



European Medicines Agency

Product Name: Aclasta
Procedure number: EMEA-H-595-II-10-AR

SCIENTIFIC DISCUSSION

I. SCIENTIFIC DISCUSSION

1.1. Introduction

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

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 non-oncology indication (Paget's disease of bone), zoledronic acid is approved under the trade name Aclasta in 50 countries as of 30 April 2006, not including the US and Australia.

Aclasta is presented as ready to use solution for infusion. It consists of 5 mg zoledronic acid in 100 ml of solution, containing mannitol as an isotonicising agent and sodium citrate as buffering agent.

The MAH has previously received 3 Scientific Advices on the development program in postmenopausal osteoporosis (PMO), in November 2001, in January 2003 and in June 2005. The first 2 advices were mainly concerned with the pre-clinical development while the last one included questions regarding the acceptability of submitting interim data from the 3-year pivotal study in PMO. It was agreed that data with a cut-off date in August 2005 would in principle be acceptable if efficacy was shown both for vertebral and hip-fractures. The cut-off date was thereafter changed to March 2006.

The purpose of the current submission for a Type II variation for Aclasta was to seek approval for the treatment of PMO. Aclasta will be administered annually as a 5 mg IV infusion over at least 15 minutes.

1.2 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. Data from cultures of osteoclasts generated *ex vivo* from murine bone marrow cells and human peripheral blood monocytes were now included in the submission supporting this variation. Additionally, mechanistic studies investigated the binding of zoledronate to bone mineral, its internalisation by osteoclasts, and the interaction of the compound with the active site of its target enzyme farnesyl pyrophosphate synthase (FPPS).

***In vivo* data**

In vivo activity was shown in short-term experiments with multiple sc dosing in intact rats, ovariectomised (OVX) rats, and animals with inflammation-induced osteolysis. Two long-term GLP studies in OVX rats (0.3 – 7.5 µg/kg/week sc for 52 weeks) and OVX monkeys (0.5 – 12.5 µg/kg/week sc for 69 weeks) were performed specifically to assess bone safety in addition to efficacy.

The MAH also submitted long-term safety studies in rabbits focusing on the effect of zoledronic acid on bone fracture healing as well as two studies in two rat models of osteonecrosis.

Discussion on non-clinical aspects

The non-clinical studies provided by the MAH support the safety and efficacy of an annual 5 mg i.v. infusion of zoledronate for the intended indication, namely the treatment of postmenopausal osteoporosis (PMO).

Evidence from enzymatic and cellular studies indicated that the nitrogen-containing bisphosphonates exert their anti-resorptive effect on osteoclasts by inhibiting a key enzyme in the mevalonate pathway, FPPS.

At the time of the initial Marketing Authorisation, the CHMP expressed concerns about the possibility that zoledronate can decrease bone quality, at least during a certain period during treatment. The CHMP considered that the new studies presented by the MAH are reassuring in this respect, even if decreased bone quality in patients cannot be ruled out based on these results in animal models.

1.3 Clinical aspects

Data from one large randomised, double-blind, placebo-controlled pivotal study, **Study 2301**, was submitted to support the efficacy claim. In addition, 2 randomised, double-blind, active-controlled trials, **Study 2313** and **Study 2315**, provide supportive efficacy data in comparison with alendronate. **Study 0041** was a double-blind, placebo-controlled, dose-ranging phase II study providing supportive efficacy data with different dose regimens of zoledronic acid. Additionally, 2 uncontrolled, supportive studies **Study 0041E1** and **Study 0041E2** in the target indication were submitted. The marketed presentation of Aclasta was used in most of the clinical studies of PMO

1.3.1 GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

1.3.2 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 one subsequent PK/PD study. Additional pharmacokinetic studies have not been performed in either patients with Paget's disease or women with postmenopausal osteoporosis.

The exposure was about 30-40% higher in patients with mild to moderate renal impairment. Multiple dosing of 4 mg i.v. every 28 days did not lead to accumulation. No dose adjustments have been considered necessary in these patients for the cancer indications or Paget's disease. Due to the paucity of data on patients with severe renal impairment, the use of zoledronic acid in this group is not recommended.

The MAH suggested that no changes were necessary concerning recommendations for special populations. A 30-40% increase in exposure in patients with mild-moderate renal impairment was not considered clinically important for the previously approved indications. However, for the more "healthy" population, women with postmenopausal osteoporosis, the CHMP considered that the safety assessment needs to take into account that bone exposure could increase slightly in patients with renal impairment (see also discussion on clinical efficacy below).

1.3.3 Clinical efficacy

Dose-response studies

Study 0041

This was a phase II, multicentre, randomised, double-blind, parallel-group, dose-ranging trial using a placebo control and 5 dose regimens of zoledronic acid. It had been previously assessed in the initial application for the indication Paget's disease. The study included 351 patients with a lumbar spine BMD T-score ≤ -2 . The results from this study provided the basis for dose selection for phase III. The primary objective of the study was to determine which of the 5 zoledronic acid dose regimens were superior to placebo in preventing bone loss over 12 months. Secondary objectives were to evaluate markers of bone turnover and drug safety. The zoledronic acid dose regimens used were 0.25 mg, 0.5 mg, and 1 mg IV (every 3 months), 2 mg IV (at Months 0 and 6), and 4 mg IV (at Month 0). Patients also received daily calcium during the 12-month treatment period. The primary efficacy variable was the percent change from baseline in bone mineral density (BMD) at Month 12.

The mean percent change in BMD at Month 12 increased for all zoledronic acid groups, ranging from 4.8% to 5.7% after 12 months of treatment. The placebo group showed a marginal increase of 0.4%.

All dosing regimens demonstrated similar and statistically indistinguishable increases in BMD over 12 months; the 1 mg dose administered every 3 months resulted in slightly smaller numerical gains in BMD than the other regimens (not statistically significant). Reductions in bone turnover markers (serum carboxy-terminal collagen crosslinks (CTx) and urine N-telopeptide cross-links (NTx)) were also similar for all dosing regimens. However, higher total doses were associated with a longer duration of effect on bone markers and since bone turnover was not controlled within the premenopausal range for all patients the decision was made to increase the dose to single 5 mg infusion administered every 12 months.

The CHMP considered that the optimal dose had not been demonstrated in this study and that there were concerns that the dose might be unnecessarily high at time of the assessment of the initial Marketing Authorisation. However, analyses of bone turnover marker data, as well as bone biopsy findings that were available at that time, created no immediate concerns for bone safety however this needed to be verified by confirmatory data from patients with Paget's disease as committed by the MAH.

Main clinical studies

Study 2301

This was a randomised, double-blind, placebo-controlled multicentre study to evaluate the safety and efficacy of zoledronic acid in the treatment of osteoporosis in postmenopausal women 65-89 years of age in support of this variation. The efficacy results initially presented by the MAH were based on interim data collected through 31 March 2006, at which time the study was still ongoing and which constitutes the primary efficacy database for this study. The additional efficacy analysis performed based on the date of 01 June 2006 (last patient completed) has been submitted by the MAH during this variation procedure and did not significantly alter the assessment of the data.

Methods

Study Participants

The trial population consisted of postmenopausal women between the ages of 65 and 89 years (inclusive) with osteoporosis.

Inclusion criteria:

Women aged 65 to 89 years with either of the two following fracture criteria: radiological evidence of at least two mild or one moderate vertebral fracture(s) and a femoral neck bone mineral density (BMD) T-score ≤ -1.5 or femoral neck BMD T-score ≤ -2.5 with or without evidence of an existing vertebral fracture.

Exclusion criteria:

No concomitant use of bisphosphonates, fluoride, strontium, systemic corticosteroids or PTH was allowed. Patients were not to have a GFR < 30 ml/min at baseline or to have had hyperparathyroidism, iritis or uveitis.

Treatments

Participants were placed into 1 of 2 treatment strata. In Stratum I no concomitant treatment for osteoporosis was permitted. In Stratum II were those who were on their 'usual care' osteoporosis medication at or prior to randomisation. 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. Within each treatment stratum, patients were randomly assigned to receive either zoledronic acid or placebo. All patients received supplemental calcium and vitamin D. An intravenous formulation of zoledronic acid was administered annually at randomisation, at Year 1, and at Year 2.

Objectives

The primary objectives of the study were to show the superiority of zoledronic acid relative to placebo in reducing the incidence of vertebral and hip fractures in postmenopausal women with osteoporosis.

In detail, the primary objectives were to show that:

- a) the proportion of patients with at least one new vertebral fracture over 3 years is significantly lower for the zoledronic acid treated group compared to the placebo group among patients not taking concomitant therapy for osteoporosis at baseline (stratum I)
- b) the time to first hip fracture is significantly longer for the zoledronic acid group compared to the placebo group among all patients (stratum I and stratum II)

The principal secondary objectives were:

- a) The relative change from baseline in biochemical markers of bone turnover (b-CTx, BSAP, P1NP)
- b) Stadiometer height change from baseline,
- c) Disability, i.e. days of disability due to a fracture or to back pain,
- d) Safety parameters
- e) Morphometric vertebral fractures,
- f) Clinical fractures,
- g) BMD.

Randomisation and Sample size

After a washout period of up to 2 months, all patients were randomised within each stratum to either zoledronic acid or placebo in a 1:1 ratio and received a single intravenous infusion of zoledronic acid (5 mg) or placebo at 0, 12, and 24 months. Chronic efficacy and safety was monitored at 6 months and at 1, 2, and 3 years. Acute renal safety was monitored 9 to 11 days after each dose in a renal safety cohort. This cohort was to include the first 600 patients enrolled into the study plus 2900 additional patients from selected clinical sites enrolled throughout the course of the trial. The actual number of patients randomised in the renal safety cohort was 5035.

Blinding

Randomisation was performed using a validated system that automated the random assignment of treatment groups to randomisation numbers. The investigators, site personnel, the sponsor, as well as

the designated clinical research organisation and the coordinating centre personnel involved in the conduct of the trial were blinded to the trial medication.

Statistical methods

Study Populations

The intent-to-treat (ITT) population included all randomised patients (excluding one centre).

The ITT population was used as the analysis population for all efficacy variables, unless otherwise specified. The modified ITT (mITT) population at each annual visit included all the ITT patients in Stratum I who were evaluable for incident vertebral fractures over the period being analysed for at least one vertebra.

The per-protocol population I was used for the analysis of the time to the first hip fracture and included the patients in the ITT population who did not have any major protocol violations that would potentially bias the analysis of the time to first hip fracture in Strata I+II.

The per-protocol population II (Analysis of proportion of patients with new morphometric vertebral fractures over 36 months) was used for the analysis of morphometric vertebral fractures. This population included the patients in the mITT population who did not have any major protocol violation that would potentially bias the analysis of the proportion of patients with at least one new morphometric vertebral fracture in Stratum I.

The safety population included all subjects in the ITT population who received at least one infusion of study drug. The safety population was used as the analysis population for all the safety assessments, unless otherwise specified.

Statistical tests

The tests of comparability were performed for descriptive purposes only, and did not serve as a basis for determining entry of explanatory variables into the respective models. When these tests yielded significant results they were considered as extra information in interpreting the statistical analyses performed on the primary and secondary efficacy variables. Different background and demographic variables were analysed to assess the baseline comparability of the two treatment groups:

For the ITT patients in Stratum I+II combined, Cochran-Mantel-Haenszel tests stratified by stratum were used to evaluate the baseline comparability of the categorical variables. Concerning the continuous variables, for the ITT patients in Stratum I+II combined, two-way analysis of variance (ANOVA) models with treatment and stratum as explanatory variables were used.

Testing for the efficacy endpoints

The analysis of morphometric vertebral fractures was performed with respect to the proportion of patients in Stratum I with at least one new vertebral fracture over 36 months. The between-treatment comparison was performed using a logistic regression model with treatment and baseline fracture status (i.e. number of vertebrae with prevalent fractures at baseline) as explanatory variables. The log-odds ratio, θ_V , was estimated by the maximum likelihood estimate of the treatment coefficient term in the logistic regression model with the 95% CI reported based on the likelihood ratio approach. The p-value was obtained based on the likelihood-ratio test.

The analysis of hip fracture was conducted with respect to the time to the first hip fracture for patients in both strata. The between-treatment comparison was conducted using a Cox proportional hazard model with treatment as a factor stratified by study stratum. The loghazard ratio, θ_H , was estimated by the maximum likelihood estimate of the treatment coefficient term in the stratified Cox proportional hazard model with the Wald-type 95% CI reported. The p-value was obtained based on the stratified log-rank test.

The estimated treatment effect along with the corresponding two-sided 95% confidence intervals and p-values were provided.

