the entry hip often involved arthroplasty, implying that any hip fractures that occurred during the study could only have occurred in the other hip, the zoledronic acid group had a numerically lower risk in hip fractures compared to the placebo group. An estimated hazard ratio of 0.70 [95% CI: 0.41 to 1.19, $p = 0.1815$] corresponds to a 30% reduction in the risk of a hip fracture over time. The requirements for the success of the 7th endpoint were not met, and, therefore, the 10-step closed testing procedure stops here.

Further secondary endpoints included measure of resource utilisation. There were no statistically significant differences between treatment groups with respect to the percentages of patients with at least one hospitalisation, clinic, or home health care visit. However, zoledronic acid-treated patients had 4% fewer emergency room (ER) visits compared with placebo-treated patients ($p = 0.0114$).

Comparison of baseline risk factors between subpopulations

The MAH presented the comparability of the baseline characteristics and incidence of fractures for the male placebo-treated patients in Study 2310 to the placebo-treated PMO patients in Study 2301. A summary of these results is provided in Table 1-5 and 1-6, where it is shown that in the placebo groups, the Kaplan-Meier estimates of cumulative incidence of clinical fractures at 24 months was nearly identical between placebo populations (8.70% in Study 2310 versus 8.59% in Study 2301).

Table 1-5 Comparison of baseline characteristics for male patients in Study 2310 to the PMO population in Study 2301.

Baseline characteristics	Men participating in Study 2310 (N=508)	PMO Women in Study 2301 (N=7736)
Age (years) mean (SD)	72.6 (10.35)	73.1 (5.37)
Weight (kg) mean (SD)	73.7 (17.84)	60.3 (11.23)
BMI (kg/m^2) mean (SD)	24.7 (4.13)	25.3 (4.32)
Active smoker? – n (%)	NA	660 (8.5%)
Prednisone usage? – n (%)	18 (3.5%)	284 (3.7%)
Active alcoholism at randomization? – n (%)	17 (3.3%)	30 (0.4%)
Active rheumatoid arthritis at randomization – n (%)	12 (2.4%)	90 (1.2%)
Femoral neck BMD T-score mean (SD)	-2.305 (0.8209)	-2.749 (0.0544)

Table 1-6 Between-treatment comparison of the incidence of first clinical fracture between placebo-treated males in Study 2301 and placebo-treated PMO patients in Study 2301

Subgroup Category	Treatment	N	n[1]	Event rate[2]	Hazard ratio (95% CI)[3]	P-value for treatment difference[4]
Study						
2310 (males)	Placebo	260	20	8.70%	0.90 (0.57, 1.43)	0.6374
2301 (PMO)	Placebo	3861	456	8.59%		

Source: Study L2310 LOQ2 Table Q1.3-1

[1] n is the number of patients with a fracture.

[2] Event rates are Kaplan-Meier estimates based on the cumulative incidence of clinical fractures at 24 months

[3] The hazard ratio and 95% CI of placebo male study 2310 vs. placebo PMO study 2301 are computed from a Cox proportional hazards regression model with treatment as a factor within the subgroup. A hazard ratio < 1 implies that placebo-treated male patients have a lower risk of having a fracture than placebo-treated PMO patients.

[4] The between-treatment group p-value is calculated from a log-rank test.

The overall risk of clinical fractures of the placebo-treated male patients in Study 2310 (20 patients, 8.70%) is similar to that of the placebo-treated PMO patients in Study 2301 (456 patients, 8.59%) (HR = 0.90, p=0.6374). Of these 20 male placebo-treated patients who had clinical fractures during study 2310, 15/20 (75.0%) experienced non-vertebral fractures, 7/20 (35.0%) experienced hip fractures, and 6/30 (30.0%) experienced clinical vertebral fractures. In comparison, of the 456 placebo-treated PMO patients from Study 2301 who had clinical fractures, 388/456 (85.1%) experienced non-vertebral fractures, 88/456 (19.3%) experienced hip fractures and 84/456 (18.4%) experienced clinical vertebral fractures.

Analysis of BMD changes by gender

Given the different reference ranges for BMD in men and women, the absolute change and percentage change from baseline was taken into account to assess the similarity of the increases in total hip BMD observed for zoledronic acid between males in Study 2310 and females in Study 2301. A summary of these results are provided in Table 1-3 and Table 1-4 for total hip BMD where it is shown that, at Month 24 for both the percentage change and the change in total hip BMD from baseline, similar increases in zoledronic acid-treated male patients from Study 2310 and zoledronic acid-treated PMO patients from Study 2301 were observed. Month 24 most accurately reflects the median treatment duration (23 months) in study 2310.

Table 1-3 Between-treatment comparison of the percentage change in total hip BMD at Month 24 relative to baseline for zoledronic acid-treated males in Study 2310 and zoledronic acid-treated PMO females in Study 2301.

Time point Gender	Treatment	n [1]	LS mean [2]	LS mean difference (95% CI) [2]	p-value [2]
Month 24					
Male Study L2310	Zoledronic acid	85	3.32	0.55 (-0.36, 1.47)	0.2357
PMO Women Study H2301	Zoledronic acid	3228	3.88		

Source: Table Q1.2-1

- Percentage change from baseline = 100x (post-baseline value - baseline value)/baseline value.

[1] n is the number of patients with evaluable measurements at both baseline and post-baseline visit as determined by efficacy window.

[2] The LS mean is the least squares mean of the percent change from baseline. The LS mean, the LS mean difference of zoledronic acid PMO Study 2301 vs. zoledronic acid Male Study 2310, 95% CI, and p-values are calculated using a contrast from a one-way analysis of variance model with study in the model.

Table 1-4 Between-treatment comparison of the change in total hip BMD to Month 24 relative to baseline for zoledronic acid-treated males in Study 2310 and zoledronic acid-treated PMO females in Study 2301.

Time point Gender	Treatment	n [1]	LS mean [2]	LS mean difference (95% CI) [2]	p-value [2]
Month 24					
Male Study L2310	Zoledronic acid	85	0.0252	-0.0003 (-0.0061, 0.0055)	0.9265
PMO Women Study H2301	Zoledronic acid	3228	0.0255		

Source: Table Q1.2-2

- Change from baseline = (post-baseline value - baseline value)

[1] n is the number of patients with evaluable measurements at both baseline and post-baseline visit as determined by efficacy window.

[2] The LS mean is the least squares mean of the change from baseline. The LS mean, the LS mean difference of zoledronic acid PMO Study 2301 vs. zoledronic acid Male Study 2310, 95% CI, and p-values are calculated using a contrast from a one-way analysis of variance model with study in the model.

Analysis of efficacy by gender

The analysis of incidence of clinical fractures by gender in study 2310 showed that zoledronic acid reduced the risk of clinical fractures in females and males by 39% and 15% respectively. Further subdivision by types of fracture (non-vertebral, hip, and clinical vertebral) indicated that zoledronic acid-treated females demonstrated a statistically significant reduction in the risk of non-vertebral fractures (HR = 0.68, 95% CI: 0.49, 0.93) and clinical vertebral fractures (HR = 0.50, 95% CI: 0.28, 0.90). For hip fractures, zoledronic acid-treated females had a 25% reduction in the risk of hip fractures during the study (HR = 0.75, 95% CI: 0.42, 1.35).

In contrast, the small number of fractures occurring for each subtype in male patients (16 in zoledronic acid-treated patients and 20 in placebo-treated patients), results in wide confidence intervals for the estimates of the hazard ratios. For non-vertebral fractures, the risk of such events was equal between the two treatment groups (HR = 1.00, 95% CI: 0.48, 2.38) while for clinical vertebral fractures, zoledronic acid-treated males had a 28% reduction in the risk of such events (HR =0.72, 95% CI: 0.41, 1.78). For hip fractures, zoledronic acid-treated males reduced the risk of hip fractures by 55% (HR = 0.45, 95% CI: 0.12, 1.75).

Total hip BMD

A between-treatment comparison of the percentage change from baseline in standardised total hip BMD by time point and gender is presented in table 4. 37.

Table 4. 37. Between-treatment comparison of the % change from baseline in standardised total hip BMD by visit and gender; study L 2310 ITT population excluding centre 0829.

Time point Gender	Treatment	n [1]	LS mean [2]	LS mean difference (95% CI) [2]	p-value [2]
Month 12					
Male	**Zoledronic acid**	**154**	**1.97**	**2.01 (0.67, 3.35)**	**0.0032**
	Placebo	**169**	**-0.03**		
Female	**Zoledronic acid**	**527**	**2.77**	**4.15 (3.40, 4.89)**	**<0.0001**
	Placebo	**514**	**-1.38**		
Month 24					
Male	**Zoledronic acid**	**85**	**3.59**	**3.81(1.38, 6.23)**	**0.0021**
	Placebo	**100**	**-0.22**		
Female	**Zoledronic acid**	**320**	**4.95**	**5.88 (4.56, 7.20)**	**<0.0001**
	Placebo	**300**	**-0.93**		
Month 36					
Male	**Zoledronic acid**	**33**	**7.27**	**7.06 (3.12, 10.99)**	**0.0005**
	Placebo	**31**	**0.22**		
Female	**Zoledronic acid**	**95**	**4.87**	**6.11 (3.82, 8.39)**	**<0.0001**
	Placebo	**93**	**-1.24**		

- Percentage change from baseline = 100x (post-baseline value - baseline value)/baseline value.

[1] n is the number of patients with evaluable measurements at both baseline and post-baseline visit as determined by efficacy window.

[2] The LS mean is the least squares mean of the percent change from baseline. The LS mean, the LS mean difference of zoledronic acid vs. placebo, 95% CI, and p-values are calculated using a contrast from a three-way analysis of variance model with treatment, region, sex, and treatment-by-sex interaction in the model.

Femoral neck BMD

A between-treatment comparison of the percentage change from baseline in standardised femoral neck BMD by time point and gender showed that for male patients, treatment with zoledronic acid resulted in increases in femoral neck BMD of 0.91%, 1.42%, and 6.53% at months 12, 24, and 36 while treatment with placebo resulted in decreases of 0.54%, 2.41% and 0.82% respectively. The differences between treatment groups were significantly greater for zoledronic acid vs. placebo at months 24 and 36 (both $p < 0.005$) but only a trend towards significance was observed at month 12 ($p = 0.0645$). For females, treatment with zoledronic acid resulted in increases in femoral neck BMD of 0.72%, 2.40%, and 2.75% at months 12, 24, and 36 while treatment with placebo resulted in decreases of 2.10%, 2.00%, and 0.57% respectively. The differences between treatment groups were significantly greater for zoledronic acid vs. placebo

Timing of first infusion and changes in BMD

Analysis of the percentage change in total hip BMD by timing of the first infusion in 2-week intervals showed that significant improvements compared to placebo at 12 months were obtained when the first infusion was given > 2 weeks after surgical hip repair for total hip BMD (Table 7-7) and $\geq$6 weeks for femoral neck BMD (Table 7-9). At 24 months, there were statistically significant improvements compared to placebo in total hip BMD at all time points (Table 7-8), and when first infusion was given > 4 weeks in femoral neck BMD (Table 7-10). However, the numerical increases in femoral neck BMD observed at Month 24 for those zoledronic acid-treated patients dosed within two weeks of hip fracture surgery (4.58%) are comparable to that which is observed in other categories; however, the small groups sizes (18 on zoledronic acid and 21 on placebo) would require huge differences to be observed for statistical significance to be demonstrated. The LS Mean difference of 4.58% is comparable to what is observed over other time periods.

Table 7-7. Between-treatment comparison of the percentage change from baseline in standardised femoral neck BMD by visit and time of receiving study drug since hip fracture surgery – Study L2310 (ITT population excluding center 0829).

Time point Time of infusion	Treatment	n [1]	LS Mean [2]	LS Mean Difference (95% CI) [2]	p-value [2]
Month 12					
≤ 6 weeks	Zoledronic acid	295	-0.70	0.57 (-0.57, 1.72)	0.3254
	Placebo	313	-1.28		
> 6 weeks	Zoledronic acid	421	1.81	3.88 (2.90, 4.87)	<.0001
	Placebo	405	-2.08		
Month 24					
≤ 6 weeks	Zoledronic acid	187	2.00	3.83 (2.10, 5.55)	<.0001
	Placebo	200	-1.82		
> 6 weeks	Zoledronic acid	241	2.37	4.69 (3.11, 6.27)	<.0001
	Placebo	223	-2.32		
Month 36					
≤ 6 weeks	Zoledronic acid	73	2.78	2.27 (-0.66, 5.20)	0.1278
	Placebo	83	0.50		
> 6 weeks	Zoledronic acid	55	4.96	7.86 (4.11, 11.62)	<.0001
	Placebo	42	-2.90		

Source: [Appendix 2 – Final CSR Study L2310 Table 14.2-2.23]

Note: Percentage change from baseline = 100x (post-baseline value - baseline value) / baseline value.

[1] n is the number of patients with evaluable measurements at both baseline and post-baseline visit as determined by efficacy window.

[2] The LS mean is the least squares mean of percent change from baseline. The LS mean, the LS mean difference of zoledronic acid vs. placebo, 95% CI, and p-values are calculated using contrasts from a three-way analysis of variance model with treatment, region, time of receiving study drug, and treatment by time of receiving study drug interaction in the model.

Table 7-8. Percent change in total hip BMD at 12 months by timing of 1st infusion (Study L2310 ITT Population).

Time of 1st infusion since hip fracture surgery	Zoledronic Acid		Placebo		LS Mean Difference (95% CI)	p-value
	n	LS Mean (SE)	n	LS Mean (SE)		
≤ 2 weeks	23	1.36 (1.30)	28	-1.42 (1.18)	2.78 (-0.59, 6.15)	0.1064
>2-4 weeks	116	1.19 (0.58)	104	-0.65 (0.61)	1.84 (0.22, 3.47)	0.0259
>4-6 weeks	156	2.20 (0.49)	177	-1.45 (0.46)	3.65 (2.34, 4.97)	<.0001
>6-8 weeks	93	4.21 (0.64)	105	-1.12 (0.60)	5.33 (3.62, 7.04)	<.0001
>8-10 weeks	101	3.56 (0.62)	89	-1.22 (0.66)	4.78 (3.04, 6.53)	<.0001
>10-12 weeks	97	3.00 (0.63)	92	-0.52 (0.65)	3.52 (1.77, 5.27)	<.0001
>12 weeks	94	2.38 (0.64)	88	-0.74 (0.66)	3.11 (1.33, 4.90)	0.0006

Source: [Appendix 1 - Table q5-6.1]

Table7-9. Percent change in total hip BMD at 24 months by timing of 1st infusion (Study L2310 ITT Population).

Time of 1st infusion since hip fracture surgery	Zoledronic Acid		Placebo		LS Mean Difference (95% CI)	p-value
	n	LS Mean (SE)	n	LS Mean (SE)		
≤ 2 weeks	19	5.61 (1.96)	19	-2.61 (1.97)	8.22 (2.90, 13.53)	0.0025
>2-4 weeks	73	5.24 (0.99)	69	0.91 (1.03)	4.33 (1.58, 7.08)	0.0021
>4-6 weeks	95	4.38 (0.87)	106	-0.95 (0.82)	5.33 (3.01, 7.64)	<0.0001
>6-8 weeks	53	4.15 (1.16)	56	-1.47 (1.12)	5.61 (2.47, 8.75)	0.0005
>8-10 weeks	57	6.78 (1.12)	48	-1.62 (1.22)	8.40 (5.19, 11.61)	<0.0001
>10-12 weeks	59	3.76 (1.11)	48	-0.79 (1.23)	4.55 (1.36, 7.73)	0.0052
>12 weeks	49	3.41 (1.21)	54	-0.03 (1.16)	3.43 (0.19, 6.68)	0.0379

Source: [Appendix 1 - Table q5-6.1]

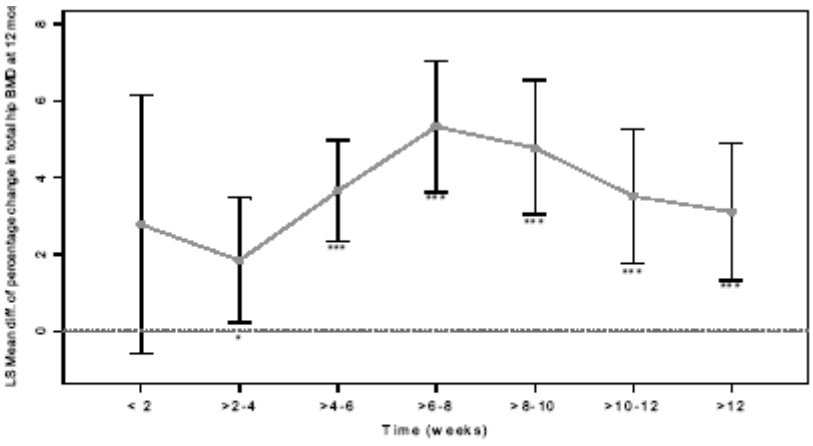
Table 7-10. Percent change in femoral neck BMD at 12 months by timing of 1st infusion (Study L2310 ITT Population).

Time of 1st infusion since hip fracture surgery	Zoledronic Acid		Placebo		LS Mean Difference (95% CI)	p-value
	n	LS Mean (SE)	n	LS Mean (SE)		
≤ 2 weeks	22	-0.74(1.56)	28	-1.68 (1.38)	0.94 (-3.08, 4.96)	0.6475
>2-4 weeks	118	-1.18 (0.67)	106	-0.76 (0.71)	-0.43 (-2.32, 1.46)	0.6568
>4-6 weeks	155	-0.34 (0.58)	179	-1.53 (0.54)	1.19 (-0.36, 2.74)	0.1311
>6-8 weeks	100	2.45 (0.73)	110	-3.13 (0.69)	5.58 (3.63, 7.53)	<0.0001
>8-10 weeks	113	1.99 (0.69)	99	-2.51 (0.73)	4.50 (2.55, 6.44)	<0.0001
>10-12 weeks	108	1.19 (0.70)	100	-0.82 (0.73)	2.02 (0.06, 3.98)	0.0436
>12 weeks	100	1.70 (0.72)	96	-1.67 (0.74)	3.37 (1.34, 5.39)	0.0011

Source: [Appendix 1 - Table q5-6.2]

In study 2310, a constant increase in BMD at all time intervals was observed at the total hip without any specific trend with timing of first infusion (Figure 5-1).

Figure 5-1 Between-treatment differences in the percentage change in total hip BMD at 12 months by timing of first study drug infusion following hip fracture repair.



Source: Study L2310 Day 90 Response Table q5-6.1

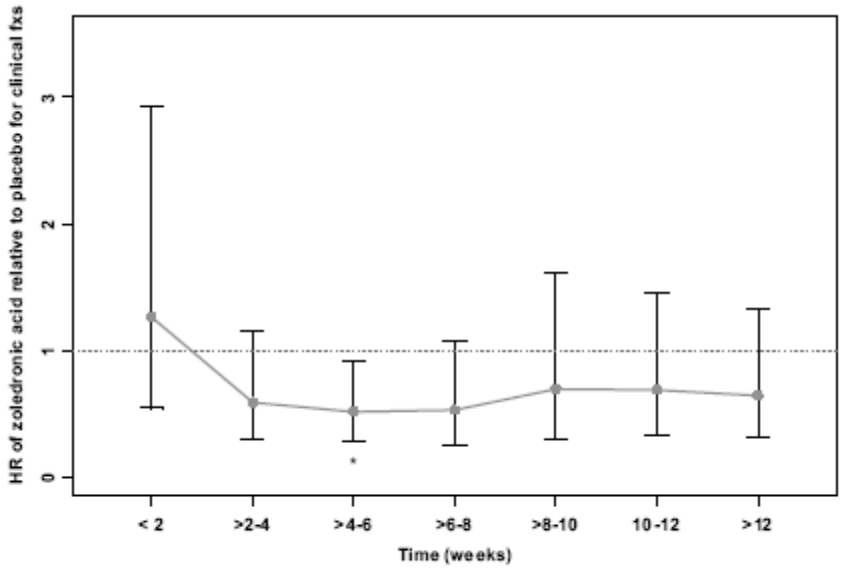
* Denotes statistical significance at 0.05 level

*** Denotes statistical significance at 0.0005 level

Timing of first infusion and changes in antifracture efficacy

In order to further analyse the relation between timing of first dose and antifracture efficacy, the MAH performed a subgroup analysis based on 2 week intervals. Results are shown in Figure 5-2.