Participant flow

Overall, 7736 patients, 6084 (78.65%) from Stratum I and 1652 (21.35%) from Stratum II, were randomised to zoledronic acid (3875 patients) or placebo (3861 patients). Of those randomised, 6517 (84.24%) patients completed the study and 1219 (15.76%) patients discontinued from the study.

The proportion of patients who discontinued was comparable for the two treatment groups. The same was true for the two most common reasons for study discontinuation: withdrawal of consent (7.66% for zoledronic acid and 7.36 % for placebo) and death (3.35% for zoledronic acid and 2.90% for placebo).

Results

Recruitment

Recruitment for study 2301 was undertaken at 240 centers in 27 countries with the randomisation stratified by stratum and center.

Baseline data (ITT population)

Baseline demographic and background characteristics were comparable for the two treatment groups. Most patients (78.97%) were Caucasian. The mean age was 73.1 years and virtually all patients (99.81%) were at least 65 years of age and 38.12% of patients were at least 75 years of age. The mean body weight was 60.3 kg, and the mean body mass index (BMI) was 25.3 kg/m². The majority were non-smokers (91.5%), naïve to prior bisphosphonate use (85.0%), and 5 through 30 years postmenopausal (77.8%).

Nearly 72% of all patients had femoral neck T-score of -2.5 or less, and 63.25% of the patients had at least one prevalent baseline vertebral fracture. The median baseline height, non-stadiometer measurement, was 153.5 cm (range: 115 to 178) and as measured by a stadiometer was 1551.0 mm (range: 1295 to 1791 mm). The mean BMI of the overall population was 25.26 kg/m².

Prior to inclusion, the most commonly used concomitant medications for non-osteoporosis indications were acetylsalicylic acid (ASA), levothyroxine sodium, and paracetamol. The other commonly used classes of drugs were reflective of the co-morbidities that were present in this patient population. Overall, the most commonly used osteoporosis medication prior to the start of study drug in both the zoledronic acid and placebo group was hormone replacement therapy (HRT), followed by bisphosphonates, calcitonin, and SERMs.

Concomitant medications

All patients as per protocol were required to be receiving 1000 to 1500 mg/day of calcium and between 400 and 1200 IU of Vitamin D after start of the study drug.

Overall, the distribution of concomitant medications was very similar between the treatment groups. The most commonly used concomitant medications/nondrug therapies for patients in either treatment group included over-the-counter pain relievers and physical/physiotherapy.

The incidence of analgesic usage was similar between the zoledronic acid and placebo groups. However, Paracetamol had a higher rate of usage in the zoledronic acid group (43.10% of patients) as compared with the placebo group (33.59%), possibly due to the protocol's recommendation of paracetamol as the analgesic to manage post-dose symptoms. The majority of patients in both treatment groups used NSAIDs or ACE inhibitors after the start of study drug (72.10% for zoledronic acid and 72.34% for placebo). The usage of both was balanced in the treatment groups.

The patient population represented the elderly female post-menopausal population at risk for osteoporotic fractures. About 40% were 75 years or older. About 60% of the patients had one or more

vertebral fracture at baseline and about 70% had osteoporosis as defined by a femoral neck T-score ≤ -2.5 . The majority of patients (about 80%) received no other anti-osteoporotic treatment (Stratum I). The majority, (85%) was bisphosphonate-naïve. The treatment groups were well balanced with regard to demographic, baseline disease and other baseline characteristics.

Numbers analysed

A total of 7736 patients were included in the ITT population: 3875 in the zoledronic acid group and 3861 in the placebo group. For each analysis population, the proportions of patients were comparable for the two treatment groups.

The analysis of new morphometric vertebral fractures over 36 months was performed on the mITT population. The analysis of time to first hip fracture was performed on the ITT population, unless otherwise specified.

The data presented was based on the intention-to treat (ITT) population of 7736 randomised patients, 6084 (78.65%) in Stratum I and 1652 (21.35%) in Stratum II. Of the 7736 randomised patients, 22 patients did not receive any study drug, 7714 received the first infusion, 6926 received the second infusion, and 6297 received the third infusion. Of the patients who were included in the ITT population, 1219 (15.76%) discontinued from the study prematurely.

The modified intent-to-treat (mITT) population at each annual visit included all the ITT patients in Stratum I who had at least one post baseline evaluable radiograph for at least 1 vertebra. Of the 6084 Stratum I patients, 5675 were evaluable for morphometric vertebral fractures over 36 months for at least one vertebra..

Outcomes and estimation

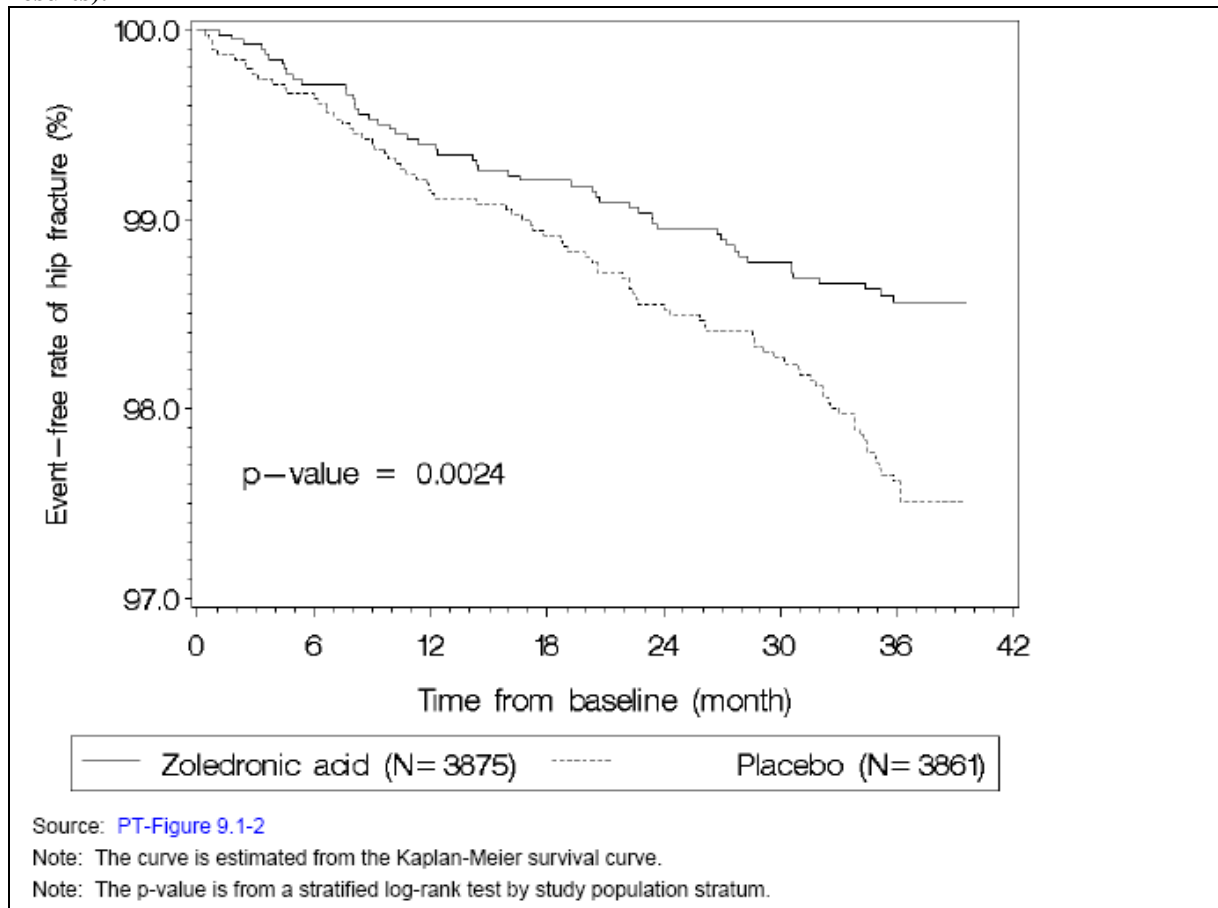
Efficacy results

Over 36 months, for the first primary efficacy variable, new morphometric vertebral fractures in the mITT population, occurred in 3.26% of zoledronic acid-treated patients compared to 10.87% of placebo-treated patients in Stratum I.

This corresponded to a relative risk reduction of 70% over 36 months (95% CI: 62%, 76%) and an odds ratio estimated from the logistic regression model of 0.27 ($p < 0.0001$; 95% CI: 0.21, 0.35). A 69% reduction in risk was also observed in the per-protocol (PP) population.

The second primary efficacy variable was time to first hip fracture in Strata I and II (ITT population). A total of 140 patients had a hip fracture, 52 patients in the zoledronic acid group and 88 in the placebo group. The three-year event rates based on Kaplan-Meier estimates were 1.44 % and 2.49% for the zoledronic acid and placebo groups, respectively. It was shown that zoledronic acid significantly reduced the risk of new hip fracture as compared with placebo. The results for zoledronic acid relative to placebo showed a 41% reduction in the risk of hip fractures ($p = 0.0024$). A summary of the results is presented in Figure 1.

Figure 1: Kaplan-Meier curve of time to first hip fracture, study 2301 ITT population (final results).



For time to first hip fracture, the event rate in bisphosphonate-naïve patients was 1.25% in zoledronic acid-treated patients (n=39) compared to 2.66% in placebo-treated patients (n=80). This corresponded to a 51% reduction in the risk of hip fracture (hazard ratio (HR) =0.49; 95% CI: 0.33, 0.72). In comparison, for those who were previously treated with bisphosphonates, zoledronic acid-treated patients had an event rate of 2.38% (n=12) compared to 1.58% (n=8) in placebo-treated patients. With a small number of events in total (n=20) this corresponded to a statistically non-significant 49% increase in the risk of hip fracture (HR=1.49; 95% CI: 0.61, 3.64).

In patients with a femoral neck BMD T-score above -2.5, the hazard ratio for hip fracture was 0.20 (95%CI 0.06, 0.69) compared with 0.66 (95%CI 0.46, 0.96) in patients with a T-score ≤ -2.5. The test for interaction was close to significance, (p=0.070). The reduction in vertebral fractures was similar in both these sub-groups.

For “time to first clinical fracture”, the event rate in bisphosphonate-naïve patients was 8.06% (n=251) compared to 12.89% in placebo-treated patients (n=392). This corresponded to a 37% reduction in the risk of clinical fractures (HR=0.63; 95% CI: 0.54, 0.74). For those who were previously treated with a bisphosphonate a smaller effect was shown with an event rate of 10.51% in zoledronic acid-treated patients (n=56) compared to 12.75% in placebo-treated patients (n=63). This corresponded to a 12% reduction in the risk of all clinical fractures (HR=0.88; 95% CI: 0.61, 1.26).

Comparable efficacy was demonstrated for vertebral fracture reduction at 36 months and in the incidence of first hip fracture over time in both Strata. The relative risk of at least 1 new vertebral fracture at 36 months in Stratum I was 0.30 (95% CI: 0.24, 0.38, p<0.0001), and in Stratum II was 0.44 (95% CI: 0.29, 0.69). The event rate for hip fracture in Stratum I was 1.48% and 2.56% for zoledronic acid and placebo respectively. In Stratum II the event rate was 1.30% in the zoledronic acid group compared to 2.24% in the placebo group. The hazard ratio of the incidence of first hip fracture

over time was 0.59 (95% CI: 0.41, 0.87, $p=0.0069$) in Stratum I and was 0.58 (95% CI: 0.27, 1.27, $p=0.1686$) in Stratum II.

The risk of a new morphometric vertebral fracture following treatment with zoledronic acid was reduced in Stratum I patients with previous bisphosphonate use (RRR=65%, 95% CI: 38%, 81%), relative to those Stratum I patients who are bisphosphonate-naïve (RRR=71%, 62%, 77%). Within Stratum II, vertebral fracture relative risk reductions of 49% and 70% were observed in bisphosphonate-naïve and previously treated patients with bisphosphonates, respectively. Within Stratum II, the number of vertebral fractures was relatively small ($n=86$ overall) compared to that in Stratum I ($n=402$ overall).

All 21 pre-specified secondary efficacy variables demonstrated superiority of zoledronic acid relative to placebo. Treatment with zoledronic acid significantly reduced the risk of developing new morphometric vertebral fractures, new or worsening vertebral fractures, and moderate/severe vertebral fractures over 12, 24 and 36 months, relative to placebo ($p < 0.0001$).

Zoledronic acid was effective in Stratum I in reducing the proportion of patients with at least one new fracture in all demographic and disease subgroups tested. The pre-specified secondary endpoints for the proportion of patients with a new vertebral fracture over 36 months in Stratum I included:

- Age 75 years and older (RRR = 60%, $p<0.0001$).
- No prevalent vertebral fracture at baseline (RRR = 70%, $p<0.0001$).
- with 1 prevalent vertebral fracture at baseline (RRR = 64%, $p<0.0001$)
- with at least 2 prevalent vertebral fractures at baseline (RRR = 72%, $p<0.0001$)

The time to first fracture in Strata I and II for any clinical fracture, clinical non-vertebral fractures, clinical vertebral fractures, and other clinical fractures for the ITT population is presented in Table 2.

Table 2: Between-treatment comparisons of the incidence of first clinical fracture over time by fracture location – placebo-controlled studies, Study 2301 (ITT population, final results)

Location	Treatment	N	n	Event rate (%) ⁴	Hazard ratio(%) 95% CI ⁵	p-value ⁶
Any clinical fracture ¹	Zoledronic acid	3875	308	8.42	0.67	<0.001
	Placebo	3861	456	12.83	(0.58, 0.77)	
Clinical vertebral fracture ²	Zoledronic acid	3875	19	0.53	0.23	<0.001
	Placebo	3861	84	2.59	(0.14, 0.37)	
Non-vertebral fracture ¹	Zoledronic acid	3875	292	7.97	0.75	<0.001
	Placebo	3861	388	10.71	(0.64, 0.87)	
Hip	Zoledronic acid	3875	52	1.44	0.59	0.0024
	Placebo	3861	88	2.49	(0.42, 0.83)	
Wrist	Zoledronic acid	3875	97	2.68	0.81	0.1242
	Placebo	3861	120	3.32	(0.62, 1.06)	
Arm	Zoledronic acid	3875	41	1.13	0.58	0.0047
	Placebo	3861	71	1.95	(0.39, 0.85)	
Rib	Zoledronic acid	3875	35	0.93	1.06	0.8021
	Placebo	3861	33	0.95	(0.66, 1.71)	
Other ³	Zoledronic acid	3875	92	2.53	0.76	0.0424
	Placebo	3861	122	3.36	(0.58, 0.99)	

Source: [PT-Table 9.2-3](#)

¹ Excluding finger, toe, and facial bone fractures.

² Clinical vertebral fracture includes thoracic spine fracture and lumbar spine fracture.

³ Other fracture excludes clinical vertebral, hip, wrist, arm, ribs, finger, toe, and facial bone fractures.

⁴ The event rate is from Kaplan-Meier estimate at Month 36.

⁵ The hazard ratio/95% CI of zoledronic acid vs. placebo is computed from a stratified Cox proportional hazards regression model with treatment as a factor and stratified by study population stratum. A hazard ratio <1 implies that a zoledronic acid-treated patient has a lower risk of having the event than a placebo-treated patient.

⁶ The p-value is calculated from a stratified log-rank test by study population stratum.

Note: Pathological fractures and fractures due to excessive trauma are excluded.

Bone biomarkers

At Month 36, zoledronic acid-treated patients had approximately a 55% greater magnitude of reduction in bone resorption as measured by serum b-CTX compared to placebo-treated patients ($p < 0.0001$). Following the third dose, the only infusion after which profiling was performed, a decrease in serum b-CTX was observed at the 9-11 day timepoint followed by a gradual increase thereafter.

At Month 36, zoledronic acid-treated patients also had approximately a 29% greater magnitude of reduction in bone formation as measured by serum BSAP compared to placebo-treated patients ($p < 0.0001$). Based on the profile following the 3rd infusion, the nadir for BSAP occurs at 3 months and increases thereafter.

A further bone formation marker, P1NP, was assessed at baseline, 12, 24 and 36 months. At Month 36, zoledronic acid-treated patients had approximately a 52% greater magnitude of reduction in bone formation as measured by serum P1NP compared to placebo-treated patients ($p < 0.0001$).

Height measurements

At the annual stadiometer measurements, patients who received zoledronic acid had a decrease in height of -1.69, -3.05, and -4.24 mm at Month 12, Month 24, and Month 36 compared to decreases of -2.18, -4.83, and -6.96 mm, respectively, for placebo-treated patients. At Month 36, zoledronic acid-treated patients had significantly less reduction relative to placebo ($p < 0.0001$).

Zoledronic acid treated patients have fewer days on average with limited activity (60.5 versus 71.9) and with bed rest (8.2 versus 9.2) relative to placebo treated patients due to back pain. Zoledronic acid

patients also have fewer days on average with limited activity (5.9 versus 9.9) and with bed rest (1.6 versus 2.2) relative to placebo treated patients due to fracture.

Bone biopsies

Bone biopsies were performed after 33 to 36 months of treatment in a subset of patients. A total of 152 biopsies were obtained, 99 of them had micro computed tomography (CT) - evaluable for all parameters. This technique showed a significantly higher trabecular bone volume in the zoledronic acid treated patients and these patients also had a significant higher trabecular number, decreased trabecular spacing and improvement in connectivity density. These findings indicated preservation of trabecular structure.

Quantitative histomorphometric analysis was performed after tetracycline double labelling on 111 evaluable biopsies; 82 of these were completely evaluable. The results showed that bone tissue turnover at the tissue level was reduced. Normal osteoid formation and mineralisation of newly formed bone was seen and no signs of osteomalacia were found. Adynamic bone was not seen in the bone biopsies performed.

The MAH presented a comparison of bone biopsy results from the Study 2301 and Study 2313, a study that was assessed for the initial Marketing Authorisation and in which a subset of patients underwent bone biopsy (n=25). The comparison of activation frequencies in Studies 2301 and 2313 showed that the absolute values for the parameter activation frequency (Ac.f) were similar. The relative reduction seen with zoledronic acid, as compared to the placebo group with bone biopsy assessment in Study 2301, was in the order of 71% to 74% in Study 2301 and Study 2313, respectively. The CHMP agreed that the values for activation frequency in both studies were similar.

Fracture rates in different age categories

The CHMP noted that the rate for hip fractures in patients ≥ 75 years (18%) compared with younger patients was marginally reduced. Study 2301 was however not powered a priori to detect statistically significant between-treatment differences for fracture endpoints within subgroups e.g. the relationship between age and anti-fracture efficacy of zoledronic acid on non-vertebral fractures. However, certain subgroups were identified in the Statistical Analysis Plan as key secondary efficacy variables (e.g. Age ≥ 75 years, number of prevalent fractures at baseline [0, 1, ≥ 2], see Table 3).

Table 3: Hip fracture relative risk reduction by age.

Age group	Zoledronic acid n/N (Event rate) ¹	Placebo n/N (Event rate)	Hazard ratio (95% CI) ²	Within-subgroup p-value ³	P-value for interaction ⁴
< 70	7/1140 (0.65)	24/1174 (2.13)	0.30 (0.13, 0.70)	0.0029	0.1222
70 - 74	13/1238 (1.10)	25/1235 (2.30)	0.53 (0.27, 1.03)	0.0556	
≥ 75	32/1497 (2.36)	39/1452 (2.96)	0.82 (0.51, 1.32)	0.3501	

¹ n is the number of patients with hip fracture over time, N is the number of patients within each subgroup, and % is Kaplan-Meier estimate of the event rate at Month 36 (the approximate median duration of follow-up).

² The hazard ratio/95% CI of zoledronic acid versus placebo is computed from a Cox proportional hazards regression model with treatment as a factor within the subgroup. A hazard ratio < 1 implies that a zoledronic acid-treated patient has a lower risk of having a hip fracture than a placebo-treated patient.

³ The within-subgroup p-value is calculated from a log-rank test.

⁴ The p-value for the subgroup and treatment interaction is from a Cox proportional hazards regression model with treatment, subgroup, and the interaction as factors

The apparent lesser reduction of hip fractures in patients over the age of 75 was not statistically significant, and subgroup analyses of other non-vertebral fractures as well as clinical vertebral fractures by age did not corroborate this trend. The presence of lower bone turnover in this patient subpopulation was not confirmed, and the treatment effect of zoledronic acid as reflected in bone histomorphometric analysis of bone turnover, bone structure preservation by μ CT and reductions in biomarker levels did not show a trend towards lesser effects in patients ≥ 75 . Thus, when analysing all

fractures as well as tissue level and biomarker responses, no consistent trend towards lesser effects of zoledronic acid in the oldest age group could be substantiated by the MAH.

The CHMP highlighted that in general, bisphosphonates are most effective at sites where bone turnover is high, i.e. where trabecular bone predominates as in the vertebrae. The relative contributions of high versus low bone turnover depending on age are difficult to determine, but it appeared that also in older patients a benefit exists in suppressing bone resorption although decreased bone formation also contributes to osteoporosis in this population. For Aclasta, the risk reduction for all non-vertebral fractures did not decrease with higher age but for wrist fractures, risk reduction decreased in patients above the age of 70. In parallel to other bisphosphonates, the effect was most prominent at the vertebrae and it could not be excluded that the decreased efficacy at non-vertebral sites such as the hip and wrist could be due to the contribution of low bone turnover in the oldest.

Efficacy in patients previously treated with bisphosphonates

Increased risk of hip fracture was shown for patients previously treated with bisphosphonates and for other clinical fractures, the reduction in the risk was marginal (12%) in previously treated patients. The number of events deriving from a sub-population within the study (only about 15% of the total population were previous users of bisphosphonates) was however low (see also discussion on efficacy below).

Concerning bone turnover in bisphosphonate-experienced patients, the reduction in bone resorption markers was less pronounced with respect to the percent change from baseline, whereas the distribution of absolute values was very similar, despite differences in absolute numbers, baseline characteristics, and applied washout schedules. This lesser reduction was caused by a lower baseline value due to previous bisphosphonate treatment. There was no further decrease in bone turnover after zoledronic acid in patients previously treated with bisphosphonates. Rather, average bone turnover in patients treated with zoledronic acid was higher after 12 months than in patients continuing on alendronate.

Overall, biochemical markers for bone resorption (b-CTx) and bone formation (BSAP, P1NP) were reduced following study drug administration with zoledronic acid and maintained within the premenopausal range at Month 6 and Month 12 regardless of whether or not previous bisphosphonate treatment was received.

Summary of final Efficacy results

The primary and secondary efficacy results of the interim analysis were confirmed by those in the final analysis; details are summarised below:

Treatment with zoledronic acid reduced the risk of new morphometric vertebral fractures by 70% ($p < 0.0001$) over 36 months. Patients who received zoledronic acid had the risk of morphometric vertebral fractures reduced by 60% over 1 year, 71% over 2 years, and 70% over 3 years compared to patients receiving placebo. New/worsening fractures and moderate/severe fractures were reduced by approximately 60%-70% over 1, 2, and 3 years. All results were significant (all $p < 0.0001$).

Zoledronic acid reduced the likelihood of having a hip fracture over time by 41% (hazard ratio of 0.59, ($p = 0.0024$)). Patients, who were treatment-naïve to bisphosphonate therapy, exhibited a risk reduction of 51% ($p < 0.001$). Consistent statistically significant reductions in the risk of morphometric vertebral fractures over 3 years were demonstrated across the pre-defined categories, including age, geographical region, BMI, baseline femoral neck BMD T-score, prior use of bisphosphonates, number of baseline vertebral fractures, and baseline renal function.

Zoledronic acid reduced the risk of clinical fractures by 33%, clinical vertebral fractures by 77%, and non-vertebral fractures by 25% (all $p < 0.001$) and was superior to placebo in increasing or preserving BMD in patients over 36 months at the total hip, femoral neck, lumbar spine, and distal radius.

Significant increases relative to placebo were observed as early as 6 months at all sites except the distal radius where significant differences were observed beginning at 12 months.

Markers of bone formation and resorption were reduced following study drug administration with zoledronic acid and were maintained within pre-menopausal levels at the end of every 12-month period. The effect on reduction of bone markers was sustained over 36 months and no further reduction of those markers was observed with repeat dosing.

Zoledronic acid significantly reduced the magnitude of stadiometer height loss at Month 24 and Month 36 (both $p < 0.0001$) and reduced the number of days of “limited activity” time and bed rest due to fracture and back pain when compared to placebo (all $p < 0.01$)

Supportive studies

Study 2313

This was a multicentre, randomised, double-blind, active-controlled trial to evaluate the safety and tolerability of single i.v. zoledronic acid 5 mg as compared with oral alendronate 70 mg/week in postmenopausal women with moderate to severe osteopenia or osteoporosis who were being treated with alendronate for at least 1 year. The mean age was 67.8 years, and nearly two-thirds were at least 65 years of age (66.2%). The baseline demographic characteristics for the ITT population were comparable between the treatment groups.