Figure 5-2 Variation in risk reduction of clinical fracture with timing of first dose over 12 weeks in 2 week intervals.



Source: LOQ2 Study L2310 Table Q2-1.5

* Denotes statistical significance at the 0.05 level

Timing of first infusion and changes in mortality

All time points except the > 12 week group have confidence intervals that crossed 1, with the ≤ 2 week group showing the largest variation (Figure 5-3). This time to effect interaction is subject to significant confounders. When the data is subdivided into 2-week time intervals, there is no treatment-by-timing interaction as was shown when analysing timing as a continuous variable in the analysis of risk factors for death. Several studies have demonstrated a very high peri- and post-operative mortality in hip fracture patients, which amounts to 9% within the first 30 days and 19% within 120 days (Moran, et al 2005; Robbins, et al 2006). Thus, patients receiving their first dose early after fracture repair may well exhibit a higher degree of fragility, and therefore higher mortality, than patients dosed later. This finding is also corroborated in study 2310. Patients in the ≤ 2 week group were older and exhibited a higher baseline prevalence of hypertension, coronary artery disease, diabetes, atrial fibrillation, and stroke (Table 5-1). Moreover, as shown in Table 5-2, these differences were reflected in higher placebo mortality in this sub-group (17.71%). In patients dosed > 2 weeks from hip fracture repair, the cumulative incidence of mortality as estimated by Kaplan-Meier varied between 20.86% in the >6-8 week group to 13.53% in the >8-10 weeks group.

Table 5-1 Morbidity differences between patients dosed less than or equal to 2 weeks and later in study 2310 in relation to timing of first dose (Study2310 safety population).

Baseline Characteristic	≤ 2weeks (N=102)	> 2-12 weeks (N=2008)
	n (%)	n (%)
Age		
< 65	13 (12.7)	350 (17.4)
65-74	17 (16.7)	555 (27.6)
75-84	45 (44.1)	842 (41.9)
> 85	27 (26.5)	261 (13.0)
Hypertension	59 (57.8)	1051 (52.3)
Active Diabetes	23 (22.5)	310 (15.4)
Active Heart failure	9 (8.8)	92 (4.2)
Active Valvular disease	7 (6.9)	81 (4.0)
Active Coronary artery disease	28 (27.5)	405 (20.0)
History of Myocardial infarction	11 (10.8)	160 (8.0)
Active tachyarrhythmia	13 (12.7)	127 (6.3)
Active atrial fibrillation	11 (10.8)	107 (5.3)
Active hypercholesterolemia	24 (23.5)	278 (13.8)
History of stroke	21 (20.6)	350 (17.4)

Source: LOQ2 response Table Q2-3.1

Table 5-2 Death rates in the placebo and zoledronic acid groups of study 2310 in relation to timing of first study drug infusion after hip fracture repair (Study 2310 Safety population).

Time to infusion from hip fracture surgery	Zoledronic acid n/N (%)[1]	Placebo n/N (%)[1]
≤ 2 weeks	12/56 (25.07%)	10/46 (17.71%)
>2-4 weeks	28/191 (23.09%)	27/176 (19.48%)
>4-6 weeks	23/231 (12.24%)	37/271 (16.55%)
>6-8 weeks	17/160 (11.65%)	23/167 (20.86%)
>8-10 weeks	8/145 (7.65%)	12/123 (13.53%)
>10-12 weeks	10/148 (7.54%)	15/130 (16.99%)
>12 weeks	3/122 (12.77%)	17/144 (17.02%)

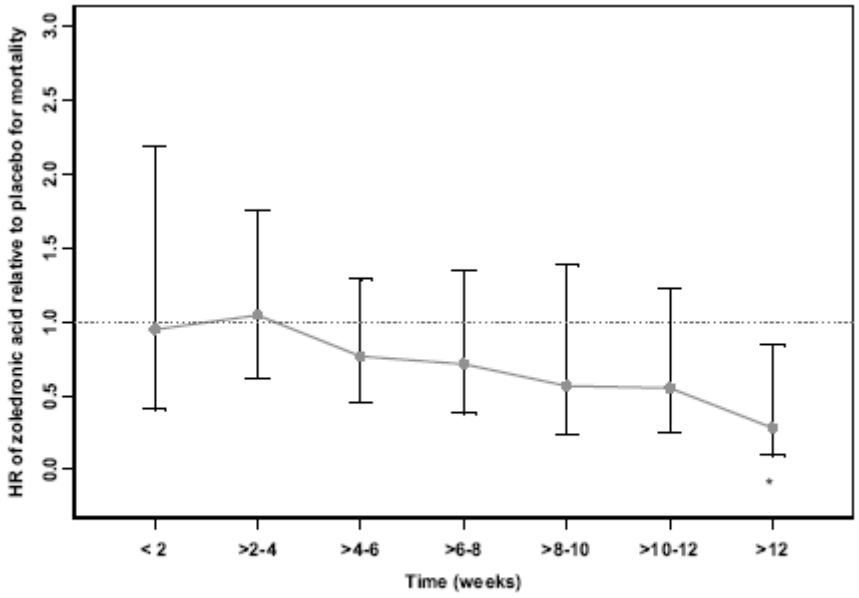
Source: LOQ2 response Table Q2-1.9

[1] Reflects Kaplan-Meier estimates of event rate at 36 months

Overall antifracture efficacy and mortality benefit after exclusion of 2 week group

From the graphical presentation of efficacy and mortality results shown above, patients dosed within 2 weeks show responses very different from the rest of the cohort. Therefore, in order to test the sensitivity of the within 2 week group on the overall results, between-treatment differences in the incidence of all clinical, non-vertebral, clinical vertebral, hip fractures, and mortality were analysed excluding patients who were dosed within 14 days or less from hip fracture repair (Figure 5-3).

Figure 5-3. Variation in hazard ratios for death over 12 weeks in 2 week intervals.



Source: LOQ2 response Table Q2-1.9

* Denotes statistical signficance at the 0.05 level

Including only those patients dosed > 2 weeks from hip fracture repair, the magnitude of reduction for all endpoints increased relative to the overall result, and leads to a significant reduction in hip fractures. Clinical fractures were reduced by 41% (p=0.0002), non-vertebral fractures 44% (p=0.0077), clinical vertebral fractures 53% (p=0.0084) and hip fractures 48% (p=0.0305). Mortality also had a significant 30% reduction (p=0.0095). Thus, exclusion of the ≤ 2 week group resulted in greater significant anti-fracture efficacy for all fracture subgroups and a more pronounced reduction of mortality. It should be noted that, in patients doses ≤ 2 weeks after fracture repair, the results within this time period show higher event rates across both treatment groups, which were considered to confound the effects observed with zoledronic acid therapy

Study 2308

This was a supportive double-blind double-dummy randomised active-controlled 2-arm trial comparing the efficacy and safety of i.v. zoledronic acid with oral alendronate for 24 months in the target population of osteoporotic men. 302 males with primary osteoporosis or significant osteoporosis secondary to hypogonadism received zoledronic acid (5 mg i.v. yearly infusion) or active control (oral alendronate 70 mg once weekly).

Inclusion criteria in this study were: age 25 - 85 years, BMD ≤ -2.0 SD at the femoral neck and ≤ -1.0 SD at the lumbar spine or ≤ -1.0 SD at the femoral neck and at least 1 prevalent vertebral deformity as defined by the modified Genant method for males or a documented history of an osteoporotic clinical fracture.
The primary efficacy objective was to show that the % change in lumbar spine BMD at month 24 relative to baseline was non-inferior to the % change in lumbar spine BMD in those men treated with alendronate. This would be shown if the lower bound of the 2-sided 95% confidence interval (CI) for the treatment difference of the percentage change in lumbar spine BMD at month 24 relative to baseline was greater than the non-inferiority margin Δ = -1.5%, in the ITT and PP populations. The non-inferiority margin was based on the results of a placebo-controlled study of oral alendronate 10 mg daily in male osteoporosis (*Orwoll et al 2000*) and a study comparing alendronate 10 mg daily and 70 mg once weekly in postmenopausal osteoporosis (*Schnitzer et al. 2000*). The "last observation carried forward" (LOCF) methodology was applied for the primary efficacy analyses.

In this study, 154 patients were included to receive zoledronic acid and 148 patients alendronate (ITT population). Patients in the alendronate group took placebo as i.v. infusion, and patients in the zoledronic acid group took placebo capsules as oral study medication. 137 patients completed the study in the zoledronic acid arm, while 124 patients completed the study under alendronate.

Efficacy results
In the tables and figures below the main study results in relation to BMD and bone formation and – resorption markers are presented.

As shown in table 4-11, in both studies the lumbar spine, hip and femoral neck BMDs increased approximately at a similar rate until month 12, while slightly higher increases in total hip and femoral neck BMD could be seen between months 12-24 in the female population from study 2301 compared with study 2308.

Table 4. 11. LS mean % change from baseline in lumbar spine, total hip and femoral neck BMD for zoledronic acid at months 12 and 24 in studies 2308 and 2301, ITT populations.

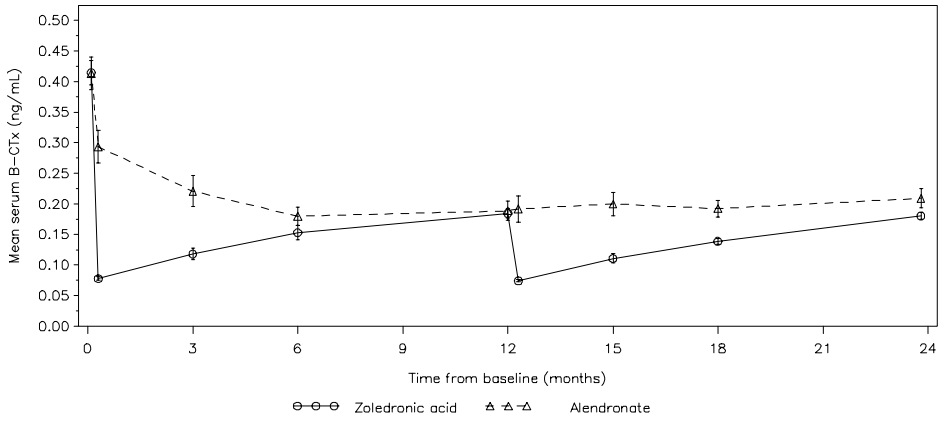
	Study 2308			Study 2301		
	Zoledronic acid			Zoledronic acid		
BMD Location Visit	n	LS mean % change (SE)	95% CI	n	LS mean % change (SE)	95% CI
Lumbar spine						
Month 12	**142**	**4.18 (0.33)**	**na**	**262†**	**3.88 (0.31)**	**3.27, 4.49**
Month 24 (1)	**152**	**6.07 (0.38)**	**5.31, 6.82**	**236†**	**5.76 (0.38)**	**5.01, 6.51**
Total hip						
Month 12	**144**	**1.77 (0.25)**	**na**	**3516**	**2.83 (0.07)**	**2.68, 2.97**
Month 24 (1)	**154**	**2.21 (0.31)**	**1.60, 2.83**	**3228**	**3.72 (0.09)**	**3.54, 3.90**
Femoral neck						
Month 12	**144**	**2.75 (0.70)**	**na**	**3522**	**2.70 (0.10)**	**2.51, 2.89**
Month 24 (1)	**154**	**3.22 (0.62)**	**2.01, 4.43**	**3234**	**3.38 (0.11)**	**3.16, 3.61**

Percentage change from baseline = 100 x (post-baseline value - baseline value)/baseline value
n is the number of randomised patients with measurements at both baseline and the relevant post-baseline visit.
For study 2308, the LS mean of the percentage change from baseline and the 95% CI are calculated from a three-way ANOVA model with treatment, center and baseline BMD in the model.
For study 2301, the LS mean of the percentage change from baseline and the 95% CI are calculated from a three-way ANOVA model with treatment, region (center was used for lumbar spine) and stratum in the model.
(1) In study 2308, for missing month 24 measurements, the last non-missing post-baseline value was carried forward (LOCF). For patients with missing baseline and/or post-baseline measurements, a value of zero was imputed for percentage change from baseline.
† Spine/distal radius population for lumbar spine BMD in Study 2301.; na = not available

Bone resorption markers
The level of bone resorption marker serum beta-CTX was significantly lower in the group that received zoledronic acid at all timepoints (except Month 12 and Month 24), with a marked drop after each injection, compared to the alendronate group, which showed a higher reduction of beta-CTX level only at Month 12 and comparable reduction at Month 24 (see figure 4.1).[A15]

Protocol CZOL446M2308

Figure 14.2–1.1 (Page 1 of 1)
Mean value of serum B–CTx over time by treatment
(Intent–to–treat population)



– Patients with measurements at baseline and at specific visits as defined by efficacy window.
– Error bars present raw means +/– standard error.
– B–CTx values below lower level of detection (LOD) are imputed using values of LOD/2,
where LOD of B–CTx is 0.01 ng/mL
– Source: Post–text table 14.2–2.11
t_bre2.sas 29OCT2007 10:26

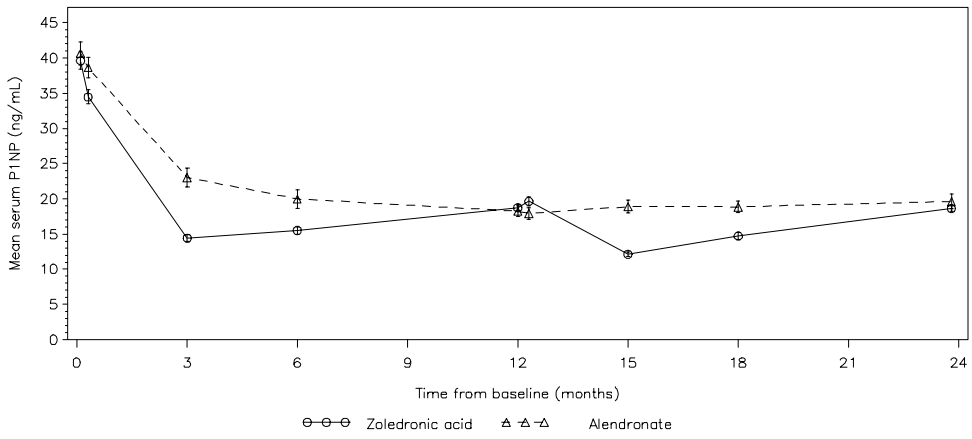
The mean ±SE of absolute value are presented.

Bone formation markers

The level of amino-terminal propeptide of type 1 procollagen (P1NP), which is produced during the build-up of collagen 1 in osteogenesis and reflects osteoblast activity, dropped after initiation of therapy for both substances, with a higher initial reduction of P1NP after each injection in the group that received zoledronic acid. However, the reduction of P1NP was greater in the alendronate group at Month 12 and 9-11 days after the second infusion and was statistically significant less prior to the second infusion and 3 and 6 months after the second infusion and was equal at Month 24 (see figure 4.2)

Protocol CZOL446M2308

Figure 14.2–1.2 (Page 1 of 1)
Mean value of serum P1NP over time by treatment
(Intent–to–treat population)



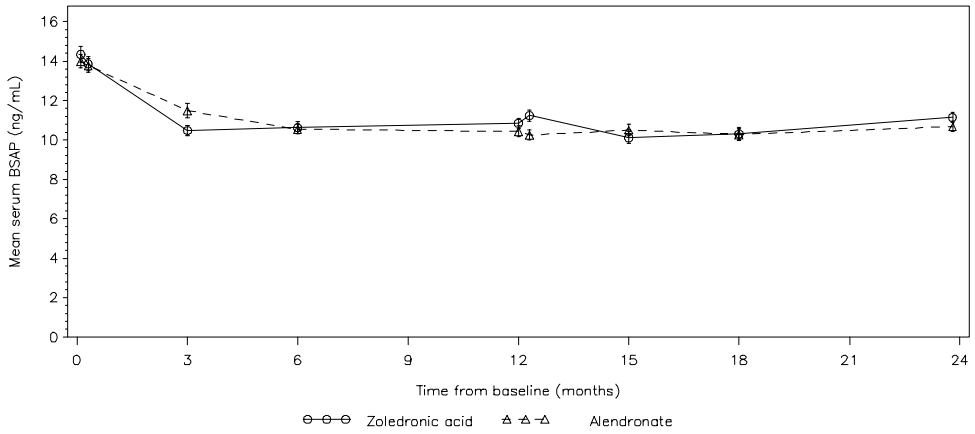
– Patients with measurements at baseline and at specific visits as defined by efficacy window.
– Error bars present raw means +/– standard error.
– P1NP values below lower level of detection (LOD) are imputed using values of LOD/2,
where LOD of P1NP is 5 ng/mL
– Source: Post–text table 14.2–2.14
t_bre3.sas 29OCT2007 10:26

The mean ±SE of absolute value are presented.

The influence of zoledronic acid or alendronate on bone specific alkaline phosphatase (BSAP) showed a comparable pattern for both substances, with the highest decrease after initiation of therapy, as shown in figure 4.3.

Protocol CZOL446M2308

Figure 14.2–1.3 (Page 1 of 1)
Mean value of serum BSAP over time by treatment
(Intent–to–treat population)



The mean ±SE of absolute value are presented.
– Patients with measurements at baseline and at specific visits as defined by efficacy window.
– Error bars present raw means +/– standard error.
– BSAP values below lower level of detection (LOD) are imputed using values of LOD/2, where LOD of BSAP is 0.07 ng/mL.
Source: Post–text table 14.2–2.17
Program: e2310t06.sas

Incidence of fractures

Study 2308 was not powered to detect treatment differences in fracture rates. There were 4 patients (2.6 %) in the zoledronic acid group and 6 patients (4.1 %) in the comparator group who had a new vertebral fracture in the study.

Discussion and conclusions on clinical efficacy

Study 2310

The efficacy results of this study showed that zoledronic acid is effective in delaying the time to subsequent clinical fracture after a hip fracture with surgery. Zoledronic acid significantly reduced the risk of clinical fractures relative to placebo in the total study population and was superior to placebo in increasing or preserving total hip BMD and femoral neck BMD at all time points Zoledronic acid demonstrated equal 35% reductions in the incidence of clinical fractures in those patients who were less than 75 years of age compared to those who were greater than or equal to 75 years of age. Unlike most other studies on osteoporosis, study 2310 did not record lumbar spine BMD routinely in the study population. It has to be emphasised that the study population consisted of patients over the age of 50 who had suffered a hip fracture caused by low energy trauma.

The CHMP also noted that the mean age in study 2310 was slightly higher than in the previously assessed postmenopausal osteoporosis study 2301. The age range in Study 2310 was 50-98 years (mean 74.5 years and median 76 years), while in Study 2301 the age range was 64-89 (mean 73.1 years and median 73 years).

The reduction in fracture rate was statistically and clinically significant. The reduction over 24 months was similar to that observed in the 2301 trial in postmenopausal osteoporosis over 36 months (event rate 8.40% versus 12.9% in the zoledronic acid group and placebo group, respectively, see variation EMEA/H/C/595/II/010), suggesting that these patients were at a higher risk for fracture compared with the study 2301 patient population, which can be expected considering that previous fracture is a well known and strong risk factor for fracture.

Stratification in study 2310 and concomitant therapy
Concerning results for the different strata the MAH presented that Study 2310 differed from the large pivotal post-menopausal trial 2301 in that patients were not randomised to a stratum based on their use of concomitant osteoporosis medications. When study 2310 began, approximately 10% or less of hip fracture patients were expected to receive therapy for their osteoporosis *(Torgerson and Dolan 1998; Colon-Emeric, et al 2000a; Colon-Emeric, et al 2000b; Kamel, et al 2000).* It was assumed that this usage level of concomitant osteoporosis therapies had no anti-fracture efficacy at the hip (e.g. calcitonin; SERMs; hormone replacement therapy [HRT]; tibolone; DHEA[s], ipriflavone; and

testosterone, as hormone replacement in the case of hypogonadal men) and would have no consequential effect on the trial's outcome and thus were permitted.