The primary efficacy variable was the percent change in lumbar spine BMD at Month 12 relative to baseline. After a mean prior exposure to alendronate of approximately four years, both treatment groups showed preservation of BMD after 12 months of treatment. No statistical difference was detected between the treatment groups for percent change in lumbar spine BMD at Month 12 relative to baseline. The criteria for non-inferiority were met as the lower bounds of the 2-sided 95% CIs at Month 12 were greater than -1.5% for both the mITT, ITT and the per protocol populations.

More patients in the zoledronic acid group than in the alendronate group withdrew due to AEs. More patients in the zoledronic acid group had AEs starting within 3 days from injection, especially headache, arthralgia and fatigue. Bone resorption markers (urine NTx and serum β -CTx levels) were more markedly suppressed at 3 months with zoledronate than with alendronate indicating more intense inhibition of osteoclast activity with zoledronate at that time point. At 12 months a reversed relationship was noted with higher levels of these markers in the zoledronate group.

Secondary endpoints included the relative change from baseline at Months 3, 6, 9, and 12 for the following biochemical markers of bone turnover: serum b-CTx, urine NTx, serum BSAP and serum PINP. At baseline, both groups were comparable. For zoledronic acid, the mean serum b-CTx level was decreased at Month 3 and then rose steadily above baseline up to Month 12, at which point the average level was approximately 15% above baseline. For alendronate, the mean serum b-CTx level decreased at Month 3, with little change thereafter up to Month 12, at which point the average level was 18% below baseline.

The same pattern was demonstrated for urine NTx and for the bone formation markers BSAP and PINP.

The CHMP considered that in this relatively small supportive study, zoledronic acid was non-inferior to alendronate with regard to increase in BMD. There was a trend for larger increase in the alendronate group compared with baseline, despite previous mean 4 years of treatment. Similar to the results from the pivotal trial there is a steady increase in BMD with prolonged treatment. The difference from baseline is less when compared with the annual changes in Study 2301, indicating that increases in BMD may level off with time after many years of treatment with bisphosphonates. However, the 2 studies are not directly comparable (younger patient population, different requirements with regard to osteopenia/osteoporosis at inclusion).

As discussed above under study 2301, the results for the biomarkers in this study also indicate that full effect is not preserved with zoledronic acid for whole 12 months as bone resorption markers in the

zoledronic group rose above baseline at the end of the year compared with the maintenance of suppressed marker in the alendronate group. Similar findings were observed for the bone formation markers.

Study 2315

This was a multicentre, randomised, double-blind, active-controlled trial to determine the rapidity of onset of action following treatment with zoledronic acid as compared with alendronate. The study was conducted in 128 postmenopausal women with moderate to severe osteopenia or osteoporosis who had not previously been treated with bisphosphonates. The primary objective of the study was to demonstrate the superiority of zoledronic acid over alendronate in onset of action of bone turnover by comparing the relative change from baseline in urine NTx in patients treated with zoledronic acid versus those treated with alendronate after 1 week of treatment.

The secondary efficacy variables were as follows:

- The relative change in urine NTx from baseline at Weeks 2, 4, 8, 12, and 24
- The relative change in serum b-CTX from baseline at Weeks 1, 2, 4, 8, 12, and 24
- The change from baseline in Nepean Dyspepsia Index-Short Form total scores at Weeks 2 and 24

In addition, the relative change from baseline in BSAP was assessed at Weeks 4, 12, and 24 as a safety assessment. For consistency with the other studies, this variable was analysed using the ITT population.

The baseline demographic characteristics for the ITT population were comparable between the treatment groups. The mean age was 63.0 years.

With zoledronic acid, the nadir urine NTx concentration was reached at Week 1, and levels increased gradually thereafter, remaining on average in the lower half of the pre-menopausal normal range after Week 8 (17.8 – 46.4 nmol BCE/mmol creatinine). Reduction with alendronate was more gradual and lower in magnitude compared with zoledronic acid and reached a nadir at approximately 12 weeks. Zoledronic acid consistently demonstrated a significantly greater reduction in urine NTx relative to alendronate for the primary efficacy endpoint at Week 1 ($p < 0.0001$) and at all other timepoints (all $p < 0.005$ for Weeks 2, 4, 8, 12, and 24). A more rapid onset of action for serum b-CTX and serum BSAP was also demonstrated.

The CHMP considered that this was a small study exploring biomarkers, and the value of this study as regards efficacy of zoledronic acid in post-menopausal osteoporosis was very limited. In contrast to Study 2301 and Study 2313, biomarker profile was done in bisphosphonate naïve patients.

The clinical relevance as regards time for onset of action could be discussed and furthermore, should be put into perspective of the clinical relevance of maintaining a prolonged action, which probably is more important for this chronic condition.

Studies 0041E1 and 0041E2

These were two uncontrolled extension studies, each of two years duration to the dose finding **Study 0041** for postmenopausal osteoporosis.

Study 0041E1 used zoledronic acid in the two doses 1 mg or 0.5 mg every 3 months for 2 years and included 279 patients.

A consistent increase in mean lumbar spine BMD of 3.25% to 4.36% was observed in all of the zoledronic acid core study treatment groups between Month 12 (start of Study 0041E1) and Month 36 (end of Study 0041E1) and placebo-treated core patients had an increase in lumbar spine BMD of 7.26%.

There was a mean increase in total hip BMD of up to 5% after 3 years of treatment with zoledronic acid.

On average, no additional decreases in serum BSAP compared to baseline were observed beyond the decreases in BSAP that were observed after one year of treatment with zoledronic acid in Study 0041 in all core study groups, showing that a stable mean reduction from baseline between 40% and 50% in BSAP was reached on the original scale. The mean percent change (decrease) from core study baseline in serum b-CTX was larger at Month 36 than at Month 12 in all study groups. The largest reduction from core study baseline was observed at Month 24 in all study groups, with a mean reduction from baseline between 70% and 80% in serum b-CTX marker on the original scale, which is twice the reduction observed during the core study. This discrepancy might be explained by variability in the measurements.

The second extension study, **Study 0041E2**, was an additional 2-year, open-label extension with the primary objective to assess the long-term safety profile of zoledronic acid 4 mg yearly in patients who participated both in the core study and the first long-term extension. A total of 119 patients entered Study 0041E2. For the purpose of analysis, patients were grouped into 3 treatment groups by how long they had received zoledronic acid across Study 0041, Study 0041E1, and Study 0041E2 (either 2, 3, or 5 years). Twenty-two patients received zoledronic acid during 2 years, 78 for 3 years and 19 for 5 years.

At Month 60, all groups demonstrated persistency of the BMD gains achieved over the first 36 months of the study. This was consistent across the different anatomical regions. The small number of patients in the 2- and 5-year groups resulted in wide standard deviations that precluded demonstration of any clinically relevant differences between the groups.

The CHMP noted that the dose was 4 mg annually as compared with the 5 mg used in the pivotal study. The CHMP agreed that the BMD results show that there is a continuous increase in BMD and at Month 36 BMD had increased by up to 9.7% compared with the baseline BMD in the core study. The increase was most prominent in the first year and was about 2% annually thereafter. This is in line with the results of the pivotal study (although for LS increases were more impressive in this extension study), indicating that 4 mg yearly may be as efficient as 5 mg, but confirmatory fracture data are lacking and the small size, as well as the explorative nature of the extension studies, preclude any conclusions in this respect. The CHMP therefore requested that biomarkers should be measured in the extension study to Study 2301.

Discussion on clinical efficacy

The CHMP considered that already the interim data from study 2301 provided efficacy results for approximately 80% of the total study population. With these interim data, the pivotal study met its endpoints showing a reduction in the occurrence of new morphometric vertebral fractures over 3 years and delay of first hip fracture. The CHMP considered further that these results were statistically significant and clinically relevant and comparable to other bisphosphonates. Although less impressive for the second primary efficacy variable, time to first hip fracture, results were comparable to other bisphosphonates despite the fact that about 20% of the ITT population analysed for this endpoint were receiving other anti-osteoporotic agents (except for other bisphosphonates).

The CHMP highlighted that efficacy in preventing hip-fractures in patients with a femoral neck BMD T-score ≤ -2.5 was less compared with patients with BMD T-score > -2.5 .

The CHMP further highlighted that the analyses on sub-groups indicate that zoledronic acid is effective in patients without any other anti-osteoporotic treatment (Stratum I) as well as in patients taking concomitant non-bisphosphonate anti-osteoporotic treatment (Stratum II).

Efficacy on new morphometric vertebral fractures was shown in both bisphosphonate naïve as well as in patients previously treated with bisphosphonates in Stratum I, although with a trend for better efficacy in bisphosphonate naïve patients.

It was also noted that the number of secondary endpoints was unusually large but the CHMP agreed that the closed testing procedure was an acceptable method for controlling for Type I error.

The results for the secondary endpoints relating to vertebral fractures confirm the results for the primary efficacy endpoint, showing a reduction in risk of vertebral fractures in various sub-groups and in clinical fractures. A statistically significant risk reduction of 60% for new vertebral fracture was seen already at 12 months. Results for clinical vertebral fractures are notably better when compared with clinical non-vertebral fractures (75% reduction versus 25%) and statistically significant results were not shown for all types of non-vertebral clinical fractures.

Bisphosphonate – experienced patients

For hip fractures and other clinical fractures, the CHMP considered that the results from the subgroup analyses in study 2301 were conflicting. Increased risk of hip fracture was shown for patients previously treated with bisphosphonates and for other clinical fractures, the reduction in the risk was marginal (12%) in previously treated patients. At least 97% of the patients met the wash-out criteria but the CHMP highlighted that it would be of interest to have data on treatment duration for patients with previous use of bisphosphonates, which were subsequently provided by the MAH. The concern was that previous treatment with bisphosphonates plus zoledronic acid could have resulted in too much suppression of bone turnover, resulting in adynamic bone and increased risk for fractures.

The CHMP agreed that the apparent increased risk for hip fracture was most likely caused by chance and was attributable to the low number of events in this subgroup. The trend was not substantiated when looking across all fractures, and bone marker analyses support the notion that previous bisphosphonate use does not interfere with the effects of zoledronic acid on the skeleton. Efficacy and biomarker data do not support the development of resistance and bone biopsies do not support oversuppression. However, “frozen bone” (adynamic bone disease, in case the bone turnover has been suppressed to the extent that there is no longer any evidence of active bone remodelling) was still considered an issue that has to be addressed long-term. The MAH therefore committed that 60 patients in the planned extension study 2301E1 will have unpaired transiliac bone biopsies following double tetracycline labelling. Micro-CT will be done prior to the histomorphometric analysis.

Possibly previous treatment with bisphosphonates plus zoledronic acid could have resulted in too much suppression of bone turnover, resulting in adynamic bone and increased risk for fractures, or secondary resistance to previous bisphosphonates may have lead to a certain kind of resistance to zoledronic acid.

The overall results on hip and other clinical fractures were reassuring but it is likely that zoledronic acid has less effect at sites where cortical bone is present compared with the vertebrae where trabecular bone predominates. Less efficacy can also be expected in involuntional osteoporosis as compared with postmenopausal osteoporosis.

Concomitant calcium and vitamin D supplementation

Considering that all patients were adequately supplemented with relative high doses of vitamin D and calcium, the CHMP considered that concomitant use of calcium and vitamin D supplementation should be recommended in the SPC. The CHMP also noted the large percentage of patients using concomitant ACE-inhibitors and NSAIDs, that are known to affect renal function and considered it important for the safety evaluation (see also section “Clinical safety” below).

Dose adjustment in patients with renal impairment

For women with postmenopausal osteoporosis, and with long-time repeat dosing, the safety assessment might need to take into account that bone exposure could increase in patients with renal impairment. The MAH was therefore asked to discuss the need for a reduced dose regimen for patients with mild to moderate renal impairment.

A pharmacokinetic study in cancer patients with renal function ranging from normal to severely impaired renal function has shown a 30 – 40 % increase in the AUC over 24 hours for those with mild to moderate renal impairment (creatinine clearance > 20 and < 60 ml/min) after a 4 mg infusion of zoledronic acid over 15 minutes (*Skerianec et al 2003*). Patients with similar grade of renal

impairment (creatinine clearance > 30 and < 60 ml/min) were included in study 2301. Patients with baseline creatinine clearance < 60 ml/min were compared with those with a baseline creatinine clearance \geq 60 ml/min in this study regarding morphometric and clinical fractures, BMD and histomorphometric parameters.

It was estimated that for oral bisphosphonates, the variability in AUC due to variability in absorption might be larger than the variability caused by renal function. Most of the previously approved oral bisphosphonates indicated for osteoporosis do not have special recommendations for mild-moderate renal impairment, while use in severe renal impairment is not recommended or even contra-indicated, due to lack of pharmacokinetic and/or efficacy/safety data and since exposure would be expected to increase even more in this population.

The MAH has also provided a summary of efficacy and safety data from patients with a renal clearance below 60 ml/min included in study 2301.

The CHMP agreed that from a bone safety perspective a dose reduction in moderate renal impairment may not be needed. However, taking the increased risk for renal impairment including acute renal failure after infusion and the available data in patients with mild to moderate renal impairment into account, the CHMP considered that patients with a renal clearance below 40 ml/min should not receive Aclasta.

Dosing intervals

The CHMP agreed that the overall efficacy data were convincing and a possible benefit of slight increase in bone turnover between the doses in repairing microdamage was considered an acceptable explanation. This, however, will have to be confirmed in longer-term trials addressing the issue of “frozen bone”.

Duration of treatment

The CHMP further discussed that bone density increased steadily over time at all sites measured in the zoledronic acid group but decreased in the placebo group. Compared with the dose-ranging study, using doses as low as 0.25 mg every 3 months, the increase was somewhat less pronounced at the lumbar spine at 12 months, about 4% compared with 4.8-5.7 in the dose-ranging study. The increase in BMD was less pronounced between the 2nd and 3rd infusion than between the 1st and 2nd infusion. At 3 years, the increase was 7% at the lumbar spine. The CHMP pointed out that it is still unclear whether this steady increase in BMD could be detrimental in the long-run, e.g. after further 3 years of treatment. The CHMP therefore considered that the planned 3-year extension study to Study 2301 with re-randomisation is important to address this concern. Additionally, an extension of the study of further 3 years was warranted addressing the issue of long-term effects on bone. The MAH agreed and committed to address these points as post-opinion commitments.

Single dose strength

The CHMP noted that 40 % of the dose used in the pivotal study 2301 was shown to significantly increase lumbar spine BMD during 12 months and that no difference in BMD as compared to higher doses of Aclasta was observed at that time. The very high doses used in order to achieve an acceptable suppression of bone turnover over one year is expected to be associated with interferences in bone metabolism different from those seen with daily or weekly dosing. The CHMP therefore asked that the effects of the proposed regimen on pharmacodynamic and histologic markers of bone metabolism (BMD, blood and urine markers of osteoclastic and osteoblastic activity, results of bone biopsies) should be compared to what is known about the effects of already approved bisphosphonate treatment regimens for osteoporosis in a general as well as based on the active controlled Study 2313.

In his response, the MAH clarified the potency of zoledronic acid in relation to other, especially to orally dosed, bisphosphonates for which more long time data exist and showed a relative risk reduction for fractures equal or superior to other bisphosphonates. Lumbar spine BMD increase over 3 years with zoledronic acid 5 mg/year is in line with BMD increase for other bisphosphonates. Bone histomorphometric parameters were not markedly different with zoledronate compared to with other bisphosphonates. However, the assumption that the lower reduction of biochemical bone turnover

markers with the lower tested doses of zoledronic acid in the dose-finding study would have provided insufficient reduction of fractures if tested in bigger studies is still unconfirmed. Since the effect of one 5 mg dose per year was shown to be effective to prevent fractures in osteoporotic women in study 2301, conducting a large study with a lower yearly dose was not considered justified by the CHMP.

Bone biomarkers

The CHMP also noted that markers of bone resorption decreased as expected from the pharmacodynamic properties of zoledronic acid. The reduction of bone resorption markers and bone formation markers, respectively, was of similar magnitude compared with placebo. The reduction in bone formation markers, however, was most pronounced at 3 months after the infusion but at the 9-11 day timepoint for bone resorption markers. Post-dose profiling was done first after the 3rd infusion but it would have been of interest to have the profile following the 1st infusion as well.

The CHMP pointed out that the profiling of biomarkers done after the 3rd infusion in Study 2301, showed that at 6 months, pre-dose levels of bone markers were reached and at 12 months after the 3rd infusion, levels are above pre-dose levels, indicating that a 12-month interval between infusions may be too long. Further results for biomarkers in Study 2313 were in line with the results of the pivotal trial, indicating that full effect is not preserved with zoledronic acid for whole 12 months as bone resorption markers in the zoledronic group rose above baseline at the end of the year compared with the maintenance of suppressed markers in the alendronate group. Similar findings were observed for the bone formation markers. Thus, the CHMP considered it possible that more frequent dosing of zoledronic acid, e.g. every 6 months, could have resulted in better bone protection.

The MAH explained that overall, biochemical markers for bone resorption (b-CTX) and formation (BSAP, P1NP) were reduced following study drug administration with zoledronic acid 5 mg once per year, and were maintained within pre-menopausal levels at the end of every 12-month period. The resorption marker b-CTX exhibited reduction to the lower half of the premenopausal level. The effect on reduction of bone markers was sustained over 36 months, and no further reduction of those markers was observed with repeat treatment. Furthermore no incidence of a cumulative effect was observed, because marker levels at 12, 24, and 36 months were all similar, indicating a reproducible effect on bone remodelling with each dose.

1.3.4 Clinical safety

The main safety data were taken from 4 trials in patients with postmenopausal osteoporosis or osteopenia, including the pivotal **Study 2301**, the supportive studies **Study 2313** and **Study 2315** and one completed, phase IV, double-blind, placebo-controlled **Study 2407**. More than 98% of the overall exposure data provided comes from Study 2301.

Data for Studies 2313 and 2315 were pooled to compare the adverse event profile of zoledronic acid with alendronate. Study 2407 was a 10 days study designed to determine whether ibuprofen, acetaminophen / paracetamol could be used to mitigate post-dose symptoms following administration with zoledronic acid.

Patient exposure

Exposure in clinical studies

A summary of overall PMO patient exposure to study drug for the major safety population (all patients who received at least 1 dose of study drug) is provided by study and treatment in Table 4. In the Aclasta program in post-menopausal osteoporosis in the completed controlled studies 4,453 patients have received at least 1 dose and up to 3 doses of Aclasta. The patient-years exposure to zoledronic acid in this dataset is over 10,890 patient-years of exposure to study medication

Table 4: Summary of overall duration of exposure by treatment

Study	Zol (5 mg) N=4053	Placebo N=3924	Alendronate N=171
2301 (final results)			
N	3862	3852	0
Mean exposure years	2.78	2.80	
Total patient years	10737.3	10797.0	
2313			
N	113		112
Mean exposure years	0.98		0.99
Total patient years	110.9		110.9
2315			
N	69		59
Mean exposure years	0.43		0.44
Total patient years	30		26.0
2407			
N	409	72	0
Mean exposure years	0.03	0.03	
Total patient years	12.0	2.1	
Overall			
N	4453	3924	171
Mean exposure years	2.45	2.75	0.8
Total patient-years	10890.3	10799.2	136.8

Exposure year of each patient is defined as the entire follow-up period in the study of that patient and is presented as the number of days of follow-up divided by 365.25.

The safety population in Study 2301 included 7714 patients who were exposed to at least one study drug infusion and the mean duration of exposure was 2-3 years. Of these patients, 5035 (65.1%) were participants in the renal safety population and had at least one post-dose renal monitoring visit following study drug infusion.

Post marketing exposure

The Marketing Authorisation Application for Aclasta in the treatment of Paget's disease is currently approved in 50 countries worldwide as of 30 April 2006, excluding the US or Australia. Zoledronic acid has also been approved in over 96 countries worldwide under the trade name Zometa for several indications including tumour-induced hypercalcaemia, treatment of patients with multiple myeloma, and treatment of bone metastases from solid tumours.

According to calculations based on worldwide sales volume, approximately 446,000 patients had received zoledronic acid for the indications hypercalcaemia of malignancy and treatment of bone metastases. The calculation was based on the assumption of 24 mg per patient (6 dose cycles at 4 mg per cycle). This corresponds to approximately 223,000 patient-years of exposure.

Approximately 1185 patients received treatment with Aclasta in investigational clinical trials sponsored by the MAH. In the latest PSUR (covering the period 01 November 2005 to 30 April 2006), approximately 2922 patients received treatment with Aclasta. An estimate of patient-years of exposure was 1700 patient-years.

There is limited post-marketing experience with zoledronic acid used in non-oncology indication, which is not unexpected, considering that Paget's disease of the bone is a relatively rare disease and that there are other bisphosphonates on the market used for the same indication.

Adverse events

Study 2301

Interim analysis

Overall, the percentage of patients experiencing AEs was similar in the zoledronic acid group (95.49%) and placebo group (93.87%) in Study 2301. In the supportive studies, the number of patients experiencing AEs in the zoledronic acid group (88.5%) and alendronate group (82.5%) were comparable. Adverse events by primary system organ class (PSOC) were presented by the MAH.

With the exception of the PSOC for “general disorders and administration site conditions”, which showed a higher incidence of AEs for the zoledronic acid group (43.1%) than the placebo group (21.7%) in the Study 2301, the incidence of AEs was similar between the zoledronic acid group and the placebo group. In the supportive studies, the incidence was 29.67% in the zoledronic acid group compared with 15.79% in the alendronate group.

Within the first 3 days of any infusion in Study 2301, 51.4% of patients who received zoledronic acid experienced at least one AE compared with 26.3% of patients who received placebo. However, 4 to 15 days after infusion, the rates were 20.48% for zoledronic acid versus 16.7% for placebo and over the remaining time periods, difference between the groups was negligible. Overall, after the first 3 days after any infusion, the adverse event rates were similar across both treatment groups (91.8% vs. 92.3%).

The most frequent AEs ($\geq 2.0\%$) observed within the first 3 days of the zoledronic acid infusions decreased from the first infusion to the second infusion and to the third infusion from 1726 (44.7%) to 570 (16.7%) to 316 (10.2%), respectively. For placebo the rates were, 14.9%, 10.3% and 8.5% at the first, second and third infusion, respectively. There was lesser incidence of pyrexia and myalgia from the supportive studies 2313 and 2315 studies due to the concomitant administration of paracetamol during the study. Results from the study 2407, showed that administration of paracetamol or ibuprofen following the infusion with zoledronic acid, reduced the change in mean temperature the following 10-48 hours. Less patients receiving paracetamol or ibuprofen reported increase in the severity of symptoms on a questionnaire and a visual analogue scale.

Most AEs were mild (15.5% vs. 16.6%) or moderate (52.4% vs. 49.7%) in severity for zoledronic acid and placebo, respectively. With respect to severe AEs, the overall reporting frequency for patients was also similar for the zoledronic acid (27.3%) and placebo (27.2%).

The greatest difference between treatment groups in the frequency of AEs was observed in the general disorders and administration site conditions PSOC. The incidence of mild, moderate, and severe AEs is 20.6%, 19.1%, and 3.4% for zoledronic acid compared to 12.4%, 7.9% and 1.4% for patients in the placebo group. Severe AEs within the general administration disorders PSOC with twofold or greater differences included: pyrexia (0.88% (34/3862) vs. 0.13% (5/3852)), influenza-like illness (0.73% (28/3862) vs. 0.03% (1/3852)) and chills (0.44% (18/3862) vs. 0.00% (0/3852)), respectively. Differences within severe AEs for the cardiac disorders PSOC were primarily driven by higher occurrences of arrhythmias such as atrial fibrillation (0.67% (26/3862) vs. 0.23% (9/3852)) and congestive cardiac failure (0.47% (18/3862) vs. 0.16% (6/3852)).

As expected in a long-term study in an elderly population, the rate of AEs was high overall in both treatment groups. Otherwise, the adverse events related to zoledronic acid were consistent with previous safety data from studies in Paget’s disease as reflected in the current SPC. The higher rates of pyrexia, myalgia, chills and influenza-like illness reflect the post-dose symptoms associated with zoledronic acid. These symptoms were 3-5 times more common in the zoledronic acid group compared with placebo.

Summary of final safety results

There was no change in the overall safety profile for zoledronic acid in the final analysis as compared to the safety findings in the interim analysis. Detailed safety results are summarised below:

The overall incidences of AEs and SAEs were comparable between treatment groups. The five most frequently occurring early onset (within 3 days) AEs are consistent with post dose symptoms: pyrexia, myalgia, influenza-like illness, headache, and arthralgia. The majority of these AEs were transient, resolving within 3-7 days.

Consistent with other bisphosphonates, there was an imbalance between zoledronic acid and placebo for reported hypocalcemia adverse events (11 [0.28%] patients vs. 5 [0.13%] patients, respectively). All were transient and asymptomatic.