It is agreed that the data observed in study 2310 support this assumption; approximately 5% of patients (53/1065, 4.98% of the zoledronic acid group and 55/1062; 5.18% of the placebo group) reported taking an osteoporosis medication prior to randomisation, and this rose to approximately 10% during the trial (99/1065 [9.3%] patients in the zoledronic acid group and 125/1062 [11.7%] patients in the placebo group).

Discussion on bridging of efficacy data in males
The inclusion of men in study 2310 provided new information regarding efficacy and safety in an additional sub-group, although the number of male patients was relatively low (less than 25% of the study population). This reflects the general higher prevalence of osteoporosis in females as compared with males.

The BMD results were seen in the light of the current concept of bridging data from postmenopausal females to males according to the recent revision of the CHMP Guideline on the evaluation of medicinal products in the treatment of primary osteoporosis. The four criteria for bridging include:
- a study duration of at least 1 year,
- justification of the dosage,
- similar risk for fractures as in postmenopausal females and
- the magnitude of the BMD changes versus placebo have to match the magnitude of changes observed in postmenopausal females.

The Guideline however refers to a separate bridging study in men, which is not the case with Study 2310, as men were only a sub-population of that study. The CHMP considered that this would be acceptable considering the relatively large sub-group of males in study 2310. Furthermore, the CHMP pointed out that supportive evidence was provided from an active controlled trial in males (Study 2308).

To justify the bridging between male and female BMD data, the MAH presented study data for total hip and femoral neck BMD for men at 12 and 24 months from study 2310. Of the males, 64 (26.2 %) received one study drug infusion, 112 (45.9 %) received two infusions, 59 (24.2 %) received three infusions and 9 (3.7 %) received four study drug infusions.

The number of patients was relatively large (approximately 25% of the total sample size), and similar to the number of patients that have been included in separate trials in men previously with other agents.

Study duration and justification of the dosage
The study duration was in line with the guideline. The justification for the dosage was previously assessed in the extension of indication to include PMO with variation II/10. In the previously assessed dose finding study, study 0041, the effect of the different doses of zoledronic acid was studied up to 12 months. Bone resorption markers reached a peak at 1 month and bone formation marker at 3 months and all markers remained suppressed until 12 months for all doses. The CHMP therefore considered it doubtful if the duration of bone turnover suppression is directly correlated with the dose. In addition, there are no data on the effects of lower doses than 5 mg of zoledronic acid on bone markers after a longer period than 12 months.

The need for a justification of the dose for Bridging in the Guideline was based on potential gender-based difference in absorption of oral forms. It is however of no importance in this case since Aclasta is administered intravenously.

Risk for fractures - comparability of the male and female populations and their baseline BMD
The fracture incidences seem to differ between the male population in study 2310 and the female population in study 2301 when the placebo groups are compared. It was therefore questioned if the

fracture risk was similar in the male population in study 2310 and the post-menopausal population in study 2301.

Men and women have different body structures due to height and weight and thus comparing baseline BMD in the traditional sense can often be confounded. This is reflected by the differences in baseline BMD shown in Table 1-1 despite the age and BMI being similar across the populations. These differences are not unexpected given that the reference values for femoral neck BMD and total hip BMD are generally about 10% higher for males than females as characterised by the data available from NHANES III (Looker, et al 1998). The differences observed between the male population from Study 2310 and the PMO population from Study 2301 are consistent with what has been observed between the observational cohort populations studies for males in the Osteoporotic Fractures in Men (MrOS) Study (*Orwoll, et al 2005)* and for females in the Study of Osteoporotic Fractures (SOF) *(Cummings, et al 2006).* A comparison of the populations studied in MrOS and SOF are presented in Table 1-2.

Table 1-1 Comparison of baseline characteristics for male patients in Study 2310 to the PMO population in Study 2301.

Baseline characteristics	Men participating in Study 2310 (N=508)	PMO Women in Study 2301 (N=7736)
Age (years) mean (SD)	72.6 (10.35)	73.1 (5.37)
BMI (kg/m^2) mean (SD)	24.7 (4.13)	25.3 (4.32)
Femoral neck BMD (g/cm^2) mean (SD)	0.691 (0.1222)	0.544 (0.0634)
Total hip BMD (g/cm^2) mean (SD)	0.770 (0.1433)	0.648 (0.0903)

Table 1-2 Comparison of baseline characteristics for male patients in MrOs to the PMO population in SOF

Baseline characteristics	Men participating in MrOS (N=5384)	PMO Women in SOF(N=7871)
Age (years) mean	73.8	73.4
BMI (kg/m^2) mean	27.4	26.2
Femoral neck BMD (g/cm^2) mean	0.78	0.67
Total hip BMD (g/cm^2) mean	0.96	0.78

It was considered acceptable to use total hip and femoral neck BMD data for bridging in this case as the Guideline does not specify what localisation the BMD should be recorded at and as practical difficulties in study 2310 precluded measuring of lumbar spine BMD. Whether the Region of Interest (ROI) should be femoral neck or total hip is currently debated. Accordingly, the recommendations differ between guidelines, such as those of the international Osteoporosis Foundation (IOF) and those of the International Society for Clinical Densitometry (ISCD). In the PMO study 2301 assessed for the extension of indication to include PMO (Variation II-10) femoral neck BMD was used for the diagnosis of osteoporosis. Therefore, for evaluation of clinical trial results, both sites were documented and analysed.

In view of the fracture risk, the CHMP noted that concerning the age distribution, in Study 2310, more than one fourth of the males were below the age of 65, although men with primary OP are usually older compared with females when they develop osteoporosis and osteoporosis-related fractures. This may imply a lower risk for fracture in this study as the fracture risk is strongly associated with age in both males and females.

The mean and median age, however, was similar comparing the patients populations, post-menopausal women in study 2301 and males in Study 2310, as a larger proportion of male patients in Study 2310 were 75 years of age or older.

Conversely to the above, this would imply a higher risk of fracture. In terms of BMD at baseline, the CHMP considered that populations differ significantly. Less than 40% of the male patients in Study 2310 were osteoporotic at baseline compared with over 70% of the females in Study 2301. As the BMD is one of the strongest risk factors for fractures, the fracture risk cannot automatically be considered the same based on these data.

On the other hand, a recent low trauma hip fracture is a strong risk factor for further fractures and in this situation was considered to override the other factors related to the risk of fractures. In Study 2310, a recent hip fracture was an entry criterion and in Study 2301, 63% had at least one prevalent vertebral fracture at baseline. Thus, both populations can be regarded as high-risk populations for fractures. Furthermore, annualised fracture rates in the placebo arms were similar in both studies (the clinical fracture rate for PMO women in Study 2301 was 4.28% and for men in Study 2310 was 4.35%).

Comparisons of the baseline risk factors between Study 2301 and Study 2310 are considered difficult given that all patients in Study 2310 were required to have a hip fracture for study entry and there are no baseline lateral spine x-rays from Study 2310 to allow for comparison of the prevalence of baseline vertebral fractures for the two populations. Furthermore, it has already been established that there are clear differences in the percentage of patients who had femoral neck BMD T-scores below the osteoporosis threshold (41% for Study 2310 and 67% for Study 2301).

The CHMP considered that fractures at baseline could not be compared between studies due to the different inclusion criteria for the studies. However, considering that all patients entering trial 2310 had to have a recent low energy trauma fracture, it can be concluded that these patients were at high risk of fracture. Similarly, patients included into the large PMO trial were patients at high risk for fracture (70 % were osteoporotic and >60 % had one or more vertebral fractures at baseline).
The CHMP noted that more men in study 2310 than women in study 2301 had active rheumatoid arthritis at study inclusion. More males than females were alcoholics. Although it must be pointed out that the number of placebo-treated males who suffered a clinical fracture in study 2310 was low, the incidence of clinical fractures did not significantly differ between placebo-treated males in study 2310 and placebo-treated PMO females in study 2301 and the point estimates are similar. Despite the low number of fractures in the male placebo population in Study 2310 (n = 20 vs. 456 in 2301), this supports a similar risk for fracture as in Study 2310. The risk reduction observed in the male population, only 15 %, however remains a concern as it is uncertain whether or not Aclasta would benefit male patients in terms of fracture prevention. The CHMP considered that this point will be answered in the ongoing fracture prevention trial with zoledronic acid in male osteoporosis. In the spirit of the Guideline, however, a bridging based on BMD alone was considered to be sufficient to extend the indication to the male population. For the elderly male population, hip fractures constitute a large public health problem and it can be concluded that similar to females, this population is in need of anti-osteoporotic treatment.

Magnitude of the BMD changes versus placebo
In relation to the BMD increases compared to placebo, the changes in total hip BMD in the zoledronic arm in the 2310 male population were significantly greater at all time-points. Comparing the results with the results for females in Study 2301, the increase in BMD was somewhat larger in females, except at 36 months but results derive from only 33 males for that comparison.

In clinical practice, it is primarily the femoral neck measurement that is used for assessing BMD in osteoporotic patients. For the femoral neck measurements, same observations are made, although at 24 months, the difference compared with placebo in males is primarily due to a decrease in BMD in the placebo group, actual increase in the active arm being only 1.42% at 24 months (compared with 3.38% for the females in Study 2301).

The risk factors for fractures, age and baseline BMD data were counterbalanced against the fact that all male patients had a low-trauma hip fracture at baseline, and as such the males in Study 2310 can be regarded a high-risk population. This is supported by the annualised fracture rates in the placebo arms, which were similar in both studies.

A main limitation was the lack of data on vertebral BMD measurements from Study 2310. This is only available from the supportive active controlled study in a different population of younger males, including males with secondary OP and with different entry criteria with respect to BMD. Supportive evidence is provided from Study 2308 regarding efficacy on lumbar spine BMD. These results, however, demonstrated similar increase in lumbar spine BMD compared to the comparator alendronate and compared with changes at the lumbar spine in post-menopausal females in study 2301.

For the bridging, comparison has been made to the population included in the main fracture prevention trial, Study 2301. Comparison with the female population in Study 2310 was also considered useful for the bridging. Male patients in Study 2310 were younger and had less osteoporosis at baseline compared with the females. This difference in baseline BMD, however, was less pronounced than when comparing baseline BMD in male patients with baseline BMD of females from Study 2301. Thus, the CHMP pointed out that the comparison with females in Study 2310 is more valid as the male population was more similar to the female population in the 2310 study.

The CHMP considered that the MAH has provided data for the absolute change in BMD from baseline for males and females during study period in studies 2310 and 2301 as requested. The absolute change in BMD for males and females were considered similar. Overall, the CHMP agreed that the between-treatment comparison of change in percentage total hip BMD relative to baseline did not differ significantly between males and females and considered that this criterion for bridging was fulfilled.

Limited data on fracture rate in males do not support any fracture reducing effect at this point in time. Females seemed to be at greater total risk of clinical fracture over time than males, so even if the majority of females in study 2301 had at least one prevalent vertebral fracture at baseline it remains to be proven that the fracture risk was similar in the male population in study 2310 and the post-menopausal female population in study 2301. An ongoing study with zoledronic acid in males using fracture as endpoint was considered to be able to answer this question in the future.

The (non-significant) reduction in clinical fractures in study 2310 was 15% in the male population in Study 2310 compared with 33% in Study 2301, however Study 2310 was not powered to show differences in fracture rates in subgroups. The fact that no significant effect on fracture rate in males could be observed is therefore reflected in the SPC section 5.1.

Extrapolation from the population of osteoporotic males after hip fracture to the general population of osteoporotic men

The question also arose whether males without a recent hip fracture would have the same risk for fracture. Therefore, a comparison between the males in 2310 and the general male osteoporosis population was conducted by the MAH.

Although there have been a high number of large observational studies conducted to examine women with post-menopausal osteoporosis, the number of large observational studies examining the determinants of fracture in men is limited. The first study to examine the risk of fracture solely in men has been the Osteoporotic Fractures in Men (MrOS) Study (*Orwoll, et al 2005*) which began recruiting patients in 2000 and is examining the causes of fracture in a cohort of 5995 men. A comparison of the baseline characteristics between this study and the men in Study 2310 is re-presented in Table 2-1.

Table 2-1 Comparison of baseline characteristics for male patients in Study 2310 to those participating in the Osteoporosis Fractures in Men Study (MrOS).

Baseline characteristics	Men participating in MrOS (N=5995)	Men participating in Study 2310 (N=508)
Height (cm) mean (SD)	174 (6.8)	173 (8.1)
Weight (kg) mean (SD)	83.2 (13.3)	73.7 (13.8)
BMI (kg/m^2) mean (SD)	27.4 (3.9)	24.7 (4.1)
Age (years) – n (%)		
< 75[1]	3477 (58.0)	260 (51.2)
≥ 75	2518 (42.0)	248 (48.8)
History of fracture – n (%)	1019 (17.0)	508 (100.0)
Femoral neck BMD (g/cm^2) mean (SD)	0.780 (0.1249)	0.691 (0.1222)
Total hip BMD (g/cm^2) mean (SD)	0.954 (0.1377)	0.770 (0.1433)

[1] Note that the lower age limit for the patient population in MrOS is 65 years while the lower age limit in Study 2310 is 50 years

While the BMD baseline data for the male populations in studies 2310 and MrOS were comparable, the CHMP however noted that the men in MrOS were nearly 10 kg heavier than the men in study 2310 and also had a significantly higher BMI. While all males in study 2310 had suffered a hip fracture, only 17 % of the males in the MrOS study had a history of fracture. The study populations were not compared for history of hormonal deficiency or glucocorticoid treatment. The comparison between baseline data in the two studies did not support a conclusion that the population of osteoporotic males after hip fracture in study 2310 is representative for the general population of osteoporotic men.

On the other hand, the Guideline only requests that the male osteoporotic population should have a fracture risk corresponding to the fracture risk in a population of postmenopausal women with an increased risk of fracture.

The CHMP therefore considered that the fracture risk for the studied group of osteoporotic males was comparable to the fracture risk in a population of postmenopausal women at increased risk of fracture.

Prevalence and characteristics of secondary osteoporosis in the male study population
Overall, 111/508 (21.9%) of male patients randomised in study 2310 had one or more factor contributing to the presence of secondary osteoporosis. The most common factor present contributing to secondary osteoporosis was Chronic obstructive pulmonary disease (COPD) which was present in 57/508 (11.2%) of the male patients. The proportion of males with hypogonadism in this cohort was 0.6%.

In two other randomised trials on treatment of male osteoporosis published so far, men with secondary osteoporosis except hypogonadism were excluded (Orwoll, et al 2003; Boonen, et al 2005). BMD T-scores for inclusion in the two studies ranged between -1 to -2.5 at the lumbar spine and was -2 at the femoral neck.

In the male cohort evaluated in Study 2310, the mean femoral neck BMD T-score was -2.31, indicative of a population at risk of osteoporotic fractures even without any pre-defined BMD entry criteria. In the two published studies, the fraction of men with hypogonadism ranged between 33 and 50%. The anti-fracture efficacy ranged between 89% relative risk reduction in the alendronate study to 53% for PTH(1-34). However, another study by *Ringe, et al (2002)* included a significant proportion of males with secondary osteoporosis (60%), and showed pronounced antifracture efficacy of the bisphosphonate tested with a 60% reduction of vertebral fractures after 1 year.

The male subpopulation of Study 2310 constitutes a group with baseline characteristics in between the two randomised trials and the study by *Ringe, et al (2002).* However, the data summarised above show

that inclusion of patients with a significant proportion of secondary osteoporosis in the study did not affect the antifracture efficacy of bisphosphonates.

The CHMP considered that males with osteoporosis in general have more secondary causes of osteoporosis than osteoporotic females. Comparison between the male population in study 2310 and the two male osteoporosis studies using other bisphosphonates with respect to secondary osteoporosis is difficult since men with other forms of secondary osteoporosis than that caused by hypogonadism were excluded from study participation in the latter studies.

On the other hand, the total number of men with secondary osteoporosis was not as high in study 2310 as in the two other male osteoporosis studies. It can be concluded that the patient population primarily consisted of elderly males with age-related (primary) osteoporosis. The MAH did not refer to the non-inferiority study 2308 in which a younger population was included and probably the proportion of patients with secondary osteoporosis was higher in that study, to support a general indication in males. Whether the patients had primary or secondary osteoporosis, however, was not considered of major importance in this case as long as the males were patients with low BMD and risk factors for future fractures. The male population in study 2310, consisting of elderly men with a recent low-energy trauma hip fracture, can be regarded as representative of a male population that would be considered for treatment with bisphosphonates.

Femoral neck BMD data
Femoral neck T-score baseline values were missing in approximately 12 % of the patients. 42 % of patients in the zoledronic acid group and 41 % of patients in the placebo group had baseline femoral neck T-score ≤ 2.5.

Altogether, approximately 24 % of the patients had missing values for femoral neck T-score or values > - 1.5 at baseline. To facilitate evaluation for male and female patients separately, baseline data was given separately for males and females.

According to the guideline, the suitable population for clinical trials are postmenopausal women at increased risk of experiencing osteoporotic fractures based on the known skeletal independent risk factors.

Having a prevalent fracture, in this study a hip fracture, is acknowledged in the guideline as a strong risk factor. All patients randomised in study 2310 suffered a low trauma (fragility) hip fracture, and thus are all considered to have osteoporosis according to the general consensus definition of osteoporosis. Using the Osteoporosis Guideline BMD criteria to define osteoporosis, 41.8% (888/2127 patients) of the ITT population (42.3% [451/1065] of zoledronic acid patients and 41.1% [437/1062] of placebo patients) had a femoral neck baseline BMD T-score < -2.5 and met this criteria. It should be noted that 12.2% (260/2127) of patients had no baseline femoral neck BMD measurement performed because of technical difficulties of obtaining a DEXA scan so soon after surgery.

The MAH also reviewed the history of additional previous fractures. The majority of patients randomised, 56% (598/1065) of the zoledronic acid group and 61% (648/1062) of the placebo group, reported no history of a fracture beyond their incident hip fracture. For those who did report a history of an additional fracture, the largest proportion (36% zoledronic acid patients and 32% placebo patients) reported only previous non-vertebral fracture(s). The remaining patients of this subgroup (8.4% zoledronic acid and 6.6% placebo) reported a previous vertebral fracture with or without a non-vertebral fracture. Thus, based on previous fracture history it appears that the zoledronic acid group had a slightly higher fracture risk at baseline.

Even if patients with a baseline femoral neck BMD T-score ≤ - 2.5 as well as patients with femoral neck BMD T-score > -2.5 at baseline had a significant lowering of the risk for clinical fracture, this does not mean that all T-score groups had their fracture risk lowered. Upon request of the CHMP, the patient group with baseline femoral neck BMD T-score > - 1.5 (12 % of the study population) was analysed separately by the MAH.

The number of female patients in study 2310 with a close to normal baseline femoral neck T-score (> -1.5) was similarly small in number (zoledronic acid N=91; placebo, N=84) to those with an unknown baseline femoral neck BMD (zoledronic acid N=103; placebo, N=99). Both sub-groups showed a reduced risk for a clinical fracture after treatment with zoledronic acid relative to placebo (44% for the missing baseline femoral neck BMD sub-group and 75% for baseline femoral neck T-score > -1.5 sub-group), however, neither sub-group was large enough to reach statistical significance. When the sub-groups were combined, the risk reduction with zoledronic acid relative to placebo (Hazards ratio of 0.46, 95% CI 0.23, 0.92) achieved statistical significance (p=0.025).

Patients with close to normal baseline femoral neck T-score as well as patients with unknown baseline femoral neck T-score had a reduced risk of clinical fracture after treatment with zoledronic acid relative to placebo but both groups were small and the results were not statistically significant.

Timing of infusion post fracture
For clinical practice, Study 2310 was considered important, as it was considered a major advantage if zoledronic acid could be administered immediately following a fracture. However such an approach has not been explored until now since in this study patients received zoledronic acid at a median time of more than 6 weeks after surgery (less than 5% received study drug between within 14 days from surgery).

The sub-group analysis with regard to the timing of administration after hip surgery suggested better efficacy when zoledronic acid is given more than 2 weeks after surgery[A20].

Currently it is very common for patients to leave hospitals after a fracture without osteoporosis prevention and subsequent follow-up has been found to be deficient. This may partly be explained by different specialities dealing with fractures and with medical treatment of osteoporosis.

The CHMP noted that patients were not randomised with regard to time from hip fracture surgery to first infusion of study drug. However, data suggested that for several of the study parameters, those patients who had their first infusion of zoledronic acid between 6 weeks and 90 days after hip surgery performed better than those who had their first infusion of zoledronic acid earlier than 6 weeks after hip fracture surgery.

The CHMP further noted that all zoledronic acid treated patients had significantly greater % change from baseline in femoral neck BMD than the placebo group. Patients who got their first zoledronic acid infusion later than 6 weeks after hip fracture surgery had markedly better % change from baseline in femoral neck BMD than those who got their first zoledronic acid infusion 6 weeks or less after the surgery.

In this respect, there were also concerns that bisphosphonates may affect fracture healing and this may be more relevant in the first period after a fracture. A recent *in vivo* study with zoledronic acid in a rat fracture model, suggested that timing of the dose played an important role in the modulation of callus properties, delaying the dose resulted in a stronger callus (*Amanat et al, 2007*). This study could possibly also explain the observed difference seen between those patients who had received their first dose of zoledronic acid early after hip fracture and those who received their first dose later due to a tendency of bisphosphonate accumulation in the healing fracture. This would prevent enough bisphosphonate to be taken up by the rest of the skeleton.

The 6-week timepoint was initially chosen by the MAH because at the time the final statistical analysis plan was created and blinded baseline data was reviewed, it was shown that six weeks was close to the approximate median time of infusion following hip fracture repair (median=46 days).

Almost all of the patients who received more than 3 study drug infusions received their first study drug infusion within 6 weeks of hip fracture repair. This is due to the fact that prior to the implementation of Amendment 3 in 2003, all patients were randomised within 6 weeks of dosing.

The CHMP agreed that imbalances in baseline factors were not significant and unlikely to explain any differences in BMD following infusion.. The observation that more patients were placed in rehabilitation centres after discharge in the ≤ 6 weeks group, could possibly be linked to worse healing. Only 42% were discharged to private residence compared with 56% in the > 6 weeks group.

The results regarding BMD confirm the findings of the sub-group analysis for fractures, i.e. that better efficacy is obtained when zoledronic acid is administered at a later stage (e.g. more than 6 weeks) compared with earlier after hip fracture. For total hip BMD at Month 12, the test for interaction was statistically significant.

The optimal timing of infusion following a recent hip fracture was therefore further discussed and it was also considered to include clear recommendation regarding administration of zoledronic acid following a hip fracture in the Product Information.

The MAH explored the timing of first infusion after surgical repair of hip fracture and has conducted more detailed analysis of BMD responses, fracture reduction and mortality in 2-week intervals and sensitivity analysis of the overall result excluding the first two weeks.

This analysis indicated that the small group of patients who received infusions within 2 weeks after fracture repair were different from patients receiving infusions later: a) they exhibited much higher variability in their responses; b) they had a significant higher mortality; c) they had more co-morbidities. Finally, analysing the anti-fracture efficacy and mortality benefit in patients infused later than 2 weeks yielded robust reductions for the primary endpoint, all fracture subgroups and mortality. This analysis shows that a 2 week cut-off for the first infusion after surgical repair of hip fracture is more appropriate than the 6 week cut-off proposed by the CHMP.

In conclusion, subgroup analyses at 2-week intervals revealed a consistent effect in favour of zoledronic acid on fractures and mortality, when the first dose was given 2 weeks or later after surgical hip fracture repair. Taking into consideration that Aclasta was not worse than placebo when patients were treated within 2 weeks after hip fracture surgery, the MAH proposed in the SPC that patients with a recent low trauma hip fracture should be dosed more than 2 weeks after hip fracture surgery. Thus, this was reflected in section 4.2 of the SPC.

The CHMP considered that in general, there is no need for immediate administration of bisphosphonates after fracture repair for the prevention of a subsequent fracture. The MAH has provided analyses based on total hip BMD data rather than femoral neck BMD data, however there is currently nothing to support superiority of one over the other for the diagnosis and management of osteoporosis. In this respect, results for total hip support a 2-week cut-off, while results for femoral neck support a 6 week cut-off. Based on the analyses, the MAH proposed a 2 week interval from fracture repair.

Overall, a relationship over time in terms of efficacy after different time points following hip fracture repair could be demonstrated, however it was considered difficult to find a clear cut-off for the timepoint of infusion. As a compromise, the lowest timeframe of infusion after hip fracture was determined to be 2 weeks. While it is acknowledged that any cut-off based on trends and indices, the CHMP recommended a cautious approach and therefore the median time of 6 weeks between the surgery and infusion in the study, was reflected in section 5.1 of the SPC to give further guidance to the treating physician.

Effect of timing of infusion on fracture rate

The reduction in clinical fractures, the primary endpoint, for which the study was powered, was maximal after 2 weeks. However due to the small subgroup sizes (range 100-500 patients) for the 2-week subgroups, the confidence limits all crossed 1 except for weeks 4-6. Moreover, of all groups, the ≤ 2 week group displayed the highest variation. Also, for the subgroups non-vertebral fractures, hip fractures and clinical vertebral fractures, no consistent variation of anti-fracture efficacy with time of infusion was seen, and the confidence intervals all crossed 1 with very few exceptions. For patients

receiving their first dose ≤ 2 weeks after surgical repair, the confidence intervals were consistently wider for all fractures. The lower limit, however, always crossed 1 in the ≤ 2week group.

The CHMP considered that the effects of timing of dosing on fracture rate show consistently less efficacy in the group of patients that received zoledronic acid 6 weeks or earlier from time of fracture. Overall, the difference was small but for the main osteoporotic fractures, vertebral fractures and hip fractures, the difference was more pronounced and is a concern. Despite the small numbers, there is a consistency and the increase in hip fracture rate by 37% plus a treatment-by-timing of infusion interaction that was statistically significant, add to the concerns. The additional analysis dividing groups into 2 weeks intervals also shows consistent results,

There is an increased risk for fractures compared with placebo for all types of fractures when patients received zoledronic acid 2 weeks or earlier following fractures. For vertebral fractures and hip fractures, a consistent decrease in fracture rate is observed only in the groups receiving zoledronic acid > 6 weeks after fracture, but the small numbers in each sub-group make interpretation difficult.

Effect of timing of first dose on mortality
When patients are dosed within 6 weeks of hip fracture repair, zoledronic acid-patients had a 10% lower risk of death than placebo-treated patients (Hazard ratio = 0.90, p=0.5472). When patients were dosed > 6 weeks after fracture repair, zoledronic acid-treated patients had a 46% lower risk of death than placebo-treated patients (Hazard ratio = 0.54, p=0.0022).

When the timing of infusion intervals are further subdivided into two-weeks intervals it could be shown that the reduction in the risk of death increases over time from an absolute risk reduction (ARR) of 0.3% within two weeks, to an ARR of 9.3% when dosing occurred more than 12 weeks from hip fracture repair. It should also be noted that in none of the timing intervals was the incidence death higher for zoledronic acid relative to placebo. Thus, consistent with what has shown earlier regarding the timing of infusion relative to reduction in the risk of fractures, the benefit is obtained from 2 weeks onward. The one exception to the results observed for fractures was that concerning mortality, there was no higher incidence of death for the small group of patients (N=102) who received their first study drug infusion within 2 weeks of hip fracture repair.

The analysis with respect to anti-fracture efficacy analysed for different fracture sites at entry did not show any interaction, but again, small numbers were considered to hamper the interpretation. The effects on mortality could be considered consistent with the anti-fracture efficacy by timing-of infusion, i.e. patients receiving zoledronic acid ≤ 6 weeks from fracture had only 10% reduced mortality compared with 46% reduction in the > 6 weeks group.

The results concerning delayed healing however did not cause a concern. Only 4% and 3.1% had delayed healing in the groups receiving infusion < 6 weeks versus > 6 weeks, respectively and furthermore, there was no difference compared with placebo in the < 6 weeks group.

The CHMP pointed out that both BMD data and fracture data however support caution, especially when giving zoledronic acid less than 2 weeks from the time of fracture. Furthermore, patients receiving zoledronic acid needed more rehabilitation and mortality was similar to placebo in the group of patients receiving zoledronic acid < 6 weeks from fracture.

For osteoporotic fractures (hip and vertebral), efficacy became only evident in the group receiving zoledronic acid > 2 weeks after the incident fracture and thus it could even be considered to restrict the use of zoledronic acid to 2 weeks following a fracture, however , the study was not powered to show a reduction in clinical fractures in men. [A24]

Indication in female patients
The results of this study in a sub-population at high risk for fractures confirm the results of the larger study 2301 in postmenopausal women, which was previously assessed for the approval of zoledronic acid for the treatment of osteoporosis in postmenopausal women at high risk for fractures. Approval of a new indication based on study 2310 was questioned as the current indication already includes

patients with osteoporosis at high risk for fractures. Comparing study populations in study 2301 and study 2310, the main difference is the recent hip fracture and the inclusion of male patients. Both osteoporosis and previous fractures are well known risk factors for fractures. In both studies 2301 and 2310 the proportion of patients with osteoporosis based on T-score and/or previous fractures was high (70% and 63% in study 2301 and 42% and 100% in study 2310). Currently, the study 2310 is only considered supportive of the study 2301. A substantial number of study patients were considered to be covered by the present indication "Treatment of osteoporosis in post-menopausal women at increased risk of fracture". Additionally, the initially proposed indication wording relating to prevention of Osteoporosis was not in line with the "Guideline on the evaluation of new medicinal products in the treatment of primary osteoporosis"

The CHMP therefore considered that study 2310 did not support a new indication for women, as the study population consisted of patients with osteoporosis and at high risk of fracture, which would already fall under the wording of the current indication.

The CHMP considered it acceptable that the initially proposed two indications "Prevention of clinical fractures after hip fractures caused by low energy trauma in women over the age of 50" and "Treatment of osteoporosis in postmenopausal women at increased risk of fracture" were merged into one common indication in accordance with the guideline on the evaluation of medicinal products in the treatment of primary osteoporosis CPMP/EWP/552/95 Rev. 2. The MAH highlighted that no other prospective designed trial has studied the effects of bisphosphonate treatment on subsequent fracture risk in patients with a prevalent hip fracture until this point in time.
The CHMP proposed that additional information to be included in section 4.1 of the SPC should be more exact than the wording proposed by the MAH. The following wording is suggested: "Treatment of osteoporosis in post-menopausal women at increased risk of fracture, including those with a recent hip fracture" This wording was considered to be in line with the latest version of SPC Guidelines for section 4.1. Taken together with the indication in males, the CHMP agreed on the final wording

"Treatment of osteoporosis
- in post-menopausal women
- in men

at increased risk of fracture, including those with a recent low-trauma hip fracture."
This wording was accepted by the MAH.

Further secondary endpoints
The CHMP considered also that the results for the secondary endpoints relating to changes in BMD and fractures confirm the results for the primary efficacy endpoints, showing a reduction in risk of clinical fractures at various sites (vertebral, non-vertebral), although for hip fractures, the reduction was not statistically significant. BMD increased in the zoledronic acid group and decreased in the placebo group as expected based on previous trials. The increase seemed to level off during the 3rd year but only few patients were left in the study at that time.

Concerning the analyses on resource utilisation and Quality of Life (QoL), these are difficult to evaluate as they were only performed on certain study sites and the proportion of patients having received their first infusion of drug early or late differed markedly between study centres. The QoL measurement method used was a simple VAS scale rating method measuring "total QoL" as a single index value.

The CHMP further pointed out that the clinical relevance of a 4% reduction in emergency room (ER) visits in the zoledronic acid group is considered questionable and is not supported by other measures of resource utilisation.

Study 2308

Although the study did not include a placebo arm, study 2308 was considered supportive of the efficacy of zoledronic acid in increasing BMD in males. The mean lumbar spine, total hip and femoral neck BMD % increase from baseline for zoledronic acid at months 12 and 24 were comparable

between studies 2308 and 2301. Lumbar spine results were considered important as these are lacking from Study 2310. Biomarker profile following infusion is similar to what has previously been observed in post-menopausal females. The rate of new morphometric fractures was similar to the rate in post-menopausal females, although the few cases make any interpretation in this respect uncertain. Information on lumbar spine BMD data from Study 2308 was included in the SPC (section 5.1)".

Clinical safety

The major safety population for this indication was provided by the pivotal placebo-controlled trial, **Study 2310**. An independent adjudication committee for the following ADRs was established: hypocalcaemia, ocular AEs, avascular necrosis and delayed union/non-union, osteonecrosis of the jaw (ONJ), Cardiac arrhythmia and atrial fibrillation, renal AEs, cardiac/cardiovascular and stroke-related AEs. For the demonstration of safety in men, Safety data from the male study 2308 were pooled with safety data from the male subpopulation in study 2310. In addition, final safety data from the trial for the treatment of PMO, **Study 2301** were also included, for side-by-side comparison with Study 2310, as well as pooled safety data from these studies. The safety data from Study 2301 have previously been assessed in a type II variation to extend the indication to include PMO (EMEA/H/C/595/II/010).

Study 2310

Patient exposure
The safety population included 2111 patients who were exposed to at least one study drug infusion. In Study 2310, 89.5% of patients received the first infusion between 14 and 90 days after hip fracture surgery. 1054 patients received zoledronic acid and 1057 patients received placebo. 616 patients received only one infusion, 850 received two infusions, 569 received three, 77 received four and one patient received five infusions of study drug. Mean exposure to study drug was 1.95 years for zoledronic acid- as well as for placebo -treated patients in the study. The mean exposure to study drug was 1.95 patient years. [A27]

Overall, of the ITT population in Study 2310, 1516 (71.3%) randomised patients completed the study, 244 patients (11.5%) died, and an additional 367 (17.3%) patients discontinued from the study. Most of the patients who discontinued had only received the first infusion.

Adverse events
Overall, the percentage of patients experiencing AEs was similar in the zoledronic acid group (82.3%) and placebo group (80.6%) in Study 2310.

The most frequently affected primary system organ classes (PSOCs, ≥ 20.0%) were 'musculoskeletal and connective tissue disorders', 'infections and infestations', 'injury, poisoning and procedural complications', 'general disorders and administration site conditions', 'gastrointestinal disorders', and 'nervous system disorders'. Among these frequently affected PSOCs, 'general disorders and administration site conditions' was the only PSOC with more than 5% difference between the treatment groups (25.1% zoledronic acid vs. 18.3% placebo).

The most frequently occurring AEs (≥ 2.0% for any group) included pyrexia, bone pain, musculoskeletal pain, and hyperthermia, which occurred with a more than twofold higher incidence in the zoledronic acid group vs. the placebo group. Osteoporosis, dizziness and chronic obstructive pulmonary disease each occurred with a twofold higher incidence in the placebo group vs. the zoledronic acid group.

Overall, within the first 3 days of any study drug infusion, 26.7% of zoledronic acid-treated patients experienced at least one AE compared with 19.1% in the placebo group. The difference between the treatment groups is accounted for by the approximate fourfold greater incidence in the general disorders and administration site conditions system organ class: 12.14% of patients in the zoledronic acid group compared with 3.12% in the placebo group.

Within 3 days of the first study drug infusion, the incidence of AEs was 19.45% for zoledronic acid vs. 10.06% for placebo. After the second drug infusion, the incidence of AEs within 3 days decreased to more comparable rates between the treatment groups (10.42% for zoledronic acid and 9.96% for placebo). After the third study drug infusion, the incidence of AEs within 3 days was 10.77% for zoledronic acid and 9.01% for placebo.

The rates of cardiac failure, chest pain and atrial fibrillation were similar in both groups, although slightly higher in the zoledronic acid group. The rate of cerebrovascular accident was slightly higher in the placebo group. Rate of decreased creatinine clearance was slightly higher in the zoledronic acid group while renal failure was slightly higher in the placebo group.

The majority of patients who experienced AEs had events that were mild (17.36% vs. 16.27%) or moderate (34.63% vs. 30.94%) in severity for zoledronic acid versus placebo, respectively. The overall reporting frequency for patients with severe AEs was 30.27% for the zoledronic acid group and 33.40% for the placebo group. The PSOCs with a more than 1% difference in the incidence of severe AEs in the zoledronic acid group versus the placebo group were cardiac disorders (5.88% vs. 8.51%, respectively) and nervous system disorders (3.80% vs. 5.20%, respectively).

The difference within the severe cardiac disorders PSOC appears to be driven by lower incidences of severe congestive heart failure and myocardial infarction in the zoledronic acid vs. placebo group (8 patients in the zoledronic acid group vs. 13 patients in the placebo group for both terms). The difference within the nervous system disorders may have been driven by the greater number of patients reporting cerebrovascular disorders in the placebo group (0 patients in the zoledronic acid group vs. 4 patients in the placebo group).

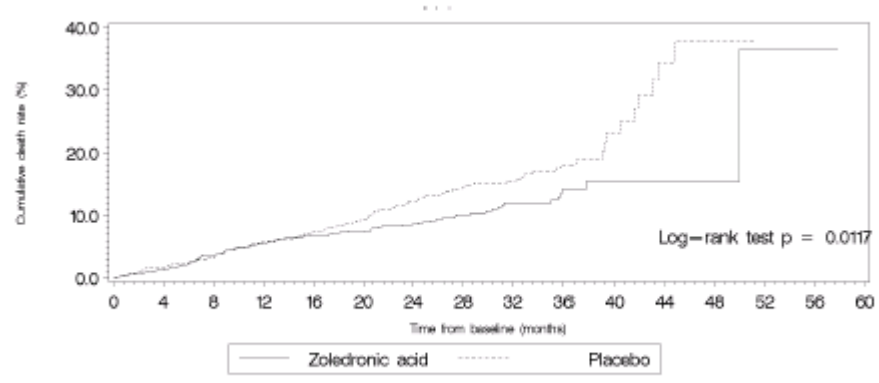
Serious adverse events and deaths
The overall mortality rate was lower in the zoledronic acid group (101 patients, 9.58%) compared with the placebo group (141 patients, 13.34%). Causes of death for the most common PSOC involved, cardiac disorders, occurred with at least a two times higher incidence than for any other PSOC, and the incidence was lower for the zoledronic acid group (36 patients, or 3.42%) compared with the placebo group (52 patients, or 4.92%).

The most common principal causes of death (≥ 0.5%) included cardiac arrest, cardiac failure, cardio-respiratory arrest, sepsis, pneumonia, cerebrovascular accident, and respiratory failure. Of these, a twofold or greater difference for zoledronic acid vs. placebo was seen for sepsis (8 [0.76%] patients vs. 4 [0.38%] patients) and cerebrovascular accident (6 [0.57%] patients vs. 3 [0.28 %] patients), and a twofold or greater difference for placebo vs. zoledronic acid was seen for cardio-respiratory arrest (5 [0.47%] patients vs. 11 [1.04%] patients), and pneumonia (4 [0.38%] patients vs. 8 [0.76%] patients).

Analysis confirmed a significant 28% decreased risk of death (Hazard ratio 0.72, 95% CI: 0.56 to 0.93, p=0.0117) with zoledronic acid compared to placebo. The cumulative death rate for both treatment groups over time is shown in Figure 12-1. There is a separation of the two treatment groups beginning at approximately Month 16, which is approximately 12 months after the earliest separation of the two treatments groups in time to first clinical fracture (approximately Month 4) and paralleled each other.

It should be noted that after Month 36 (Day 1080), the changes in the Kaplan-Meier curves become oversensitive to the occurrence of death due to the small number of patients who were still being followed up in the study after that time point (149 on placebo and 144 on zoledronic acid). As such, every death that occurs has considerable influence on the cumulative incidence of deaths as well as the shape of the Kaplan-Meier curves.

Figure 12-1 Cumulative death rate (Safety population)



– P-value is from log-rank test.
– Cumulative discontinuation rate is estimated from Kaplan-Meier approach.