Zoledronic acid showed a small (0.7% absolute and 26% relative) increased risk of developing ocular adverse events over placebo.

Zoledronic acid did not exert any adverse effects on fracture healing, nor did it increase the risk of avascular necrosis in this study.

Maxillofacial events meeting adjudication criteria for osteonecrosis of the jaw were rare and equally distributed between patients treated with zoledronic acid and placebo (one in the zoledronic acid and one in the placebo group).

There was no difference between zoledronic acid and placebo in long-term renal function parameters, as reflected in changes in serum creatinine and creatinine clearance. Transient, short-term changes in renal function, as demonstrated by increases in serum creatinine > 0.5 mg/dL from pre-dose to post-dose (9-11 days), occurred more commonly after dosing with zoledronic acid (31 [1.34%] patients vs. 10 [0.43%] patients for zoledronic acid vs. placebo, respectively).

While overall cardiovascular AEs were similar between groups, patients treated with zoledronic acid exhibited an increased rate of atrial fibrillation SAEs relative to placebo. This imbalance was not observed in a separate ECG substudy, nor consistent with the rate of nonserious atrial fibrillation AEs. Further, the vast majority of these events occurred more than 30 days after study drug infusion and, therefore, this suggests that these events are most likely not drug-related.

Bone biopsies demonstrated reductions in bone turnover with normal bone quality. All but one patient with evaluable bone biopsy samples had evidence of labelling in either trabecular or cortical bone, indicating persistence of bone turnover.

Markers of bone turnover were reduced to premenopausal levels at each pre-dose assessment and exhibited an increase over time between yearly dosings, further demonstrating preservation of remodelling capacity of bone after treatment with zoledronic acid.

Study 2407

This was a randomised, double-blind study of acetaminophen/paracetamol or ibuprofen compared to placebo in postmenopausal women with a low bone mass who received a single dose of intravenous zoledronate (5 mg) or placebo, with the primary objective to assess the effect of acetaminophen/paracetamol and ibuprofen relative to oral placebo in preventing oral body temperature increases of at least 1 degree Celsius (1.8 F) from baseline for 3 days after an i.v. dose of zoledronic acid. Secondary objectives were to assess the effect on severity of symptoms of (1) feeling feverish, (2) headache, or (3) aches and pains of muscles and joints, or other symptomatology for 3 days.

The following treatment group definitions were used:

- Group 1 = i.v. zoledronic acid 5 mg + oral acetaminophen/paracetamol (ZOL+APAP)
- Group 2 = i.v. zoledronic acid 5 mg + oral ibuprofen (ZOL+IBU)
- Group 3 = i.v. zoledronic acid 5 mg + oral placebo (ZOL+PLAC)
- Group 4 = i.v. placebo + oral placebo (PLAC+PLAC)

In total 481 patients were randomised: 135 to the ZOL+APAP group, 137 to the ZOL+IBU group, 137 to the ZOL+PLAC group, and 72 to the PLAC+PLAC group.

Results: Of the 481 patients who were randomised to treatment, 55 (11.4%) discontinued from the study prematurely. The most common reason for discontinuation was adverse events (n=40, 8.3%), and this occurred most frequently in the ZOL+PLAC treatment group (20/137, 14.6%) compared with the ZOL+APAP (11/135, 8.1%) and ZOL+IBU (9/137, 6.6%) treatment groups. No discontinuations were observed in the PLAC+PLAC group.

The results for the primary safety variable are summarised in table 5 below.

Table 5

Between treatment comparisons of the proportion of patients with a clinically significant increase in oral body temperature in the 3-day period after receiving i.v. study drug (MITT population)				
Treatment	N	Patients with events n (proportion)	Difference in proportion (95% CI) (1)	p-value (2)
ZOL+APAP	134	50 (0.373)	-0.262 (-0.384, -0.140)	<0.0001 *
ZOL+IBU	136	50 (0.368)	-0.267 (-0.389, -0.146)	<0.0001 *
ZOL+PLAC	137	87 (0.635)	---	---

(1) The difference is relative to the ZOL+PLAC group, 95% CI for the difference is calculated using the normal approximation to binomial distribution with Yates' correction factor.
(2) p-value calculated from Fisher's exact test.
* Both ZOL+APAP and ZOL+IBU are statistically significantly different from the ZOL+PLAC group, based on Hochberg's procedure (both p-values < 0.05).

For the secondary safety variables, symptom severity was solicited using a questionnaire and the visual analogue scale (VAS).

A major increase in severity of symptoms was observed in 46.3% of ZOL+APAP patients and 48.5% of ZOL+IBU patients, compared with 75.9% of ZOL+PLAC patients (both, $p < 0.0001$). The proportion of patients with severe symptoms was 23.9% of ZOL+APAP patients and 26.5% of ZOL+IBU patients, compared with 48.9% of ZOL+PLAC patients (both, $p \leq 0.0002$).

The number of patients reporting “unbearable” symptoms using the VAS scale (i.e. ≥ 75 mm) was greatest on Day 2 in comparison to Days 1 and 3. Almost one-fifth of all patients in the ZOL+PLAC group (19.4%) reported unbearable symptoms on Day 2 compared with 8.5% of patients in the ZOL+APAP group and 5.5% of patients in the ZOL+IBU group. No patient in the PLAC+PLAC group reported unbearable symptoms at any time.

Identified adverse events

Post-dose symptoms

All intravenous bisphosphonates have been associated with side effects caused by an increased liberation of pro-inflammatory cytokines. In clinical trial experience, the most common early onset AEs ($\geq 5\%$) within 3 days of any infusion included a wide variety of symptoms: pyrexia, myalgia, influenza-like illness, headache, gastrointestinal symptoms and arthralgia.

While in study 2407 the mean temperature increase in the “ZOL+PLAC” group was a little below 1°C, 33% in this group experienced temperatures above 38.5°C in a sub-group analysis. Unbearable symptoms were reported in 19% of the group of patients not receiving concomitant treatment with paracetamol/ibuprofen but much less frequent in the other groups. For other symptoms, the use of paracetamol and ibuprofen for 3 days following the intravenous administration of zoledronic acid resulted in an approximate 50% reduction in solicited post-dose symptoms. Therefore, the information that paracetamol/ibuprofen following zoledronic acid infusion can reduce post-dose symptoms was included in the SPC.

Ocular adverse events

Ocular adverse events such as uveitis, iritis, episcleritis and conjunctivitis are known class effects of bisphosphonates. In clinical trial experience, the incidence of confirmed, adjudicated ocular adverse events was seen in less than 3.0% of patients treated with Aclasta vs. 2.3% 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. The majority of ocular events were reported within 15 days of dosing. These adverse events were not visually threatening and could be treated conservatively.

The ocular data further demonstrate that zoledronic acid has a small (0.7% absolute and 30% relative) increased risk of developing ocular adverse events over placebo. Serious ocular AEs were equal in both treatment groups (n=42, 1.09%). The majority of events of eye pain, uveitis, episcleritis, and iridocyclitis were reported within 15 days of dosing. None of the eye disorders reported in studies 2313, 2315, and 2407 matched the predefined search term events. The ocular disorders reported by the investigators and those confirmed by expert review for Study 2301 were presented by the MAH. No post-marketing reports of ocular adverse events after treatment with Aclasta were received.

The SPC was updated to reflect the ocular events related to zoledronic acid. Particularly those events occurring within 15 days of infusion and with the highest frequency compared with placebo, i.e. eye pain, uveitis, episcleritis and iritis, warranted mentioning.

Hypocalcaemia

Transient hypocalcaemia is a well characterised side effect to the treatment with bisphosphonates. In clinical trial experience, cases of laboratory hypocalcaemia were uncommon. None of the cases were symptomatic and they generally occurred in patients with pre-existing conditions such as parathyroidectomy or malabsorption of calcium.

To objectively and independently assess hypocalcaemia and laboratory abnormalities and to identify possible causal relationships, an adjudication committee for hypocalcaemia was established. An expert review on hypocalcaemia was also presented by the MAH. The incidence of serum calcium less than 2.075 mmol/l (lower limit of the reference range) assessed 9-11 days following the 1st, 2nd, and 3rd infusion was 2.3% (49/2015), 0.1% (2/1594) and 0.3% (5/1483) in patients receiving zoledronic acid. At each timepoint there was one patient in the placebo group whose serum calcium was below the reference range. There were 9 patients in the zoledronic acid group and 5 in the placebo group with clinically notable low serum calcium levels (<1.87 mmol/l). None of the hypocalcaemia adverse events were serious and all were asymptomatic. No patients discontinued the study due to a hypocalcaemia AE. No patients in any of the supportive studies had a clinically notable low serum calcium level.

Based on post-marketing reports there have been 4 cases of hypocalcaemia (4/2207 patient-years). The time to onset ranged typically between hours and 2 days from infusion, with full recovery either spontaneously or following supplementation of calcium.

While most cases of hypocalcaemia in Paget's disease and in the osteoporosis studies were transient and asymptomatic, few cases have been symptomatic, despite all patients receiving vitamin D and calcium supplementation. The rate of hypocalcaemia in the Study 2301, when measured 9-11 days after the first infusion (2.3%), was similar when compared with the Paget's population receiving single infusion. The current SPC for Paget's disease is considered adequate in its recommendations and warnings related to the risk of hypocalcaemia, but the SPC was amended to recommend concomitant use of vitamin D and calcium to all patients receiving infusions with zoledronic acid to prevent hypocalcaemia. This is particularly important as regards the first infusion. The information that the incidence of hypocalcaemia in the PMO population decreases with repeated infusions was included in the SPC.

Dyspepsia

The Nepean Dyspepsia Index - Short Form Symptom Checklist was used to assess the frequency, intensity, and 'bothersomeness' of dyspepsia in study 2315 (study design see section "clinical efficacy" above). Between-treatment comparisons showed no significant differences between zoledronic acid and alendronate with respect to the mean changes from baseline in the total score, total frequency score, total intensity score, and total bothersomeness score at Weeks 2 and 24.

Results with regard to dyspepsia indicate that dyspeptic symptoms are equally common with i.v. zoledronic acid as with oral alendronate in study 2315. However, it is noteworthy that overall in the

active controlled studies, dyspepsia was more frequent with zoledronic acid compared with alendronate. The main therapeutic gain, however, seems to be the one year infusion compared with daily/weekly tablet, a dosing strategy preferred by most patients in studies 2313 and 2315 based on patient preference questionnaire.

Renal adverse events

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.

Over the entire study, the frequency of adverse events associated with a change in renal function confirmed by adjudication, regardless of study drug relationship, was greater in the zoledronic acid treatment group compared with the placebo treatment group (2.20% vs. 1.64%, respectively). This difference is due primarily to the higher number of adverse events reported as blood creatinine increased in the zoledronic acid group 23 (0.60%) compared to the placebo group 3 (0.08%)

Overall for patients receiving zoledronic acid and placebo, respectively, 383 (9.92%) and 336 (8.72%) reported adverse events within the renal and urinary disorders. Serious adverse events were reported for 47/3862 (1.22%) of zoledronic acid-treated patients and 45/3852 (1.17%) of placebo-treated patients.

Among the adverse events associated with change in renal function confirmed by adjudication in study 2301 it is noted that there were 8 cases of acute renal failure in the Aclasta group vs. 1 in the placebo group.

Atrial fibrillation

The most frequently reported SAE in the zoledronic acid group was atrial fibrillation. This SAE has been thoroughly discussed in variation II-14 adopted in parallel to this procedure and has been included in the Product Information.

Cerebrovascular events

Cardiac deaths' and 'cerebrovascular/nervous system disorder deaths' represented the largest number of fatal adverse events. Following adjudication, the number of deaths due to cerebrovascular/nervous system disorder were for zoledronic acid and placebo 16 (0.41%) and 6 (0.16%) respectively, following adjudication and 22 versus 12 respectively as reported by investigators. The number of deaths due to cardiac disease was approximately equal for both treatment groups [17 events (0.44%) for zoledronic acid and 18 events (0.47%) for placebo] and decreased significantly from what was reported by the investigator [investigator reported 39 for zoledronic acid (1.01%) and 31 for placebo (0.80%)]. For other causes of death, the rate was similar in both treatment groups. Deaths did not occur in the supportive studies.

Due to numerous confounding factors the MAH considered that this finding could not be explained based on the known mechanisms of bisphosphonates. However, as committed by the MAH, ongoing trials will further elucidate these findings.

Compared with published figures on the estimated risk in this age-group, the rate of cerebrovascular deaths was unexpectedly low. Due to this fact and the low numbers, it was impossible to draw any conclusion as regards this observed increased incidence of cerebrovascular deaths in the zoledronic acid group. According to the MAH, very few of the cerebrovascular adverse events were associated with atrial fibrillation. The incidence of fatal stroke in the Aclasta group may at least partially be related to the observed higher incidence of AF in this group and thus this observation adds to the concern for a causal relationship between Aclasta treatment and atrial fibrillation. Currently, this observation is not a cause of concern but cerebrovascular and cardiac events and deaths should be closely monitored post-marketing and further data can be expected from planned and ongoing studies, including the large extension study 2301E1 (see also section "Risk management plan" below).

Bone biopsy results (interim data)

Changes in bone quality through bone biopsies were assessed in a subset of 131 patients between Month 33 and Month 36 in Study 2301.

Of the 131 biopsies, 93 underwent qualitative histological assessment. All 93 biopsies were found to contain tetracycline labelling in either trabecular or cortical bone, indicating a continuation of bone remodelling. In the 67 bone biopsies that were evaluable for quantitative histomorphometry analysis, as expected, significant reductions were found in the zoledronic acid group as compared with placebo with regard to activation frequency, mineralising surface, osteoid surface, osteoid volume, and volume referent bone formation rate. These changes were reflective of a reduction in bone turnover, in accordance with the known mechanism of action of bisphosphonates (73% reduction based on activation frequency).

These findings confirm previous results from Study 2313, in which transiliac bone biopsies were obtained in a subset of 25 patients (23 were adequate for examination, 10 in the zoledronic acid group and 13 in the alendronate group) at the end of the study. The study showed very similar effects of zoledronic acid and alendronate on various histomorphometric measures, with no evidence of marrow fibrosis or mineralisation defects. In both treatment groups the activation frequencies were reduced below those seen in patients with untreated postmenopausal osteoporosis (median 0.42). They did not differ significantly from healthy premenopausal women (median 0.13).

Following a Scientific Advice, the MAH had committed to collect and analyse bone biopsies from 215 patients in the phase III trials. In a follow-up advice, CHMP maintained the proposal of at least 200 bone biopsies (100 in each treatment group) but accepted submission of 60 biopsies per group at the interim analysis. The MAH has provided results from 152 bone biopsies during the procedure; 111 of these were evaluable and are regarded sufficient for the extension of the indication.

There has been a concern that long-term treatment with potent bisphosphonates could lead to diminished bone formation and possibly “frozen bone” that would be prone to fractures. It should be born in mind that zoledronic acid is a highly potent bisphosphonate.

The clinical data on fractures, however, do not indicate that there is an increased risk for fractures due to “frozen bone”. For long-term risk of frozen bone, further biopsy data that will be collected in the follow-up study of study 2301 are of importance and post-marketing safety studies will address this concern, as outlined in the Risk Management Plan (RMP).

Serious adverse events and deaths

The number of deaths in Study 2301 was relatively small and comparable for both groups. There were 130(3.37%) deaths in the zoledronic acid group and 112(2.91%) deaths in the placebo group . Kaplan-Meier estimates of time to death from Study 2301 at 36 months indicate a death rate of 3.54% for zoledronic acid-treated patients and 3.05% for placebo-treated patients. A hazard ratio of 1.19 (95% CI: 0.92, 1.54) indicates an approximately 19% greater risk of death for zoledronic acid treated patients than placebo; however, this difference was not statistically significant (p=0.1800).

The overall incidence of serious adverse events (SAEs) in Study 2301 was 29.2% in the zoledronic acid group compared to 30.1% in placebo. In the supportive studies the incidence of SAEs was 7.69% in the zoledronic acid group compared to 8.19% in alendronate-treated patients. The incidence of SAEs was comparable in all PSOCs for the pivotal and supportive studies. When SAEs were reviewed by preferred term, they were comparable across the pivotal and supportive studies with the exception of atrial fibrillation. The overall death rate was similar in the zoledronic acid and the placebo group, respectively, and partly reflected the elderly age-group in the trial. The increased rate of deaths related to the cerebrovascular/nervous system with zoledronic acid is discussed above.

Laboratory findings

In Study 2301, the occurrences of treatment-emergent clinically notable serum chemistry abnormalities were low and did not indicate a major difference between the treatment groups. The below laboratory data for study 2301 were presented in the interim report.

Renal laboratory events

The majority of patients (54.6%) in the ITT population had normal renal function at baseline, represented by a creatinine clearance ≥ 60 ml /min and a urinary protein level of +1 or less (98.33%).

The results for zoledronic acid and placebo patients were similar at annual visits. At Month 12 there was a twofold increase in the incidence of the number of patients receiving zoledronic acid who had increased serum creatinine > 0.5 mg/dl relative to baseline (0.52%) compared with patients receiving placebo (0.25%). At Month 24 and Month 36 the incidence of patients with greater than 0.5 mg/dl increases in serum creatinine was 0.11% and 0.21% higher in the placebo group (0.49% vs. 0.60%; and 0.97% vs. 1.18% respectively).

There was an increased number of all renal laboratory events in patients with lower renal function at baseline for both zoledronic acid- and placebo-treated patients. This finding is consistent in patients with higher serum creatinine, lower creatinine clearance, higher serum BUN, and lower hematocrit. There was a notable effect of age, and active hypertension. No increased risk was noted with NSAID use or in patients with low BMI

A subset of patients was monitored for short-term changes in renal function at 9 to 11 days after each infusion (Renal safety population). Serum creatinine levels and urine protein (dipstick results) were measured and compared with pre-treatment levels.

Overall there was a 1.00% difference in the incidence between groups, with 1.81% of zoledronic acid treated and 0.81% of placebo patients reporting an increase in serum creatinine that was > 0.5 mg/dl compared with baseline. Among zoledronic acid-treated patients, the incidence of an increase in serum creatinine > 0.5 mg/dl was similar in patients whose baseline creatinine clearance was < 60 ml /min compared with those whose baseline creatinine clearance was ≥ 60 ml /min (21 [1.98%] of 1054 patients vs. 21 [1.66%] of 1266 patients, respectively). The highest incidence of elevated serum creatinine occurred in those zoledronic acid patients with baseline creatinine clearance of 30-35 ml /min (5/47, 10.64%).

A small, but consistently 2-fold incidence of urine dipstick results $> 2+$ over baseline was observed for patients in the zoledronic acid treatment group compared with patients in the placebo treatment group, overall and after each infusion of study drug. The overall number of events was 14 (0.63%) versus 4 (0.18%) in the zoledronic acid and placebo groups respectively. No trend was apparent relative to baseline creatinine clearance.

Overall there were 31 patients (1.34%), in the zoledronic acid group and 10 patients (0.43%), in the placebo group who were reported to have had a serum creatinine increase > 0.5 mg/dl from pre-infusion to 9-11 days post infusion. The incidence per infusion ranged from 0.51%- 0.72% for zoledronic acid and from 0.06% - 0.28% for placebo. In a sub-group analysis, hypertension markedly affected the event rate of short-term changes, which still were transient and resolved prior to subsequent infusions,

Overall, short-term, transient increases in creatinine and proteinuria were observed following zoledronic acid infusions and in few cases, transient glomerulonephritis. In contrast to the post-infusion reactions, these renal effects were not less frequent following repeated infusions. The MAH agreed to include the short-term adverse renal events associated with zoledronic acid infusions in the SPC. Long-term, there was a higher incidence of increase in serum creatinine prior to the infusions compared with placebo (1% difference), and this was mainly driven by increased incidence prior to the 2nd infusion. At other timepoints, the incidence was actually lower in the zoledronic acid group. The significance of these observed long-term changes is uncertain.

About half of the population included in the Study 2301 had creatinine clearance < 60 ml /min, which is reassuring as regards administration of zoledronic acid to patients with mild renal impairment. However, for more severe renal impairment, the CHMP considered that caution should be taken, and the Product Information was revised not recommending Aclasta for use in patients with a creatinine clearance of < 40 ml /min.

Hepatic laboratory events

There were 18 patients (0.49%) with elevated Alanine Aminotransferase (ALT) in the zoledronic acid group and 17 patients in the placebo (0.46%) group and 16 patients with elevated AST (0.44%) in the zoledronic acid group and 12 patients (0.33%) in the placebo group in study 2301. In the supportive studies, 2315 and 2313, 3 patients showed notably increased Aspartate Aminotransferase (ALT) levels (> 110 U/L) following administration of zoledronic acid, one of whom also had a clinically notable AST elevation (> 100 U/L). No ALT or AST elevations were observed in the alendronate group. These changes are possibly related to receiving concomitant treatment with acetaminophen. None of the increases resulted in discontinuation from the study and all resolved spontaneously. In Study 2407, shifts outside of the normal range at baseline to high at Day 10 were seen for ALT in more patients in the ZOL + APAP group (23 patients, 17.4%) than the other treatment groups (6 [4.5%] patients in the ZOL + IBU group, 7 [5.2%] patients in the ZOL + PLAC group, and 3 [4.2%] patients in the PLAC + PLAC group). Most of these elevations were to levels slightly above the upper limit of the reference range. Peak levels were observed at 10 days with values declining thereafter into the reference range. There were no changes observed in AST, alkaline phosphatase, or bilirubin.

The elevated liver enzymes in the supportive studies do not raise a concern, especially as the incidence of elevated liver enzymes was low and not different from placebo in the large Study 2301, and furthermore, for Study 2407, the explanation that these could be related to paracetamol administration seemed plausible, as relatively high doses of paracetamol were given (4g/day for 3 days).

Discontinuation due to adverse events

The discontinuation rate in study 2301 was similar in the large placebo controlled study, while in the active controlled studies withdrawals and adverse events were more common in the zoledronic acid group. This indicates that there is not a major difference in the tolerability of these alternative treatments, i.e. zoledronic acid i.v. versus oral alendronate.

There was no difference in AEs or laboratory abnormalities leading to discontinuation in the zoledronic acid and the placebo group, respectively, in the Study 2301. In Study 2301, 209 (5.41%) patients in the zoledronic acid group and 187 (4.85%) patients in the placebo group experienced at least 1 AE that led to premature discontinuation from study drug. The three most common AEs that led to study drug discontinuation included cerebrovascular accident (0.34% (13/3862) for zoledronic acid and 0.16% (6/3852) for placebo), acute myocardial infarction (0.16% (6/3862) for zoledronic acid and 0.03% (1/3852) for placebo), and breast cancer (0.16% (6/3862) for zoledronic acid and 0.05% (2/3852) for placebo).

Discussion on clinical safety

Atrial fibrillation

The final safety data from Study 2301 have been submitted during the procedure and confirm the findings of the interim analysis. There is an increased rate of serious atrial fibrillation events in the zoledronic acid group that is unlikely to be due to chance considering the size of the study. The most frequently reported SAE in the zoledronic acid group was atrial fibrillation. This AE is being included in the SPC via variation II-14 adopted in parallel to this procedure.

The CHMP considered that the increased rate of serious atrial fibrillation events in the zoledronic acid group that was unlikely to be due to chance considering the size of the study. Post-marketing reports cannot be considered a sensitive measure for this adverse event, as AF is very common in the elderly population and until now would not have been suspected to be related to bisphosphonates.

ONJ

The risk for development of ONJ is reported to be higher for patients treated with Zometa for oncology indication than with Aclasta for benign indications. However, there are increasing numbers of reports of ONJ also in association with bisphosphonate treatment for osteoporosis and as zoledronic acid is the most potent of the bisphosphonates, there is a theoretical risk that it will cause an increased risk of ONJ. Furthermore, it has been shown that the number of bisphosphonate infusions increases the

risk for ONJ, making the long-term risk for this condition unknown and thus emphasising the need for long-term studies.

Bone related AEs

Available bone biopsy data from clinical studies do not now show signs of fragile bone. However, for bone safety, 6 years might not be a sufficient time period for evaluating the potentially negative effects on bone healing and bone biopsies from patients on long time treatment with zoledronic acid for postmenopausal osteoporosis are needed.

Renal AEs

Renal adverse events were more frequent in the zoledronic acid group compared with placebo. The CHMP raised concern about the somewhat higher incidence of renal deterioration among the Aclasta treated patients after infusion and after one year. The renal AEs with higher frequency are mainly increased in serum creatinine (33 versus 10 if the term “azotaemia” is included) but also a higher rate of acute renal failure and glomerulonephritis has been observed, even if these were rare. Decreased creatinine clearance and renal impairment occurred, however, at a similar rate, which was considered reassuring. An expert report on renal safety was included in the submission from the MAH.