Zoledronic-acid treated patients who received their first study drug infusion more than 6 weeks after hip fracture surgery had a 46% reduction in death compared to the placebo-treated patients, shown by an estimated hazard ratio of 0.54 (95% CI: 0.36 to 0.81, p=0.0022). Zoledronic acid-treated patients who received their first study drug infusion within 6 weeks following hip fracture surgery had a lower reduction in the risk of death, as shown by an estimated hazard ratio of 0.90 (95% CI, 0.65 to 1.26, p=0.5472).

SAEs were reported most frequently in the following PSOCs (data are presented for zoledronic acid vs. placebo, respectively): 'injury, poisoning and procedural complications' (10.8% vs. 13.2%), 'infections and infestations' (9.3% vs. 9.3%), 'cardiac disorders' (9.1% vs. 10.0%); 'nervous system disorders' (6.9% vs. 6.7%), and 'musculoskeletal disorders' (6.4% vs. 5.7%).

For the most frequently reported SAEs (≥ 1.0%) he overall frequency of SAEs was comparable for the zoledronic acid (38.33%) and placebo (41.25%) treatment groups. For the five most frequently reported SAEs (pneumonia, post-procedural complication, arthralgia, cerebrovascular accident, and congestive cardiac failure) in the zoledronic acid group, there were no major differences compared to the placebo group. The overall incidence of stroke related SAE was slightly higher in the zoledronic acid group when compared to placebo (4.4% vs. 3.6%, respectively).

SAEs suspected to be related to study drug occurred for 8 (0.76%) patients in the zoledronic acid group and 9 (0.85%) patients in the placebo group.

Discontinuation due to AEs
The most common AEs leading to premature discontinuation from study drug (≥ 0.25%) are presented in Table 12-10. Patients who discontinued from study drug were encouraged to remain in the study for safety and efficacy follow-up evaluations. The percentage of patients discontinuing treatment due to AEs was comparable between treatment groups (5.31% vs. 4.73%).

Table 12-10 Most frequent AEs (at least 0.25% in any group) leading to premature discontinuation from study drug (Safety population)

Preferred term	Zoledronic acid N=1054 n (%)	Placebo N=1057 n (%)
Total no. of patients with an AE leading to discontinuation from study drug	56 (5.31)	50 (4.73)
Creatinine renal clearance decrease	5 (0.47)	4 (0.38)
Renal failure	5 (0.47)	2 (0.19)
Sepsis	4 (0.38)	1 (0.09)
Cardiac failure	3 (0.28)	1 (0.09)
General physical health deterioration	3 (0.28)	0 (0.00)
Cardiac arrest	2 (0.19)	3 (0.28)
Cerebrovascular accident	2 (0.19)	4 (0.38)
Cardio-respiratory arrest	0 (0.00)	4 (0.38)

Laboratory findings
The number of patients with selected laboratory tests meeting the 'clinical notable' criteria were summarised by treatment. For a patient to meet the criteria for a clinically notable change, the patient's baseline value for that parameter must not have been clinically notable. Guidelines for clinically notable criteria for laboratory tests are based on the Division of Neuropharmacology Guidelines for 'Markedly Abnormal' clinical laboratory values for adults in SI units.

No post-baseline haematology and urinalysis measurements were planned in the study.

With the exception of high calcium, there were no clinically relevant differences between the treatment groups for any of the parameters, which had patients meeting the criteria[A30].

Ocular Adverse Events
In Study 2310, most cases of ocular Adverse Events were conjunctivitis (infectious, irritant, and allergic), blepharitis, and eye pain. No cases of uveitis or iridiocyclitis were reported in either treatment group. The overall incidence of confirmed ocular AEs was low in the zoledronic acid and placebo groups (21 [2.0%] vs. 16 [1.5%], respectively). Of these, 4 (0.4%) zoledronic acid-treated patients and 1 (0.1%) placebo-treated patient had ocular events that were considered possibly or probably related to study drug by blinded expert review. Of the ocular conditions known to be related to bisphosphonate use, only one case of moderate iritis, in a zoledronic acid treated patient, was found to be clinically significant and possibly related to study drug by adjudication.

Within 3 days of study drug infusion, the only confirmed event observed in Study 2310 was eye pain in one zoledronic acid patient.

In study 2301, ocular events suspected to be related to zoledronic acid was seen in 0.7 % of the zoledronic acid treatments. Most of these events were conjunctivitis and the majority of the events occurred within 2 weeks after infusion of zoledronic acid and were transient.

Hypocalcaemia
In Study 2310, 9 (0.9%) patients in the zoledronic acid group and 3 (0.3%) patients in the placebo group experienced hypocalcaemia adverse laboratory events. Of these, 3 (0.3%) patients in the zoledronic acid group and no patient in the placebo group had confirmed events of hypocalcaemia.

For one of these three zoledronic acid-treated patients with confirmed hypocalcaemia, the event occurred on the day following the first day of treatment and resolved within 5 days. This event was mild, and was thought to be related to study medication. For the other two zoledronic acid-treated patients, the events occurred more than 50 days after an infusion, and were considered not to be related to study medication.

Only one of the three patients had symptomatic hypocalcaemia. This patient, who became acutely hypocalcaemic one day after a radical thyroidectomy (due to thyroid malignancy), was successfully treated with intravenous calcium. The event occurred 360 days after her first dose of study medication, and was suspected to be related to the thyroidectomy.

The rate of hypocalcaemia was lower than in study 2301 which is not surprising as hypocalcaemia was an exclusion criterion in study 2310. Symptomless hypocalcaemia was seen in 2.3 % of patients after first study drug infusion in the zoledronic acid group in study 2301, compared to an incidence of 0.3 % after the second and 0.1 % after the third infusion.

Avascular necrosis and delayed union/non-union
In Study 2310, a total of 23 (2.2%) patients in the zoledronic acid group and 26 (2.5%) patients in the placebo group had AVN events. All but three patients in each treatment group had AVN involving the hip. Six (0.6%) patients in the zoledronic acid group and 3 (0.3%) patients in the placebo group had adjudicated confirmed events of AVN all of which involved the hip.

The percentage of patients with delayed healing of the study entry hip fracture confirmed by adjudication was comparable for the two treatment groups (34 [3.2%] in the zoledronic acid group vs. 29 [2.7%] in the placebo group).
From the search of the clinical trial database, a total of 9 (0.9%) patients in the zoledronic acid group and 8 (0.8%) of placebo patients experienced delayed union/nonunion. Of the 9 cases of delayed union/non-union in the zoledronic acid group, 7 were incident hip, 1 was contralateral hip, and 1 was in the humerus. Of the 8 cases in the placebo group, 3 were wrist, 2 were shoulder, 2 were incident hip, and 1 was contralateral hip. The cases that were adjudicated as confirmed events of delayed union/nonunion were: 3 (0.3%) patients in the zoledronic acid group (2 incident hip and 1 humerus) and 3 (0.3%) patients in the placebo group (1 incident hip, 1 contralateral hip, and 1 shoulder).
Combining the information obtained from both methods, a total of 36 (3.4%) patients in the zoledronic acid group and 30 (2.8%) patients in the placebo group had adjudicated confirmed delayed hip fracture healing or delayed union/nonunion of the incident hip.

Osteonecrosis of the Jaw (ONJ)
In Study 2310, the search of the safety database revealed maxillofacial events in a total of 6 (0.6%) patients in the zoledronic acid group and 11 (1.0%) patients in the placebo group. One patient in the placebo group had an event adjudicated as indeterminate, while the remaining events were adjudicated as not clinically relevant cases of ONJ.

Renal events
In Study 2310, long-term renal safety was evaluated by monitoring changes in serum creatinine and calculated Creatinine Clearance (CrCl) annually within 4 weeks prior to each scheduled study drug infusion in addition to evaluating reported AEs that met the pre-specified criteria for change in renal function. The following laboratory criteria were developed to monitor for significant declines in renal function:
• increase in serum creatinine > than 0.5 mg/dl relative to baseline,
• treatment-emergent calculated CrCl < 30 ml/min, or
• decrease in CrCl ≥ 30% and CrCl ≤ 60 ml/min at baseline.

Measurements of serum creatinine and calculation of GFR were made at baseline and then once yearly, before each study drug infusion.

The overall incidence rates for each of the three categories of renal abnormalities at any time during the study were comparable for the two treatment groups. There was no evidence of an increased risk for renal impairment with zoledronic acid treatment even in those patients with mild-to-moderate renal impairment (baseline CrCl of ≥ 35 ml/min).

Adverse events associated with a change in renal function were similar in both groups with 60 patients (5.69%) in the zoledronic acid group compared to 61 patients (5.77%) in the placebo group. Events reported in more than 1.0% of the patients in either treatment group were: decreased creatinine renal clearance (22 [2.09%] zoledronic acid vs. 18 [1.70%] placebo), renal failure (17 [1.61%] zoledronic acid vs. 24 [2.27%] placebo), and acute renal failure (12 [1.14%] zoledronic acid vs. 15 [1.42%] placebo).

A total of 160 (15.18%) patients in the zoledronic acid group and 146 (13.81%) patients in the placebo group had renal events (renal function AEs and/or pre-determined laboratory abnormalities) that were sent to the adjudication committee for review. Of these, 87 (8.25%) patients in the zoledronic acid group and 90 (8.51%) patients in the placebo group had confirmed clinically significant renal events.

Cardiac arrhythmia and atrial fibrillation
Overall, in Study 2310, cardiac arrhythmia AEs were reported in fewer zoledronic acid treated patients (72 [6.8%]) than placebo-treated patients (85 [8.0%]). With the exception of a higher incidence of tachycardia in the zoledronic acid group (7 [0.7%] than the placebo group (3 [0.3%]) and a comparable incidence of atrial fibrillation in the zoledronic acid group (29 [2.8%] and the placebo group (27 [2.6%]), all common arrhythmias occurred at a lower rate in the zoledronic acid group compared to the placebo group.

A total of 24 (2.28%) patients in the zoledronic acid group and 39 (3.69%) patients in the placebo group had arrhythmia SAEs. Of these, 19 (1.80%) patients in the zoledronic acid group and 28 (2.65%) patients in the placebo group had adjudicated confirmed arrhythmia SAEs. The most common arrhythmia SAE confirmed via adjudication was atrial fibrillation. The incidence of atrial fibrillation SAEs was lower in the zoledronic acid group compared to placebo (11 [1.0%] vs. 13 [1.2%], respectively). Within 30 days following study drug infusion, all three patients with arrhythmia SAEs in Study 2310 were in the placebo group (and none occurred in the zoledronic acid group). In both studies, more than 90% of the arrhythmia SAEs, including atrial fibrillation, occurred more than 30 days after infusion.

Safety in men with osteoporosis

Safety data from study 2308 were pooled with safety data from the male subpopulation in study 2310 to provide an integrated safety profile. Despite the differences in study design and population in the two studies, the combination of the data from both studies increased the number of patients in the zoledronic acid treatment group in the analysis, and therefore maximised the chance of identifying potential safety signals specific to the male osteoporosis population. The information from the individual studies was presented by the MAH along with the pooled results for zoledronic acid from the two studies.

The overall extent of drug exposure from all studies in male osteoporosis is shown in Table 4.15. A total of 397 male patients received 5 mg zoledronic acid/100 ml once-yearly as an i.v. infusion over 15 minutes.

Table 4. 15. Overall patient exposure to study drug.

	Zoledronic Acid	Alendronate	Placebo
Male osteoporosis			
2308 (Safety population)			
No. patients	153	148	0
Mean exposure years	1.93	1.88	
Total patient years	294.5	278.3	
2310 (Male patients)			
No. patients	244	0	261
Mean exposure years	1.88		1.93
Total patient years	459.6		503.6
Overall Male OP safety population			
No. patients	397	148	261
Mean exposure years	1.90	1.88	1.93
Total patient years	754.2	278.3	503.6

Exposure years for each patient are defined as the number of days of follow-up divided by 365.25.

Demographic characteristics were similar between treatment groups of the individual studies. Patients in Study 2310 were approximately 8-9 years older than patients in Study 2308; approximately 49% of male patients in Study 2310 were ≥ 75 years of age, while only approximately 16% of patients in Study 2308 were ≥ 75 years of age. The mean and median weights and body mass index (BMI) were slightly lower in Study 2310 relative to Study 2308

The treatment groups within each individual study were well matched and similar with respect to creatinine clearance and serum calcium. Overall, the majority of patients in both studies had normal baseline renal function, as defined by a baseline creatinine clearance ≥ 60 ml/min. For those with baseline renal impairment, patients in study 2310 tended to have more pronounced renal impairment (lower creatinine clearances) which is attributed to its generally older patient population.

The three most commonly used concomitant medications during the studies other than calcium or vitamin D supplementation were over-the-counter medications which included paracetamol,

acetylsalicylic acid, and ibuprofen. Of note, unless contraindicated, patients in study 2310 were given the standard labelled dose of oral paracetamol at each infusion of study medication, and instructed to use it for up to 72 hours afterwards as needed. In study 2308, at the discretion of the investigator, acetaminophen in usual labelled doses was allowed for the management of post-dose symptoms.

Adverse Events
The percentage of patients experiencing at least one AE was highest in patients receiving alendronate (93.2%) and lowest in the placebo group (80.5%) relative to zoledronic acid (86.9%). However, in the individual studies, the percentage of patients experiencing at least one AE was comparable between treatment groups. In study 2308, the percentage of patients experiencing at least one AE was 93.5% in the zoledronic acid group, and 93.2% in the alendronate group.

In the male population of study 2310, the percentage of patients experiencing at least one AE was 82.8% in the zoledronic acid group, and 80.5% in the placebo group. The incidence of AEs in Study 2310 was lower than that observed in Study 2308, presumably due to the recommended use of acetaminophen (paracetamol) to prevent the occurrence of post-dose symptoms in Study 2310.

The most frequently affected PSOCs were musculoskeletal and connective tissue disorders, general disorders and administration site conditions, infections and infestations, gastrointestinal disorders, and nervous system disorders. Among these frequently affected PSOCs, general disorders and administration site conditions was the only PSOC with a 10% or greater incidence in the total zoledronic acid group than either other treatment group (37.3% zoledronic acid vs. 27.0% alendronate vs. 19.9% placebo).

This difference was mainly driven by a higher occurrence of pyrexia fatigue, and pain, often associated with post-dose symptoms observed with i.v. and high dose oral bisphosphonates. In Study 2308, there was a 10% or greater incidence of nervous system disorders in the zoledronic acid group (37.3%) relative to the alendronate group (19.6%), which was mainly driven by a higher incidence of headache in the zoledronic acid group (15.0%) relative to the alendronate group (6.1%).

Events suspected to be drug related
Such AEs occurred in 34.5 % of zoledronic acid- and in 26.4 % of placebo-treated patients. The incidence of AEs was highest following the first infusion (zoledronic acid 79.6 %, alendronate 83.8 %, placebo 69.7 %). Between the second and third infusion, the incidence of AEs decreased (zoledronic acid 63.7%; alendronate, 72.0%; placebo, 60.3%). Following the third infusion, the incidence decreased further to 54.4% for zoledronic acid and 50.0% for placebo. Within 3 days of any infusion, the incidence of pyrexia (11.3 %) and myalgia (8.3 %) in zoledronic acid-treated patients were more than 3 times those of alendronate- or placebo-treated patients.

Mitigation of post-dose symptoms[A31]
In order to mitigate the incidence of post-dose symptoms in studies 2310, H2313 and H2315, patients were provided with oral paracetamol at the time of i.v. administration of study medication, and were instructed to use as needed for the next 72 hours. The incidence of AEs which started within 3 days of the first study drug infusion in all three studies was less than 2-fold higher in the zoledronic acid group than in the comparator group: 19.5% vs. 10.6% in study 2310; 36.3 % vs. 21.4% in study H2313; and 63.8% vs. 37.3% in study H2315. In study H2407, patients were provided with oral paracetamol or ibuprofen at the time of i.v. administration of study medication, and were instructed to use as needed for the next 72 hours. The incidence of AEs was more than 2-fold higher in patients treated with zoledronic acid but without analgesics (60.7%) than in the placebo group (25.0%); however, the incidence was lower in patients treated with zoledronic acid and paracetamol (46.6%) or ibuprofen (44.1%).

Deaths
The male populations in study 2308 and study 2310 differed in terms of mortality and cardiovascular/cerebrovascular event risk. The Study 2310 population was at a higher risk of mortality due to their older age and a recent hip fracture at randomisation, as compared to the Study 2308 population, which included patients with osteoporosis, but did not require a recent hip fracture.

A greater proportion of the patients in Study 2310 ≥ 75 years of age which, when combined with the higher baseline rates of hypertension, diabetes, coronary artery disease, and previous stroke, implies that the Study 2310 population was at a higher risk for subsequent cardiovascular/cerebrovascular events than the Study 2308 population.

A total of 84 patients died, primarily in study 2310. In study 2308, only one patient in each treatment group died (zoledronic acid group, respiratory failure; alendronate group, pulmonary embolism).
In Study 2310, the percentage of patients in the zoledronic acid group who died was less than that in the placebo group (zoledronic acid group, 13.1%; placebo group, 19.5%). The causes of death per investigator that occurred in more than one patient in the zoledronic acid group included respiratory failure, pneumonia, sepsis, cardiac arrest, cardiac failure, and cerebrovascular accident.

The overall death rate adjusted for exposure was lower in Study 2308 (both zoledronic acid and alendronate groups, death rate per patient year < 0.01 per patient year) than in Study 2310 (death rate per patient year, 0.07 in the zoledronic acid group vs. 0.10 in the placebo group). This would be expected due to the greater mortality risk given their recent hip fracture, greater prevalence of multiple cardiovascular and cerebrovascular risk factors, and the greater age of the patient population in Study 2310.

Adjudicated cause of death
The majority of the causes of death were adjudicated as 'other' or 'unknown'. The total number of deaths to be due to a cardiac condition was ten, two in the zoledronic acid group and eight in the placebo group (Table 4-25). Two deaths, one in the zoledronic acid group and one in the placebo group, were adjudicated as being cerebrovascular.

Table 4. 25. Underlying disease that initiated the sequence of pathological events leading to death confirmed via adjudication, male OP safety population.

	Study 2308		Study 2310 (male only)		Total
Underlying disease	Zoledronic Acid N=153 n (%)	Alendronate N=148 n (%)	Zoledronic Acid N=244 n (%)	Placebo N=261 n (%)	Zoledronic Acid N=397 n (%)
Total no. of patients	1 (0.7)	1 (0.7)	32 (13.1)	51 (19.5)	33 (8.3)
Due to cardiac	0 (0.00)	0 (0.00)	2 (0.8)	8 (3.1)	2 (0.5)
Due to cerebrovascular	0 (0.00)	0 (0.00)	1 (0.4)	1 (0.4)	1 (0.3)
Other	1 (0.7)	0 (0.00)	13 (5.3)	17 (6.5)	14 (3.5)
Unknown	0 (0.00)	1 (0.7)	16 (6.6)	25 (9.6)	16 (4.0)

- N= the number of patients in the analysis population
- n= the number of patients meeting the criterion
- (%)= 100*n/N

Renal AEs
The following criteria were used to search the clinical database in order to identify cases:
• Laboratory findings of a) an increase in serum creatinine of > 0.5 mg/dl, b) a calculated CrCl < 30 ml/min or c) a CrCl ≤ 60 ml/min at baseline and a post-baseline decrease in CrCl ≥ 30 % or significant proteinuria as urine dipstick > 2+
• Occurrence of AEs associated with a change in renal function

For the pooled male osteoporosis populations, laboratory renal criteria of increase in serum creatinine > 0.5 mg/dl were reported for 23 (6.4%)zoledronic acid, 1 (0.7%) alendronate and 16 (7.4%) placebo patients, CrCl < 30 ml/min for 9 (2.6%) zoledronic acid, 1 (0.7%) alendronate and 11 (5.1%) placebo patients, and baseline CrCl ≤ 60 ml/min and declined ≥ 30% for 10 (15.6%) zoledronic acid, 1 (5.9%) alendronate, and 12 (17.9%) placebo patients, and were sent to the adjudication committee for review.

While the incidence of patients who met one of the laboratory criteria was higher for the zoledronic acid group compared to alendronate (due to the transient increases in 9-11 day labs in study 2308 in the zoledronic acid group), it was comparable to placebo. Of note, Study 2310 did not include 9-11 day labs so no transient rises in serum creatinine were observed. Clinically significant renal laboratory events confirmed by the adjudication committee are presented in table 4. 27. In study 2308, the proportion of patients who demonstrated an increase in serum creatinine from baseline > 0.5mg/dl was higher in the zoledronic acid group (7 patients, or 4.6%) compared with the alendronate group (1 patient, or 0.7%) (study 2308). This was driven by a higher number of patients in the zoledronic acid group with transient creatinine elevations 9-11 day post-infusion, which subsequently decreased to baseline or near baseline levels. For each of these patients, the increase in serum creatinine was adjudicated as possibly or probably related to study drug (table 4. 27). The overall incidences for the other laboratory categories at any time during the study were low and comparable for both treatment groups in study 2308: CrCl <30 ml/min for 1 (0.7%) of patients in both treatment groups, and decrease in CrCl ≥ 30% and ≤60 ml/min at baseline for 1 (5.6%) zoledronic acid and 1 (5.9%) alendronate patient (study 2308).

Table 4. 27. Renal laboratory criteria confirmed as a clinically significant renal event by adjudication; male OP safety population.

	Study 2308		Study 2310 (male only)		Total
	Zoledronic Acid N=153 n (%)	Alendro-nate N=148 n (%)	Zoledronic Acid N=244 n (%)	Placebo N=261 n (%)	Zoledronic Acid N=397 n (%)
Overall	7 (4.6)	2 (1.4)	20 (8.2)	23 (8.8)	27 (6.8)
Renal adverse event*	7 (4.6)	2 (1.4)	20 (8.2)	23 (8.8)	27 (6.8)
Increase in serum creatinine > 0.5 mg/dl	7 (4.6)	1 (0.7)	17 (7.0)	21 (8.0)	24 (6.0)
Creatinine clearance < 30 ml/min	2 (1.3)	1 (0.7)	4 (1.6)	11 (4.2)	6 (1.5)
Baseline CrCl <=60 and declined >= 30%	6 (3.9)	1 (0.7)	10 (4.1)	16 (6.1)	16 (4.0)
Significant proteinuria	1 (0.7)	0 (0.0)	1 (0.4)	1 (0.4)	2 (0.5)

- N = the number of patients in the analysis population.
- n=the number of patients with the event.
(%) = 100*n/N.
* The adjudication committee determined that a clinically significant renal adverse event had occurred independent of an event being reported by the investigator.

AEs associated with a change in renal function based on the pre-specified MedDRA search criteria were summarised by the MAH for the safety population of MO. The incidence was 19 (4.8%) in the zoledronic acid group, 6 (4.1%) in the alendronate group, and 16 (6.1%) in the placebo group. The incidence of AEs associated with a change in renal function and confirmed by adjudication was 10 (2.5%) in the zoledronic acid group, 2 (1.4%) in the alendronate group, and 12 (4.6%) in the placebo group. AEs (based on the pre-specified MedDRA search criteria) associated with a change in renal function confirmed by adjudication were examined by infusion. There was no evidence of increased incidence of events with greater cumulative exposure to zoledronic acid with 6 (1.5%) patients in the zoledronic acid group compared to 8 (3.1%) patients in the placebo group having events between the 1st and 2nd dose and 4 (1.3%) patients in the zoledronic acid group and 4 (2.1%) patients in the placebo group having events after the 2nd dose.

A total of 42 (10.6%) patients in the zoledronic acid group, 6 (4.1%) patients in the alendronate group, and 31 (11.9%) patients in the placebo group had renal events (pre-specified MedDRA search criteria AEs and/or pre-specified laboratory criteria) that were sent to the adjudication committee for review. Of these, a higher number of patients (27, 6.8%) in the zoledronic acid group relative to the alendronate (2, 1.4%) group had clinically significant renal events confirmed by the expert adjudication committee; the incidence was highest in the placebo group (23, 8.8%).

The incidence of change in renal function confirmed by the adjudication committee was higher for those patients with risk factors, although the number of events was too small to draw meaningful conclusions.

Cardiac/cardiovascular and stroke-related AEs
All (serious and non-serious) cardiac arrhythmia AEs are summarised for the male osteoporosis safety population in table 4.28. There were 9 (5.9%) patients in the zoledronic acid group and 7 (4.7%) patients in the alendronate group who had an AE associated with cardiac arrhythmia in Study 2308. Atrial fibrillation/atrial flutter were reported for 5 (3.3%) patients in the zoledronic acid group and 3 (2.0%) patients in the alendronate group. The only atrial fibrillation SAE occurred in the alendronate group.

A greater proportion of the patients in Study 2310 were more than 75 years of age which, when combined with the higher baseline rates of hypertension, diabetes, coronary artery disease, and previous stroke, implies that the Study 2310 population was at a higher risk for subsequent cardiovascular/cerebrovascular events than the Study 2308 population (see table 4. 21). This was evident in the placebo group, which experienced a higher rate of cardiac arrhythmias (27 patients, [10.3%]) than either treatment group in Study 2308 and was also higher than the corresponding study 2310 zoledronic acid treated group (13 patients [5.3%]). Atrial fibrillation/atrial flutter (both serious and non-serious) were reported at similar rates for both placebo and zoledronic acid groups (7 [2.9%] zoledronic groups and 6 [2.3%] placebo) in Study 2310 (see table 4-28).

Table 4. 21. Baseline cardiovascular risk factor rates, male OP safety population.

	Study M2308		**Study L2310 (male only)**		**Total**
Baseline risk factors	**Zoledronic Acid N=153 n (%)**	**Alendronate N=148 n (%)**	**Zoledronic Acid N=244 n (%)**	**Placebo N=261 n (%)**	**Zoledronic Acid N=397 n (%)**
Age ≥ 75	**24 (15.7)**	**24 (16.2)**	**119 (48.8)**	**127 (48.7)**	**143 (36.0)**
Hypertension	**54 (35.3)**	**55 (37.2)**	**105 (43.0)**	**125 (47.9)**	**159 (40.1)**
Diabetes	**18 (11.8)**	**8 (5.4)**	**38 (15.6)**	**40 (15.3)**	**56 (14.1)**
Coronary artery disease	**12 (7.8)**	**14 (9.5)**	**53 (21.7)**	**68 (26.1)**	**65 (16.4)**
Hypercholesterolemia	**43 (28.1)**	**50 (33.8)**	**25 (10.2)**	**44 (16.9)**	**68 (17.1)**
History of stroke	**3 (2.0)**	**9 (6.1)**	**43 (17.6)**	**50 (19.2)**	**46 (11.6)**

Risk factors combined logically-related preferred terms in addition to the term displayed. Therefore, the incidence represented within this table may differ from the incidence reported for the preferred term.

Table 4. 28. Number and % of patients with cardiovascular and cerebrovascular AEs; male OP safety population.

	Study 2308		Study 2310 (male only)		Total
Preferred Term	Zoledronic Acid N=153 n (%)	Alendro-nate N=148 n (%)	Zoledronic Acid N=244 n (%)	Placebo N=261 n (%)	Zoledronic Acid N=397 n (%)
Cardiac arrhythmias AEs	9 (5.9)	7 (4.7)	13 (5.3)	27 (10.3)	22 (5.5)
Cardiac arrhythmia SAEs	1 (0.7)	2 (1.4)	9 (3.7)	17 (6.5)	10 (2.5)
Adjudicated arrhythmia SAEs	0 (0.0)	2 (1.4)	6 (2.5)	8 (3.1)	6 (1.5)
Atrial fibrillation/atrial flutter AEs	5 (3.3)	3 (2.0)	7 (2.9)	6 (2.3)	12 (3.0)
Atrial fibrillation/atrial flutter SAEs	0 (0.0)	1 (0.7)	3 (1.2)	2 (0.8)	3 (0.8)
Congestive/cardiac heart failure AEs	1 (0.7)	2 (1.4)	9 (3.7)	18 (6.9)	10 (2.5)
Stroke-related AEs	3 (2.0)	2 (1.4)	14 (5.7)	17 (6.5)	17 (4.3)
Stroke-related SAEs	2 (1.3)	2 (1.4)	10 (4.1)	10 (3.8)	12 (3.0)

- N= the number of patients in the analysis population
- n= the number of patients meeting the criterion
- (%)= n/N*100
- Preferred terms are sorted in decreasing order of frequency with respect to the total zoledronic acid group

Between-treatment differences for time to first cardiac arrhythmia AE/SAE and time to first atrial fibrillation/atrial flutter AE/SAE showed no statistically significant between-treatment differences between the pooled zoledronic acid group and the placebo treatment group.

Baseline risk factors for cardiac arrhythmia AEs
The number and percentage of patients who experienced cardiac arrhythmia AEs (serious and non-serious) in the Male osteoporosis safety population were summarised by baseline risk factors: age group, active hypertension, active diabetes mellitus, active congestive/cardiac heart failure, active valvular heart disease, active coronary artery disease, history of myocardial infarction, active cardiomyopathy, active left ventricular hypertrophy, active tachyarrhythmia, active bradyarrhythmia, active atrial fibrillation/flutter, active hypercholesterolemia, prior history of stroke and active hyperthyroidism. The number of patients in each specific risk category and the number of events observed were considered too small to make clinical conclusions.

Adjudication of arrhythmia SAEs
Arrhythmia SAEs confirmed by adjudication for the male osteoporosis safety population were summarised by the MAH. Of those sent for adjudication, a total of 16 patients (6 patients (1.5%) in the zoledronic acid group, 2 patients (1.4%) in the alendronate group, and 8 patients (3.1%) in the placebo group) were confirmed by the adjudication committee. Atrial fibrillation was confirmed by adjudication in 5 patients (3 patients, zoledronic acid group; 1 patient, alendronate group; 1 patient, placebo group). A between-treatment comparison of time to first arrhythmia SAE confirmed showed that zoledronic acid reduced the risk of arrhythmia SAEs confirmed by adjudication compared to placebo by 15% (p-value=0.7713, Hazard ratio = 0.85, 95% CI: 0.30, 2.47). Within 30 days following study drug infusion, no patients experienced an arrhythmia SAE confirmed by adjudication; all confirmed arrhythmia SAEs occurred more than 30 days from dosing. This supports the lack of a causal relationship between zoledronic acid and arrhythmia SAEs. A summary of arrhythmia SAEs confirmed via adjudication is presented by underlying medical condition was presented by the MAH. The most common underlying condition was pre-existing arrhythmia. Both patients in the alendronate group had a previous myocardial infarction.

Congestive/cardiac heart failure
The incidence of all congestive/cardiac heart failure AEs reported by investigators was 10 (2.5%) zoledronic acid-treated patients, 2 (1.4%) alendronate-treated patients, and 18 (6.9%) placebo-treated patients). A between-treatment comparison of time to first congestive/cardiac heart failure AE is presented showed that zoledronic acid reduced the risk of congestive/cardiac failure adverse events compared to placebo by 45%; however the result was not statistically significant (p-value=0.1320, Hazard ratio = 0.55, 95% CI: 0.24, 1.22).

Stroke-related AEs
The incidence of all stroke-related AEs (serious and non-serious) for the male osteoporosis safety population reported by investigators was 17 (4.3%) in the zoledronic acid group, 2 (1.4%) in the alendronate group, and 17 (6.5%) in the placebo group. The majority of stroke-related AEs were cerebrovascular accidents (CVA): 8 (2.0%) in the zoledronic acid group, 1 (0.7%) in the alendronate group, and 8 (3.1%) in the placebo group. Zoledronic acid reduced the risk of stroke-related AEs by 9%; however the result was not statistically significant (p-value=0.7982, Hazard ratio = 0.91, 95% CI: (0.45, 1.85).

Stroke-related SAEs
The incidence of all stroke-related SAEs reported by investigators was 12 (3.0%) in the zoledronic acid group, 2 (1.4%) in the alendronate group and 10 (3.8%) in the placebo group. The majority of stroke-related SAEs were cerebrovascular accidents (CVA): 6 (1.5%) in the zoledronic acid group, 1 (0.7%) in the alendronate group and 5 (1.9%) in the placebo group. A between-treatment comparison of time to first stroke-related SAE showed that zoledronic acid increased the risk of stroke-related SAEs by 10%; however the result was not statistically significant (p-value=0.8372, Hazard ratio = 1.10, 95% CI: 0.46, 2.64).

Ocular events

Rare reports of ocular inflammation, such as nonspecific conjunctivitis, uveitis and episcleritis, have been described in association with administration of all marketed bisphosphonates, such as alendronate, pamidronate, risedronate and zoledronic acid. To objectively and independently assess ocular AEs and to identify possible causal relationships, an AE review process was established. Data were reviewed by an independent and blinded ophthalmology expert in assessing bisphosphonate-associated ocular AEs. A list of preferred terms was created by the expert and the clinical database was searched to identify potential cases. Follow-up forms were sent to investigators to collect additional details, and then the event was adjudicated. All ocular events sent for expert review in the Male osteoporosis safety population were adjudicated as confirmed ocular events: zoledronic acid, 11 patients (2.8%); alendronate, 3 patients (2.0%), and placebo, 4 patients, (1.5%).

Hypocalcaemia
Hypocalcaemia is a known potential consequence of bisphosphonate therapy, and because zoledronic acid has a rapid effect on bone turnover, transient hypocalcaemia may develop soon after dosing and usually following the first infusion of zoledronic acid. Three patients in the zoledronic acid group (0.7%), 1 patient in the alendronate group (0.7%), and 1 patient in the placebo group (0.4%) had clinical events that met the pre-specified criteria for hypocalcaemia and were sent to the adjudication committee for review. Only one patient in the zoledronic acid group (0.25%) and one patient in the alendronate group (0.68%) were adjudicated to have experienced confirmed events of hypocalcaemia; no symptoms were reported.

Avascular necrosis (AVN) of long bones and delayed union/nonunion following a fracture
Three patients in the zoledronic acid group (0.8%), no patients in the alendronate group and 10 patients in the placebo group (3.8%) had cases of potential AVN events that were sent to the adjudication committee for review. Only 2 cases, both in the placebo group, were adjudicated as confirmed. To assess delayed healing/non-union of a fracture, the same adjudication committee reviewed cases identified by searching the safety database for preferred MedDRA terms agreed to by the committee. Overall, there were 2 (0.5%) male patients in the zoledronic acid group and 3 (1.15%) in the placebo group who had a potential delayed healing/non-union of a fracture identified. Of these, 1 (0.25%) zoledronic acid patient and 2 (0.77%) placebo patients had confirmed delayed healing/non-union of their fracture. No patient in Study 2308 had an event which met the adjudication criteria for non-healing/delayed union of a fracture. Additionally, in study 2310, a parallel process was implemented to identify potential cases of delayed healing of the fractured hip which defined entry into the study. This process identified 36 patients (14.8% of Study 2310 male patients) in the zoledronic acid group and 31 (11.9%) male patients in the placebo group for adjudication, which confirmed 11 (4.5%) of Study 2310 male patients) in the zoledronic acid group and 9 (3.45%) in the placebo group. Overall, there was no evidence of an increased risk of delayed healing or non-union of a fracture regardless of anatomic site.

Maxillofacial complications
ONJ was confirmed if there was 'exposed bone of the jaw despite 6 weeks of appropriate medical care.' This definition is consistent with the original descriptions by (***Ruggiero et al 2004)*** and is described further based on the published results from the PMO population (*Grbic et al 2008*). There were no spontaneous reports of ONJ. Five patients in the zoledronic acid group (1.3%), 5 patients in the alendronate group (3.4%), and 1 patient in the placebo group (0.4%) had maxillofacial events. There were no patients who experienced events that were confirmed by adjudication.

Clinical chemistry
Analyses of selected biochemistry parameters of creatinine, BUN, phosphorous, albumin, calcium, corrected calcium and magnesium was performed for the pooled Male osteoporosis safety population. Data interpretation is difficult due to the differences in patient populations of the two studies pooled. The overall incidence for increases in serum creatinine from baseline (> 0.5 mg/dl) was higher in the zoledronic acid group (7 patients, or 4.6%) compared with the alendronate group (one patient, or 0.7%) in study 2308. In general, for other selected biochemistry parameters, no clinically relevant differences between treatment groups were observed, when examined overall and from the perspective of the individual studies.

Post marketing experience
According to the latest PSUR for Aclasta, covering the period from 01 November 2006 to 30 April 2007, approximately 2625 patients received treatment with Aclasta in investigational clinical trials sponsored by the MAH. In the previous PSUR, approximately 1185 patients received treatment with Aclasta. Approximately 107 patients received Aclasta in Post-Marketing-Surveillance studies. An estimate of patient-years of exposure is based on calculations of worldwide sales volume in grams of active substance sold during the review period divided by the defined dose (DD). The sales volume of Aclasta during the review period is 14.7 g; divided by the defined DD of 5 mg. The estimated exposure is 6226 patient-years.

Discussion on clinical safety

The presentation of safety results was presented side-by-side with safety results from the large study 2301 in postmenopausal osteoporosis, which has recently been assessed. The safety data from these two studies in a similar study population were pooled.

The CHMP noted that the rate of SAEs was in general similar in the 2 treatment groups. Only for anaemia, was the rate higher (>2 times) in the zoledronic acid group and for cardio-respiratory arrest and femoral neck fracture in the placebo group. The numbers, however, are small but it is observed that also in study 2301, the rate of anaemia was twice as common in the zoledronic acid group compared with placebo. Overall for SAE, there were no unexpected or new adverse events.

The CHMP noted that the rates of hyperthermia and pyrexia were high. When combined, the rate was 11% and 3.4% in the zoledronic acid and placebo group, respectively.

The CHMP also considered that the results were in compliance with previous findings with regard to ocular adverse reactions observed with zoledronic acid.

The CHMP considered that concerning ONJ, the results are in line with previous observations, i.e. that the risk of ONJ is low in non-oncology indications with zoledronic acid and that the current SPC adequately addresses this issue.

For other SAEs, there were no significant differences between the treatment groups, including atrial fibrillation SAE and stroke related death.

Concomitant use of antipyretic medication
As expected the rate of post-dose symptoms was lower compared to the rate observed in previous studies (e.g. study 2301) where paracetamol or ibuprofen has not been recommended to reduce post-dose symptoms. A recommendation for the use of paracetamol or ibuprofen to reduce post-dose symptoms has already been introduced into the SPC for Aclasta. It was highlighted that paracetamol (acetaminophen) was not given proactively in study 2301 to mitigate the incidence of post-dose symptoms.

In study 2301, the most common AEs by preferred term in the zoledronic acid group were the post-dose symptoms (pyrexia, myalgia, influenza-like illness, headache, arthralgia), all of which occurred at approximately 4- to 9-fold higher incidence than in the placebo group. Pyrexia was the most common AE in study 2301 and study 2310. Although the incidence was relatively consistent in the comparator groups (0.7 to 1.7%), the incidence in the zoledronic acid group in study 2301 was considerably higher (15.5%) than in the other studies (1.8% to 6.9%). All patients in Study 2310 were allowed to take paracetamol to prevent post-dose symptoms, with no control group included in this study for paracetamol use.

Study US136 is currently ongoing to assess the effect of acetaminophen or fluvastatin in the prevention of transient post-dose symptoms following an i.v. infusion of a single dose of zoledronic acid in postmenopausal women with low bone mass, and the CHMP considered that a change to the Summary of Product Characteristics may be appropriate when these results are available.

Limited information on laboratory changes is available and only data on clinically notable results was presented. However, these results did not give rise to concerns.

Vitamin D supplementation
Despite loading dose of vitamin D to all patients prior to infusion and subsequent vitamin D and calcium supplementation, hypocalcaemia occurred with zoledronic acid. This confirms findings from previous studies. The symptomatic event is most likely related to thyroidectomy. The current SPC addresses the risk for hypocalcaemia and the need for adequate vitamin D and calcium substitution in relation to infusion with Aclasta. Whether there is a need for additional loading dose in patients with recent hip fracture was discussed by the MAH .

Hypocalcaemia occurred with zoledronic acid, despite the administration of a loading dose of vitamin D prior to infusion. This should therefore be recommended in the SPC for patients with recent fracture, but demand for calcium may be higher in that population and therefore there could be increased risk of hypocalcaemia following zoledronic acid infusion.

Based on previous studies, the incidence of vitamin D deficiency and osteoporosis was expected to be relatively high in the population of Study 2310 (*Mosekilde 2005*). In this study vitamin D levels were not routinely measured but the majority of patients received a loading dose of vitamin D (75,000 – 125,000 units of vitamin D2 or 50,000 – 75,000 units of vitamin D3 i.m. or orally) prior to the infusion of zoledronic acid, followed by a maintenance dose of 800 – 1200 IU of vitamin D p.o. daily and elemental calcium (1000 - 1500 mg p.o. daily in a divided dose).

In study 2310, of the three adjudicated confirmed cases of hypocalcaemia in the zoledronic acid group, one was thought to be related to study medication by the adjudication committee, and none of the cases were symptomatic. The data from the 2301 and 2310 studies, demonstrate overall a very low risk of hypocalcaemia.

The CHMP considered that it would be possible that as the demand for calcium is increased following a fracture, without a loading dose, the risk of hypocalcaemia with administration of zoledronic acid could be increased. It was further agreed that the fact that all patients received a loading dose of vitamin D before the infusion, probably influenced the low rate of hypocalcaemia in the Study 2310. Therefore, a statement on loading dose of vitamin D in Aclasta treatment after fracture was added to section 4.2 of the SPC.

Fracture healing
The study 2310 provided important information with regard to the concern whether bisphosphonates could affect fracture healing adversely. The rate of delayed healing/non-union was not increased in the zoledronic acid group, which was considered reassuring. Overall, there were similar rates of delayed union/non-union in the 2 treatment groups, 3.4% vs. 2.8% in the zoledronic acid and the placebo group, respectively. This is of importance considering the design of the study where zoledronic acid was given to patients with recent fracture but there have been concerns that bisphosphonates might affect bone healing negatively. Delayed healing/non-union has not been observed in previous studies, but rates have been much lower (0.3% in the large post-menopausal study).

The CHMP considered that the question whether infusion immediately following a fracture could affect fracture healing, however remained unanswered.

Fractures were more frequent in the patients receiving zoledronic acid within 6 weeks compared with patients receiving infusion > 6 weeks after surgery. Apart from this, the sub-group analysis supports further the possible greater benefit/risk for zoledronic acid when given several weeks after hip fracture. As discussed above in the section on efficacy, the study was however not powered to show a reduction in clinical fractures in men. Therefore the decision on the earliest timepoint of infusion after hip fracture repair was based on BMD data, which supported the recommendation to give the Aclasta infusion two or more weeks after hip fracture repair.

Mortality
Overall, the risk of death was decreased in the zoledronic acid group by 28%. This is difficult to explain but may be indirectly related to the reduction in fracture rate, as hip fractures in the elderly population in general are associated with mortality as well as significant morbidity.

Unadjudicated, the death due to cerebrovascular event is 6 patients treated with zoledronic acid compared with 3 patients in the placebo group. Following adjudication, the rates are 7 versus 7 deaths in each group. This was considered unusual as rates of other AEs are often only presented as following adjudication, e.g. rates for hypocalcaemia and AVN.

The rate of death appeared high (11%), even somewhat higher than calculated in the study plan, but not unexpected considering the elderly population with common co-morbidities, including a recent hip fracture with surgery.

Hip fracture mortality was higher for men than for women, increases with age and is greater for those with co-existing illnesses and poor pre-fracture functional status (*Cooper et al 1992)., Osteoporosis International; 2(6):285-9].* It can also be explained by the high age of patients in the study and the high rate of cardiovascular risk factors at baseline.

However, this explains only a certain part of the difference in death rate (14 more patients in the zoledronic acid group than in the placebo group died after a refracture) and the rest of the difference in mortality remains unexplained.

The difference in death rates between treatment groups are likely to depend on a number of factors including a) the increased risk of mortality due to their entry hip fracture b) the timing of randomisation following hip fracture repair c) the increased risk of mortality due to subsequent osteoporotic fracture(s) following randomisation d) excessive bone loss rate as a marker of frailty e) pre-existing medical conditions at the time of randomisation which could increase a patient´s risk of death above and beyond the study entry hip fracture (e. g. the association between CV disease and osteoporosis) and f) medical conditions that developed during the course of the study that would increase a subject´s risk of death.
There were 92 zoledronic acid- and 139 placebo-treated patients who had one or more new clinical fractures during the study. 11/92 (12 %) of zoledronic acid-treated patients died compared to 24/139 (17.3 %) of placebo-patients, corresponding to an absolute risk reduction of 3.4 %. This difference did not reach statistical significance (p = 0.0994).

No apparent mortality benefit was seen during the first year following randomisation which is confirmed by the hazard ratio of 0.97. After this point, zoledronic acid appears to develop a consistent reduction in the mortality risk that is consistent at year 2 and year 3 and overall with the risk reduction ranging between 25 and 28 %. This suggests that other factors contribute to the reduction in mortality since most of the overall 36 % fracture risk reduction achieved by zoledronic acid occurred during the 1st year (hazard ratio = 0.68, 95 % CI: 0.49 to 0.96). In the literature it has generally been accepted that the risk of death is high in all patients during the first 6 – 12 months following hip fracture surgery. Therefore the risk of death during the first year should be comparable and any benefit obtained by treatment with zoledronic acid would be observed after the first year of follow-up.

In long-term trials where physical health of the population is expected to deteriorate over time, conditions and events occurring may affect efficacy and mortality/morbidity outcomes. To examine this further, the following additional post-randomisation events were examined with respect to relationship with subsequent death: change in total hip BMD from end of study to baseline, the occurrence of a fall reported as an AE and the occurrence of pneumonia reported as an AE. The occurrence of the latter two AEs has been shown to be associated with increased incidence of cardiovascular disease and subsequent mortality. Both falls and pneumonia occurred in > 5 % of patients in each treatment group and thus the number of patients who had an event would be considered adequate to be able to test for whether or not these factors explain the rate of death observed in study 2310.

The MAH has shown baseline and incidence data for multiple factors influencing mortality in study 2310. Apart from the frequency of re-fractures, age (especially the age group 65 - 74 years), BMI < 19, pneumonia as adverse event, baseline mental status and previous stroke were risk factors for death. Prevalent or incident cardiovascular disease and diabetes also predisposed to mortality. Altogether, no clear explanation could be provided for the lower mortality rate in the actively treated group in study 2310 and no conclusions with regard to a possible association with the treatment and/or the lower re-fracture rates can be made. Thus, although it may be a chance finding it seems to be an area of interest for further investigation.

Discontinuations
The Discontinuation rate was high in study 2310, even somewhat higher than calculated in the study plan. This could be explained by the high death rate in the study. The rate of discontinuation due to other causes was not higher than would be expected (17%) and was similar in both treatment groups. However, overall there were more study completers in the placebo group when death was excluded as a reason for discontinuation [A38] .The placebo group had more patients who died while the zoledronic acid group had more patients who discontinued the study for reasons other than death.

Atrial fibrillation and arrhythmia
The increased frequency of serious AEs from atrial fibrillation in the Aclasta treatment group as well as an increased risk for stroke related death in this group observed in study 2301 could not be observed in study 2310. This result is in contrast with findings from study 2301, where 0.7 % of zoledronic acid treated patients had atrial fibrillation, compared to 0.2 % of placebo treated patients in that study. Since study 2310 is a smaller study than 2301 and as patients were not followed prospectively with respect to cardiac complications, these observations have to be interpreted with caution.

While in Study 2310 the rate of arrhythmia in general was not increased in the group that received zoledronic acid, the rate of tachyarrythmias (tachycardia and atrial fibrillation) is higher in the zoledronic acid group. The numbers, however, were low and the difference was not considered significant, but the observation has to be interpreted in the perspective of the unexpectedly higher rate of atrial fibrillation SAE in the larger postmenopausal study.

The findings from study 2310 cannot override the findings of that much larger study 2301 with a longer study duration. As in study 2301, most atrial fibrillation events occurred more than 30 days from infusion and thus appear not to be related to study infusion. Other mechanisms may exist. Increased atrial fibrillation has been observed in large long-term studies with other bisphosphonates. The CHMP highlighted, that in the previous type II variation procedure (II/014), however an analysis of safety data from study 2310 showed unexpectedly that previous use of bisphosphonates was an independent risk factor for the development of atrial fibrillation.

The frequencies of arrhythmia SAEs in study 2310 can however not be directly compared to that in study 2301 as these two study populations differ in a number of aspects. None of the studies were designed to prospectively evaluate atrial fibrillation or other cardiovascular events. ECGs were recorded in a substudy of 2301 but not at all in study 2310.

As atrial fibrillation is very common in elderly patients, often asymptomatic and paroxysmal and may go undetected even in large studies not specially designed to monitor for atrial fibrillation, the circumstance that no safety signals concerning atrial fibrillation have come up for bisphosphonates in study 2310 does not exclude the possibility of a causal relationship.

Renal safety
Concerning renal adverse events, the circumstance that zoledronic acid treated patients in study 2310 did not exhibit an overrepresentation of renal failure cannot override safety data from earlier clinical studies (especially study 2301). Data on renal safety cannot be directly compared to renal safety data from the postmenopausal osteoporosis study 2301 that included 7736 patients, as that study collected data on proteinuria and also measured serum creatinine and calculated GFR 10 days after infusion.

The CHMP highlighted that short-term renal effects were not studied but sufficient data was provided in the large postmenopausal study 2301. Transient increases in creatinine following infusion are common and of importance for the population with recent hip fracture and surgery. The current SPC, however, adequately addresses this issue. With regard to long-term effects, the results confirm those of previous trials in non-oncology indications.

The higher incidence of transient renal dysfunction after infusion of zoledronic acid in study 2301 however remains to be of concern. Such transient renal dysfunction episodes may, especially in an elderly patient population, result in a more severe renal insufficiency. In clinical routine, as opposed to in clinical studies, and in elderly patients without post infusion monitoring, there is very limited experience in patients with an estimated creatinine clearance below 40 ml/min.

The MAH presented further justification to lower the limit for creatinine clearance from 40 to 35 ml/min in the SPC for the use of Aclasta taking into account all safety data from clinical trials and post marketing.

The renal safety of zoledronic acid established in the pivotal fracture study 2301 was further corroborated in the 2310 study. The population studied in 2310, although smaller in absolute numbers, had a much higher degree of fragility as highlighted by their more than threefold higher mortality rate (Aclasta 9.6%, placebo 13.3%) than the death rate in study 2301 (3.4% vs. 2.9%) with a mean age of 75 years. In both studies patients needed to have a calculated creatinine clearance (CrCl) above 30.0 ml/min. Besides older age, hypertension and increased glucose, other atherosclerotic risk factors, such as hyperlipidaemia, were also considered to have impact on renal function, even when no underlying kidney disease is present.

Patients with a serum creatinine clearance between 30 and 35 ml/min had a higher incidence of renal laboratory deterioration in the zoledronic acid treated males than the placebo treated males in study 2310. For patients with a baseline serum creatinine clearance between 35 and 45 ml/min, renal laboratory deterioration was seen somewhat more often in the placebo group than in the zoledronic acid group. No significant differences were seen between treatment groups with respect to creatinine clearance decreases $\geq$ 30 % with baseline value $\leq$ 60 ml/min and the MAH's proposal to change the lower GFR limit for treatment with Aclasta, from 40 to 35 ml/min, can therefore be accepted.

Pooled safety data
The MAH further provided pooled safety data from studies 2310 and 2301 for post-dose symptoms and for atrial fibrillation/atrial flutter. The tendency to an increased incidence of atrial fibrillation/atrial flutter SAEs in the zoledronic treated patient group persisted after pooling of data, with a 1.7-fold greater incidence in this group. The MAH has suggested a new wording for adverse events in section 4.8 of the SPC, where the numbers for frequency of post-dose symptoms have been exchanged from the numbers from study 2301 to the pooled safety data. Since patients in study 2310 received prophylaxis against post-dose symptoms, such symptoms occurred less frequently in that study. The inclusion of information on pooled study data for atrial fibrillation/atrial flutter SAEs was also suggested by the MAH.

Since baseline data, especially with respect to age and gender, as well as the recommendations given to patients for prophylaxis against post-dose symptoms, differed between studies 2301 and 2310 and as 2301 is a much larger study the additional information was added in section 4.8 in the SPC ^to explain in what aspects AEs differed between the studies 2310 and 2301.

Safety in the male population
Due to the different populations and study designs, the CHMP considered that pooling of safety data from the Studies 2310 and 2308 could be questioned. The males in study 2310 were nearly a decade older than the study population in study 2308 and many males over the age of 75 were included in 2310. Especially, incidence of some age related AEs in the placebo controlled Study 2310 are diluted by this pooling, such as renal AEs and these should therefore be presented per study. For arrhythmias and other cardiovascular AEs, this has been done in the table but not in the text, explaining why rates are generally lower in the text compared with rates in the table for the Study 2310.

Atrial fibrillation did not occur with increased rate, although adjudicated cases confirmed AF SAE in 3 patients treated with zoledronic acid compared with 1 patient in each of the other groups (placebo and alendronate). Atrial fibrillation is currently being monitored within the RMP for Aclasta and furthermore, is under review for all bisphosphonates by the PhVWP. Stroke related AEs were not increased in the zoledronic acid group. Hypocalcaemia was observed in 3 patients receiving zoledronic acid compared with 1 in each of the other groups, but all patients received vitamin D and calcium supplementation and in Study 2310, a loading dose of vitamin D was given prior to infusion. The difference in the rate of post-infusion reactions can be explained by different recommendations on prophylaxis with paracetamol/NSAID.

The higher number of patients with transient creatinine elevations observed in the zoledronic acid group in study 2308 can not directly be compared to data from 2310 as the latter study did not record lab values at 9 – 11 days post infusion. The significance of these transient elevations of creatinine remains unclear. In general, there was a higher incidence of renal events in study 2310 than in 2308, possibly related to the older study population in 2310. The frequency of renal events did not significantly differ between study groups in study 2310. In study 2308, renal events were more common in alendronate-treated than in zoledronic acid-treated patients.

Overall, there were no new or unexpected AEs or SAEs observed in the male population compared with the post-menopausal female population.

Post-marketing experience
There is limited post-marketing experience with zoledronic acid used in non-oncology indications. Based on results from a large long-term study in postmenopausal osteoporosis, a type II variation to add atrial fibrillation to the list of adverse events was finalised recently (II-14). During the PSUR period, there were 6 cases of hypocalcaemia despite vitamin D and calcium supplementation. The MAH committed to continue to monitor hypocalcaemia. No other new safety signals were observed, but the MAH will also continue to monitor ONJ, renal dysfunction, ocular disorders, avascular necrosis, atrial fibrillation and cerebrovascular events.

PHARMACOVIGILANCE PLAN AND RISK MANAGEMENT PLAN (RMP)

The elements of the proposed risk management plan (RMP) are consistent with the recommendations made in the ICH E2E Guideline on Pharmacovigilance and the CHMP Guideline on Risk Management Systems for Medicinal Products for Human Use (November 20, 2005). The structure and content of the initial RMP were satisfactory, however it did not follow the template for EU RMP (September 2006). The MAH therefore presented a revised RMP during the procedure.

Risk management plan (RMP) for Aclasta

The MAH updated the RMP with relevant information related to the extension of indication, including the proposed change the recommendation not to treat patients with a creatinine clearance cut-off less than 40 ml/min to 35 ml/min. Relevant parts of this RMP are summarised below.

Limitation of the human safety database

Children and adolescents	No adequate data.
Pregnancy and lactation	No adequate data.
Men	In the clinical study for the prevention of clinical fractures after hip fracture (study 2310), 23.88% of the patient population were men.
Hepatic insufficiency	Not studied. No dosage adjustment required. Zoledronic acid does not

	inhibit human P450 enzymes *in vitro*, shows no biotransformation and in animal studies < 3% of the administered dose was recovered in the faeces suggesting no relevant role of liver function in the pharmacokinetics of zoledronic acid and no required dosage adjustment.
Renal insufficiency	Not studied in patients with a creatinine clearance of < 30 ml/min Not recommended for use in patients with severe renal impairment (creatinine clearance < 35 ml/min). No dosage adjustment required in patients with a creatinine clearance ≥ 35ml/min

Size of the study population

The Aclasta program in post-menopausal osteoporosis in the completed controlled studies has 10675 patients (studies 2301/2313/2315/2407/2310) with approximately 5504 having received at least one dose and up to 5 doses of Aclasta. The patient-years exposure to zoledronic acid in this dataset is over 12947 patient-years of exposure to study medication.

The key safety population is from study 2301, a multicentre, double-blind, randomised, placebo-controlled study to evaluate the safety and efficacy of zoledronic acid in the treatment of osteoporosis in PMO women taking calcium and vitamin D.

Safety risks

Identified safety risks in patients with postmenopausal osteoporosis

Post dose symptoms
In Study 2301, the most common early onset AEs (=5%) within 3 days of any infusion included fever, myalgia, influenza-like illness, headache, gastrointestinal symptoms, pain in extremity and arthralgia. The incidence of post dose symptoms decreased after each annual infusion. The incidence rates of the transient post-dose symptoms were much lower in study 2310 than what was seen in study 2301, which could be attributed to patients without contraindication to acetaminophen (paracetamol) being provided with the standard labelled dose of oral acetaminophen (paracetamol) at the time of i.v. administration of study medication and were instructed to use as needed for the next 72 hours after infusion and as labelled in the respective country.

The incidence of AEs which started within 3 days of the first study drug infusion was 3-fold higher in the zoledronic acid group than in the placebo group (44.7% vs. 14.8%). The median number of infusions was 2.

Renal dysfunction
Bisphosphonates are excreted by the kidney and are known to have the potential to affect renal function, especially when given intravenously and administered as a bolus. In study 2301 systematic assessment of patients 9-11 days following infusion was able to detect short-term increases in serum creatinine (1.8% in zoledronic acid vs. 0.8% in placebo) and proteinuria (0.6% in patients on zoledronic acid vs. 0.18% on placebo). Long-term effects on renal function over 36 months, which represents the aggregate effect of multiple annual doses, did not demonstrate any difference between groups with respect to serum creatinine increases, creatinine clearance decreases or proteinuria. In study 2310 the results were comparable between treatment groups for renal and urinary disorders overall (9.49% for zoledronic acid vs. 9.93% for placebo). In the updated version of the RMP, renal dysfunction is consistently classified as an identified risk.

Ocular adverse events
Ocular adverse events such as uveitis, iritis, episcleritis and conjunctivitis are known class effects of bisphosphonates. In study 2301, the incidence of confirmed adjudicated ocular adverse events was less than 3.3% in patients treated with zoledronic acid vs. 2.7% in placebo. Of this, conjunctivitis was seen most frequently followed by uveitis and episcleritis. Patients treated with Aclasta exhibited a 30%

higher relative risk of developing ocular adverse events. These adverse events were not visually threatening and could be treated conservatively with topical therapy using either steroids or antibiotics. In study 2310 the results were comparable between treatment groups.

Hypocalcaemia
Transient hypocalcaemia is a well characterised side effect to the treatment with bisphosphonates. In study 2301, serum calcium values below 1.87 mmol/l were detectable in 0.24% of patients treated with zoledronic acid vs. 0.13% in placebo. None of the cases were symptomatic and they generally occurred in patients with pre-existing conditions such as parathyroidectomy or malabsorption of calcium.
In study 2310 after adjudication, the figures for AEs of hypocalcaemia were 3 (0.28%) for zoledronic acid patients versus 0 for placebo patients.

Osteonecrosis of the jaw
As of 30th April 2007, one case of osteomyelitis of the jaw and no cases of osteonecrosis have been reported as adverse events in the studies on postmenopausal osteoporosis or Paget's disease with zoledronic acid. Maxillofacial adjudication of the total HORIZON safety database after a systematic MedDRA search for maxillofacial events found 1 case in the zoledronic acid group and 1 case [A40]in the placebo group meeting predefined adjudication criteria for ONJ. No reports of osteonecrosis or osteomyelitis of the jaw have been received from post-marketing sources. No cases of ONJ were reported in study 2310.

Potential risks in patients with postmenopausal osteoporosis

Osteonecrosis outside the jaw and non-union or delayed fracture healing
Four patients in the zoledronic acid group and 3 patients in the placebo group revealed osteonecrosis outside the maxillofacial area. One patient in the zoledronic acid group and one patient in the placebo group had a report of a non-union fracture. Thus, from these study data there was no evidence that administration of zoledronic acid is associated with increased risk of osteonecrosis outside the jaw or impaired fracture healing. No cases of osteonecrosis outside the jaw or delayed/non-union were reported in study 2310.

The RMP has been amended with the number of post-marketing reports of osteonecrosis outside the jaw and delayed/non-union observed in study 2310.

Cerebrovascular events
In study 2301, there was a greater number of deaths with a cerebrovascular event as underlying condition for zoledronic acid (0.34%) than for placebo (0.13%). The total number of strokes between the 2 treatment groups was, however, similar, and overall prevalence of stroke less than that seen in previous cross-sectional studies of populations with characteristics similar to those of patients in study 2301. Study 2310 did not confirm the finding observed in study 2301 (adjudicated cerebrovascular deaths 0.66% in the zoledronic acid group vs. 0.66% in the placebo group).

Atrial fibrillation
Cardiovascular side effects have not been associated with bisphosphonates in previous studies. In study 2301, patients treated with zoledronic acid exhibited a threefold greater incidence of atrial fibrillation SAE's. A statistically significant increase in the risk of all atrial fibrillation events was not demonstrated and an ECG study in a subgroup of patients did not reveal any differences between the zoledronic acid and placebo groups. The events did not occur early after infusion, when drug concentrations in serum were the highest. Oncology patients subjected to doses much higher than those used in Paget's disease and postmenopausal osteoporosis have not revealed increased incidence of atrial fibrillation. In study 2310, the rate of atrial fibrillation/atrial flutter AEs were comparable between the zoledronic acid group and the placebo group (2.85% vs. 2.65%) and so were the atrial fibrillation/atrial flutter SAEs (1.14 in the zoledronic acid group vs. 1.42% in the placebo group).

A causal relationship between zoledronic acid and development of atrial fibrillation is difficult to establish at present, and for the time being it is therefore considered acceptable to classify atrial

fibrillation as an important potential risk. The MAH has presented Pharmacovigilance activities for this potential risk in the Pharmacovigilance Plan (committed to perform a long-term observational epidemiological study with the end-points skeletal and cardiovascular complications and an extension of study 2301E for a total of 9 years).

In the revised RMP, the MAH has amended the section "Populations not studied in the pre-authorisation phase use" with use in children/adolescents, pregnancy/lactation and in patients with CrCl <30 ml/min. Moreover risk minimisation activities (information in the SPC) have been specified.

Gastrointestinal adverse events
In study 2301, the overall incidence of gastrointestinal AEs was similar between patients treated with Aclasta (38.24%) and placebo (35.28%). In study 2313 and study 2315, the incidence rates were 28.0% for Aclasta and 24.6% for alendronate. Nausea, vomiting and diarrhoea were seen more often in patients treated with Aclasta during the first 3 days following infusions as part of the post dose symptoms but these imbalances disappeared at later time points. In study 2310, the incidence of gastrointestinal AEs was similar between patients treated with Aclasta (24.9%) and placebo (25.3%).

Summary of the risk management plan for Aclasta

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activates (routine and additional)
Important identified risks		
Post dose symptoms	Routine pharmacovigilance Cumulative analysis in PSUR	Detailed information in section 4.8 of the CDS. Guide for healthcare professionals. Patient and healthcare professional education initiative.
Renal dysfunction	Close monitoring, medical review, and targeted follow-up of all serious post-marketing and clinical trial reports, using a targeted questionnaire. Cumulative analysis in PSUR. Adjudication of serious clinical trial cases.	Detailed information in section 4.4 of the CDS. Guide for healthcare professionals. Patient and healthcare professional education initiative.
Ocular adverse events	Close monitoring, medical review, and targeted follow-up of all serious post-marketing and clinical trial reports, using a targeted questionnaire. Cumulative analysis in PSUR.	Listed in ADR section 4.8 of the CDS. Guide for healthcare professionals Patient and healthcare professional education initiative.
Hypocalcaemia	Close monitoring, medical review, and targeted follow-up of all serious post-marketing and clinical trial reports, using a targeted questionnaire. Cumulative analysis in PSUR. Post US approval voluntary registry study (Study ZOL446K2401)	Detailed information in sections 4.4 and 4.8 of the CDS. Listed in ADR section 4.8 of the CDS. Guide for healthcare professionals. Patient and healthcare professional education initiative.
Osteonecrosis of the jaw	Close monitoring, medical review, and targeted follow-up of all post-marketing and clinical trial reports, using a targeted questionnaire. Cumulative analysis in PSUR. Special 15-day expedited reporting of ONJ regardless of seriousness, listedness and causality will be provided to EEA and USA Health Authorities. Adjudication of post-marketing and clinical trials reports of purported ONJ. Study ZOL446H2413 Scandinavian Registry study Extension studies ZOL446H2301E1 and ZOL446H 2301E2 (cardiovascular and bone health)	Detailed information in section 4.4 of the CDS. Guide for healthcare professionals Patient and healthcare professional education initiative.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activates (routine and additional)
Important potential risks		
AVN/fracture nonunion and/or delayed union	Close monitoring, medical review, and targeted follow-up of all post-marketing and clinical trial reports, using a targeted questionnaire. Cumulative analysis in PSUR.. Adjudication of serious clinical trial cases. Scandinavian Registry study Extension studies ZOL446H2301E1 and ZOL446H 2301E2 (cardiovascular and bone health)	Guide for healthcare professionals Patient and healthcare professional education initiative
Cerebrovascular AEs	Close monitoring, medical review, and targeted follow-up of all post-marketing and clinical trial reports, using a targeted questionnaire. Cumulative analysis in PSUR. Adjudication of serious clinical trial cases. Scandinavian Registry study Extension studies ZOL446H 2301E1 and ZOL446H 2301E2.	Guide for healthcare professionals Patient and healthcare professional education initiative
Atrial fibrillation	Close monitoring, medical review, and targeted follow-up of all post-marketing and clinical trial reports, using a targeted questionnaire. Cumulative analysis in PSUR. Adjudication of serious clinical trial cases. Scandinavian Registry study Extension studies ZOL446H 2301E1 and ZOL446H 2301E2.	Listed in ADR section 4.8 of the CDS. Guide for healthcare professionals Patient and healthcare professional education initiative.
Gastrointestinal adverse events	Routine pharmacovigilance	Listed in ADR section 4.8 of the CDS. Guide for healthcare professionals. Patient and healthcare professional education initiative.
Potential interactions		
Products that can significantly affect renal function	In addition to routine pharmacovigilance, drug interactions will be monitored through post-marketing on a case-specific basis for suspected interactions, with targeted follow-up as appropriate.	Warning in Section 4.5 of the CDS
Paracetamol	In addition to routine pharmacovigilance, drug interactions will be monitored through post-marketing on a case-specific basis for suspected interactions, with targeted follow-up as appropriate.	None as the effects are mild, transient and not clearly related to Zoledronic acid 5 mg

Discussion of the RMP
The MAH has submitted an updated RMP (version 004) with minor changes compared to the previous version assessed in the frame of the extension of indication to include postmenopausal osteoporosis during the procedure.

In the updated version of the RMP, renal dysfunction is consistently classified as an identified risk and gastrointestinal adverse events as potential risks.

Gastrointestinal adverse events are consistently classified as potential risk and have been included into the table "Ongoing safety concerns" and the pharmacovigilance and risk minimisation activities have been included into the table "Summary of Activities for Each Safety Concern". Although gastrointestinal AEs are a class effect mainly of oral bisphosphonates, the risk of gastric and oesophageal erosions and bleedings due to direct toxic effects from bisphosphonate tablets on the mucosa is eliminated by the intravenous route of administration.

For that reason GI adverse events are considered a potential risk. Gastrointestinal side effects such as nausea, vomiting and diarrhoea seen after administration of zoledronic acid are part of the post-dose symptom complex. These symptoms are transient, mostly mild and have no impact on gastrointestinal safety.

The RMP has been amended with the number of post-marketing reports of osteonecrosis outside the jaw and delayed/non-union observed in study 2310 as requested.
It is agreed that a causal relationship between zoledronic acid and development of atrial fibrillation is difficult to establish at present, and for the time being it is therefore considered acceptable to classify atrial fibrillation as an important potential risk. The MAH has presented pharmacovigilance activities for this potential risk in the Pharmacovigilance Plan.

In the revised RMP, the MAH has amended the section "Populations not studied in the pre-authorisation phase use" with use in children/adolescents, pregnancy/lactation and in patients with CrCl <30 ml/min. Moreover risk minimisation activities (information in the SPC) have been specified.

The MAH also provided revised educational material for patients and physicians reflecting data submitted in support of this extension of indication and the new indication. The CHMP considered these documents acceptable.

Due to the unknown long-term safety effects with zoledronic acid treatment the MAH has committed to perform a retrospective study in non-oncology patients (Australia) and a long-term observational epidemiological study for 10 years with the end-points; skeletal and cardiovascular complications after being prescribed Aclasta compared to patients being prescribed oral bisphosphonates. All patients who were being prescribed Aclasta in the three Scandinavian countries will be included.
The MAH has committed to including patients according to all approved indications in this follow-up safety study, i.e. now also "men at increased risk of fracture, including those with a recent low-trauma hip fracture" This extension of the scope for the Scandinavian study is expected to be included in the awaited response to the Follow up Measure (FUMs 016.2, 017.3, 019) concerning the revised protocol of this study.

Moreover, the MAH has committed to present a revised protocol for the study 2301E (extension study for 3 years in the treatment of osteoporosis in PMO women) with further efforts to capture cases of atrial fibrillation including ECGs prior to and after infusions, increased vigilance for symptoms and an intensified follow-up of patients with symptoms, as well as to present a study protocol for an extension of study 2301E for an addition of 3 years (total of 9 years).These commitments were included in the MAH's Letter of Undertaking.

Environmental Risk Assessment

The predicted environmental concentration (PEC) was calculated by the formula proposed in guideline EMEA/CHMP/SWP/4447/00.

The present assessment suggests that, based on the very low amount of active ingredient put on the market and the very low dose per patient, the placement of the foreseen amounts of Aclasta on the EU market does not constitute any significant risk to the environment. No specific labelling or risk mitigation measures are deemed necessary. As with all non-readily biodegradable human medicines, unused Aclasta should not be disposed off via domestic sewage.

The MAH accepted to use the default Fpen of 1%, which results in a PECsw value that exceeds the trigger value of 0.01 µg/l. Consequently the MAH was requested to proceed to a phase II fate and analysis according to CHMP/SWP/4447/00. The use of toxicity data for structural analogues in view of zoledronic acid was considered not acceptable in this analysis. The MAH therefore committed to follow up on this outstanding issue as outlined in the MAH's Letter of Undertaking.

Conclusions and Benefit / Risk Assessment

Conclusion on non-clinical aspects
The CHMP concluded that additional studies performed since 2004 confirm the earlier findings and have increased the understanding of the mechanisms of action of zoledronic acid. No new concerns have emerged from these studies.

Overall, the data from the 4 studies discussed above indicate that clinically relevant doses of zoledronic acid administered peri- or post-operatively prolong the retention of trabecular bone in the callus of a healing fracture, thereby increasing bone mass and mechanical strength at the fracture site. Apart from the cosmetic effect of transient retention of a larger callus, no long-term deleterious effects on fracture healing were observed in animals treated with zoledronic acid.

The CHMP considered that all three animal models showed increased callus formation after zoledronic acid was given at an early stage of fracture repair. The quality of the newly formed bone was considered sufficient, despite the expected transient delay of remodelling.

Conclusion on clinical efficacy
The CHMP overall concluded that prevention of re-fracture after low energy trauma hip fracture has been convincingly demonstrated by the MAH in study 2310. It was therefore considered reasonable to include this group of patients in the wording of the indication. However, the initialy proposed wording relating to prevention of osteoporosis was considered not to be in line with the current guidelines on osteoporosis and was therefore further modified.

Concerning the inclusion of treatment of osteoporotic men in the indication for Aclasta, the MAH has provided complementary data on the difference in baseline BMD and BMD increases from baseline between males and females in study 2310 (fracture prevention after low energy trauma hip fracture). Furthermore the differences in baseline BMD and BMD increases between the males in study 2310 and the women in study 2301 (postmenopausal osteoporosis) have been compared.

The absolute change in BMD for males and females from baseline during study period in studies 2310 and 2301 were similar. The between-treatment comparison of change in percentage total hip BMD relative to baseline did not significantly differ between males and females.
It was agreed by the CHMP that in this case it is acceptable to use hip BMD data for bridging data in males to a PMO population. It was also accepted that male osteoporotic patients can have a somewhat higher basal BMD than a female osteoporotic population.

Although some risk factors for fractures in baseline data are not identical between the males in study 2310 and the PMO women in study 2301, the males are considered to have a total risk of fracture comparable to that of the 2301 study population. The circumstances that these men had already

suffered a low energy hip fracture and that the placebo group of males in study 2310 had a fracture rate comparable to the placebo group in 2301 are important for the CHMP's conclusion that the male subpopulation in study 2310 had a similar risk of fracture as the PMO population in study 2301. To some extent the estimation of fracture risk in the male population of study 2310 is also supported by external literature data.
The population of males studied, including the population in Study 2308 was considered representative of the target population and supports an indication in male osteoporosis.

The CHMP concluded that the MAH has performed thorough analyses of the risk factors for fractures in the osteoporotic male population in comparison to populations of postmenopausal women and to populations of osteoporotic men in other studies. Due to differences between sexes in factors such as hormonal status and intercurrent diseases, the baseline data can not be expected to be exactly identical in the different study populations.

Overall, the CHMP considered that efficacy in the general male osteoporotic population was convincingly shown, according to the Guideline on Primary Osteoporosis, as all four above-mentioned criteria for bridging were fulfilled. The bridging of the postmenopausal osteoporosis efficacy data to the male population of the efficacy study was therefore considered sufficiently justified.

Thus in the CHMP's opinion, the criteria for bridging data from the males in study 2310 to the PMO population have therefore been fulfilled and the indication male osteoporosis can be accepted for Aclasta.

Conclusions on clinical safety
The CHMP considered that the adverse event profile is consistent with adverse events observed in previous studies with zoledronic acid in non-oncology indications. No new safety signals have emerged. Adverse reactions were mainly post-infusion reactions, such as pyrexia and influenza-like illness, which occur within 3 days. The incidence of post-dose symptoms decreased with subsequent infusion, confirming the results of previous studies with repeated infusions. The CHMP further concluded that the safety in men with osteoporosis was comparable to the data in postmenopausal women with osteoporosis.

Benefit / Risk Assessment
The CHMP concluded that an appropriate risk/benefit could be demonstrated in postmenopausal women after hip fracture. This population is already covered by the existing indication (osteoporosis in post-menopausal women at increased risk of fracture). The fact that this population is included in the existing indication was however reflected in the new indication. The bridging to extend the indication to include male osteoporosis was considered to be sufficiently justified in line with the Guideline on Primary Osteoporosis. It could further be demonstrated that the data from the population studied in study 2310 could also be extrapolated to men at risk of fracture that did not have a previous hip fracture. Concerning Safety, no new worrying signals were detected, and it could be demonstrated that post-infusion reactions decrease with the number of subsequent infusions. The introduction of a loading dose of vitamin D before infusion with Aclasta for the group of patients that suffered a recent low-trauma hip fracture was considered beneficial[A42]. The study data also supported a change in the recommendation not to use Aclasta in patients with creatinine clearance from <40 ml/min to <35 ml/min. Overall, the CHMP therefore concluded that the benefit/risk continues to be favourable.

CHANGES TO THE PRODUCT INFORMATION

The detailed changes can be found in the final approved highlighted SPC/Annex II/ Labelling/ PL attached to this report.

Changes were also made to Annex II in section "Conditions or restrictions with regard to the safe and effective use of the medicinal product" to reflect that revised educational material for healthcare professionals and patients will be made available following the launch of the new indication.

Further to the assessment and the scientific discussions held at the CHMP, the following changes to the Product Information were requested and subsequently implemented by the MAH.
The PL was updated accordingly.

SPC:

Section 4.1 Therapeutic Indications
The CHMP proposed that additional information to be included in section 4.1 of the SPC should be more exact than the wording proposed by the MAH. Additionally, the initially proposed indication wording relating to prevention of Osteoporosis was not in line with the "Guideline on the evaluation of new medicinal products in the treatment of primary osteoporosis". The following wording was proposed: "Treatment of osteoporosis in post-menopausal women at increased risk of fracture, including those with a recent hip fracture" This wording was considered to be line with the latest version of SPC Guidelines for section 4.1. Taken together with the fact that the CHMP also agreed to include males in the indication, the CHMP agreed on the final wording (changes are highlighted in bold)

"Treatment of osteoporosis
- in post-menopausal women
- **in men**

at increased risk of fracture, **including those with a recent low-trauma hip fracture.**"

Section 4.2: Posology and method of administration
It seemed very likely that delayed dosing in humans would give better results than dosing immediately after fracture. The CHMP agreed that patients with a recent low trauma hip fracture should be dosed at least 2 weeks after hip fracture surgery. Thus, information about the ideal timing after fracture repair was included in sections 4.2 and 5.1 of the SPC.

The CHMP considered that it would be possible that as the demand for calcium is increased following a fracture, without a loading dose, the risk of hypocalcaemia with administration of zoledronic acid could be increased. Therefore, a statement on loading dose of vitamin D in Aclasta treatment after fracture was added to section 4.2 of the SPC.

Section 4.4 Special warnings and precautions for use
This section was revised in line with the changes regarding the loading dose of vitamin D in section 4.2.

Section 4.8: Undesirable effects
This section has been further revised to reflect the final safety data from study 2308 and 2310.
Since baseline data, especially with respect to age and gender, as well as the recommendations given to patients for prophylaxis against post-dose symptoms, differed between studies 2301 and 2310 and as 2301 is a much larger study, the additional information on the differences in terms of AEs between the studies 2310 and 2301 was included in the SPC.

Section 5.1: Pharmacodynamic properties
Overall, this section was revised to enhance readability by reduction of the size of the text.

The fact that no significant effect on fracture rate in males could be observed is reflected in this section of the SPC .

The rate of new morphometric fractures was similar to the rate in post-menopausal females, although the few cases make any interpretation in this respect uncertain. Information on lumbar spine BMD data from Study 2308 was also included.

The (non-significant) reduction in clinical fractures in study 2310 was 15% in the male population in Study 2310 compared with 33% in Study 2301, however Study 2310 was not powered to show

differences in fracture rates in subgroups. The fact that no significant effect on fracture rate in males could be observed is therefore reflected in the SPC section 5.1.

Labelling
The CHMP agreed to the justification of the MAH not to include Braille, as Aclasta will only be administered by healthcare professionals. Therefore the text in section 16 “Information in Braille” (on folding box only) was removed.

CONCLUSION

On 24 July 2008 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, Labelling and Package Leaflet.

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
Non-clinical	The MAH commits to provide a phase II fate and effects analysis according to the CHMP/SWP/447/00 guideline on the environmental risk assessment of medicinal products for human use.	Tier A completed Q4 2009; Further studies (if needed) to be decided later.
Clinical/Pharmacovigilance	The MAH commits to provide results (efficacy and safety) from the extension study 2301E1 (6 years) should be provided.	Q1 – 2010
Pharmacovigilance	The MAH commits to perform an extension of study 2301E1 for an addition of 3 years. A study protocol should be presented within 3 months.	Q1 - 2013
Pharmacovigilance	The MAH commits to perform a long-term observational epidemiological study (for at least 10 years) with the end-points; cardio- and cerebrovascular disease and fractures/delayed fracture healing. A study protocol should be presented within 3 months. At 5 years an interim analysis will be performed to determine how many patients are still treated with Aclasta that will guide whether a further 5 years will be justified . The MAH commits to update the study protocol to cover the extended target population.	interim report by Q3-2013 final report by Q3-2018 Updated protocol Q3 2008
Pharmacovigilance	An updated RMP will be submitted to provide a revised description of the long-term observational epidemiological study to include the extended target population.	Q3 - 2008