The MAH was asked to provide dosing recommendations in the product information that are in line with what is recommended for Zometa. The dosing instructions in renal impairment for treatment of Paget’s disease were also reconsidered and the Product Information was revised not recommending Aclasta for use in patients with a creatinine clearance of < 40 ml /min.

Long-term treatment

Due to the long retention of bisphosphonates in bone, concern has been raised in literature about the long term safety of bisphosphonates¹. There have been reports of patients, who sustained unusual spontaneous non-spinal fractures while on alendronate therapy for 3 to 8 years^{2, 3}. Some of these patients had also delayed or absent fracture healing during alendronate therapy. Bone biopsies showed markedly suppressed bone turnover². After prolonged severe suppression of bone turnover negative effects including brittle bone formation, due to increased mineralisation⁴ and accumulation of microdamage⁵ have been observed.¹

The CHMP considered that the safety data accumulated for alendronate can not automatically be applied to zoledronic acid 5 mg given as yearly infusions in postmenopausal osteoporosis.

The reason for this is, that alendronate and zoledronic acid are not exactly comparable, zoledronic acid being a more potent agent. Neither are the forms of administration, daily or weekly oral intake for alendronate and yearly i.v. infusions for zoledronic acid, exactly comparable.

Safety data from long-term treatment of osteoporotic women with a yearly 5 mg i.v. dose of zoledronic acid are still sparse and serious safety signals have occurred in the treatment of patients with malignant disease in other indications. The fact that Aclasta has been studied for 3 years in postmenopausal women with osteoporosis in a large clinical trial is reflected in the SPC.

¹ References:

1. Ott SM. Long term safety of bisphosphonates. JCEM 2005; 90: 1897-1899
2. Odvina CV et al. Severely suppressed bone turnover: a potential complication of alendronate therapy. JCEM 2005; 90; 1294-1301
3. Schneider JP. Should bisphosphonates be continued indefinitely? An unusual fracture in a healthy woman on long-term alendronate. Geriatrics 2006;1: 31-33
4. Ciarella TE et al. Effects of vertebral bone fragility and bone formation rate on the mineralization levels of cancellous bone from white females. Bone 2003; 32: 311-315
5. Mashiba T et al. Suppressed bone turnover by bisphosphonates increases microdamage accumulation and reduces biomechanical properties in dog rib. J Bone Miner Res 2000; 15: 613-620

1.4 Detailed description of the Pharmacovigilance system

At the time of the submission of this variation, the MAH submitted a description of the Pharmacovigilance system and indicated that a cross-functional Medical Safety Review Board was established in September 2006, which meets on regular basis as appropriate, and will ensure that all steps are taken to address safety risks of the MAH's compounds/products, including the review of all risk management plans. With the implementation of this board any required procedures are documented to support its function.

1.5 Risk Management Plan (RMP)

The MAH submitted a risk management plan, which included a risk minimisation plan

The elements of the RMP were 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 content of the RMP was considered to be satisfactory, and the MAH agreed to revise the structure of the RMP according to current guidelines including the template for EU RMP as a post opinion commitment

Pharmacovigilance plan

Routine Pharmacovigilance activities

New safety information will be collated, reviewed and analysed from multiple sources, including spontaneous reports, post-approval clinical studies, reports from the Health Authorities and published literatures on an ongoing basis. Detection of emerging potential safety signals will be performed by periodic cumulative evaluation of AEs reported. Special analysis and discussion of areas of interest will be included. The results will be compiled in the Periodic Safety Update Report, with summaries and conclusions submitted to the Health Authorities. The PSURs will include the following specific targeted areas of interest: hypocalcaemia, renal dysfunction, ONJ, ocular adverse events, atrial fibrillation and cerebrovascular AEs.

Summary of important identified and potential risks

Identified risks

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, extremity pain and arthralgia. The incidence of post dose symptoms decreased after each annual infusion. Post dose symptoms do not pose any risk to the overall health of the patient.

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 Aclasta. 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 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.

The CHMP considered that the risk of ONJ should be included as an identified risk and not as a potential risk as initially proposed by the MAH. It was identified with both the same active substance and the class and it is not known whether this ADR is dose dependent, so the lower dose of zoledronic acid in Aclasta in PMO patients is not a reason for labelling this risk as a potential only.

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 seen in less than 3.3% of patients treated with Aclasta 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.

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. Therefore, particular attention was paid to evaluate any signs of potential renal problems. 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 ZOL vs. 0.8% in placebo) and proteinuria (0.6% in patients on ZOL vs. 0.182% on placebo). In general, there would appear to be no pattern of increased risk of renal events above a baseline creatinine clearance of 40 ml/min.

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 Aclasta vs. 0.13% in patients treated with placebo. None of the cases were symptomatic and they generally occurred in patients with pre-existing conditions such as parathyroidectomy or malabsorption of calcium.

Potential risks

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, confirmed by the adjudication committee. Thus no evidence that administration of zoledronic acid is associated with increased risk of osteonecrosis outside the jaw or impaired fracture healing.

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. This finding can however not be explained based on the known mechanisms of bisphosphonates, and might constitute spurious findings. However, the ongoing trials will be monitored to further elucidate these findings.

The CHMP did not consider the higher rate of AF as an SAE as a chance finding only, as other factors that support a relationship to Aclasta for AF are the observed increased incidence of congestive heart failure and sick sinus syndrome and stroke related death as compared with placebo. All of these conditions are known to be associated with AF. Furthermore, in study 2301, previous use of bisphosphonates was an independent risk factor for AF together with well known risk factors such as age and heart failure. This was unexpected and may indicate a cumulative dose related effect. Lastly, plausible mechanisms have been identified, such as effects on calcium homeostasis and on cytokine release. However, a significant confounding factor could be the association between osteoporosis and cardiovascular disease. The MAH pointed out that it could be that patients, evaluated as being so osteoporotic they demanded treatment with bisphosphonates by their physicians prior to participating in the clinical trial, also had more severe CV disease. The presence of coronary artery disease as a

significant risk factor of the occurrence of cardiac arrhythmias was also demonstrated in Study 2301, therefore AF was considered only a potential risk at this stage.

Cerebrovascular events

In study 2301, there was a greater number of deaths for which a cerebrovascular event as underlying condition for zoledronic (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. Due to the numerous confounding factors the cardiovascular experts considered this finding can not be explained based on the known mechanisms of bisphosphonates, and might constitute spurious findings. However, the ongoing trials will further elucidate these findings.

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, these imbalances disappeared at later time points.

The CHMP pointed out that gastrointestinal adverse events as identified risk can however be questioned. In all studies performed, the incidence of these events has been similar in Aclasta treated patients as in placebo groups and also when compared with alendronate, gastrointestinal side effects were similar. The CHMP therefore recommended to include it as a potential risk only.

Enhanced Pharmacovigilance activities

In addition to the previously reported Pharmacovigilance activities the MAH has committed to perform one epidemiological cohort study for the assessment of bone and cardiovascular safety and one study to further elucidate hypocalcaemia effects. In the hypocalcaemia study the effectiveness of patient and health care provider education strategies about calcium and vitamin D supplementation will be assessed. The incidence of treatment-emergent hypocalcaemia at day 9-11 in this study will be compared to the incidence seen in the pivotal Paget's study.

Risk minimisation

After launch of Aclasta for PMO, the MAH proposed to collect prescribing information periodically to ensure that Aclasta is appropriately prescribed in accordance to the approved SPC. Additionally, a specific leaflet drafted in lay language will be in the patient information pack and available to the patient when they are prescribed Aclasta. The MAH will proactively provide information on the safety/tolerability profile of Aclasta for healthcare professionals and patients to encourage proper product use. A prescription database covering France, Germany, Italy, Spain and UK will also be used to gather further data. The information is derived from doctor-patient consultations and the treatment given. The data is collected from a representative sample of doctors practising in the primary care sector of each country that is being monitored. The MAH committed to submit the materials reflecting the content of the physician educational material and the patient information pack to the CHMP for review as a Follow-Up measure.

Specific strategies for communication initiatives, as appropriate for each of the identified and potential safety concerns will include:

- SPC and PL - labelling of the appropriate identified and potential risks were included in the SPC and PL.
- Guide for Healthcare Professionals - to reduce the risk of prescribing to inappropriate patients, the prescribers will be provided with a "Guide for Healthcare Professionals" to assist them in identifying patients suitable for Aclasta treatment

- Patient and Healthcare Professionals Education Initiatives - the programme will include educational materials containing the key safety messages for the appropriate clinical management of identified and potential risks

In addition to the risk minimisation activities described above, information about the incidence rates for atrial fibrillation in Study 2301 was included into the SPC and PL in variation II-14. An overview on the Pharmacovigilance and risk minimisation activities is presented in table 7.

Table 7: Summary of the RMP for Aclasta.

Safety concern	Proposed Pharmacovigilance activities	Proposed risk minimisation activities
<i>Identified risks</i>		
Post dose symptoms	Routine pharmacovigilance	Detailed information in section 4.8 of the SPC Guide for healthcare professionals Patient and healthcare professional education initiative
Renal dysfunction	-Close monitoring and cumulative analysis in PSURs -Special follow up of cases -Adjudication of all clinical trial cases	Detailed information in section 4.4 of the SPC Guide for healthcare professionals Patient and healthcare professional education initiative
Ocular adverse events	-Close monitoring and cumulative analysis in PSURs -Special follow up of cases -Adjudication of all clinical trial cases	Listed in ADR section 4.8 of the SMPC Guide for healthcare professionals Patient and healthcare professional education initiative
Hypocalcaemia	-Close monitoring and cumulative analysis in PSURs -Special follow up of cases -Study to explore adherence to Calcium and Vitamin D supplementation recommendations and incidence of hypocalcemia	Detailed information in section 4.8 and 4.4 of the SPC Guide for healthcare professionals Patient and healthcare professional education initiative
Osteonecrosis of the jaw	-15 day expedited reporting -Close monitoring and cumulative analysis in PSURs -Special follow up of cases -Adjudication of all postmarketing and clinical trial cases -Research activities to further elucidate ONJ -Epidemiological cohort study -Retrospective study in non oncology patients (Australia) -Long term safety data: 3 Year Extension to Study 2301E1	Detailed information in section 4.4 of the SPC Guide for healthcare professionals Patient and healthcare professional education initiative
<i>Potential risks</i>		
Osteonecrosis outside the jaw	-Close monitoring and cumulative analysis in PSURs	Guide for healthcare professionals Patient and healthcare professional education

Safety concern	Proposed Pharmacovigilance activities	Proposed risk minimisation activities
	-Special follow up of cases -Adjudication of all clinical trial cases Epidemiological cohort study -Long term safety data: 3 Year Extension to Study 2301E1	initiative
Non union/delayed union	-Close monitoring and cumulative analysis in PSURs -Adjudication of all clinical trial cases -Epidemiological cohort study -Long term safety data: 3 Year Extension to Study 2301E1	Guide for healthcare professionals Patient and healthcare professional education initiative
Cerebrovascular events	-Close monitoring and cumulative analysis in PSURs -Special follow up of cases -Adjudication of all clinical trial cases -Epidemiological cohort study -Long term safety data: 3 Year Extension to Study 2301E1	Guide for healthcare professionals Patient and healthcare professional education initiative
Atrial fibrillation	-Close monitoring and cumulative analysis in PSURs -Special follow up of cases -Adjudication of all clinical trial cases -Epidemiological cohort study -Enhanced monitoring activities in extension trials of Study 2301 -Long term safety data: 3 Year Extension to Study 2301E1	Listed in ADR section 4.8 of the SPC Guide for healthcare professionals Patient and healthcare professional education initiative
Gastrointestinal adverse events	Routine pharmacovigilance	Listed in ADR section 4.8 of the SPC Guide for healthcare professionals Patient and healthcare professional education initiative

The CHMP, having considered the data submitted in the application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

The Marketing Authorisation Holder (MAH) shall ensure that all physicians who are expected to prescribe/use Aclasta in this new indication with a physician information pack containing the following:

- Physician educational material
- Patient information pack

The physician educational material should contain the following key elements:

- The Summary of Product Characteristics
- Reminder card with the following key messages:
 - Need to measure serum creatinine before treatment with Aclasta
 - Recommendation not to use Aclasta in patients with creatinine clearance < 40 ml/min

- Contraindication in pregnancy and in breast-feeding women due to potential teratogenicity
- Need to ensure appropriate hydration of the patient
- Need to infuse Aclasta slowly over a period of no less than 15 minutes
- One-yearly dosing regime
- Adequate calcium and vitamin D intake is recommended in association with Aclasta administration.
- Need for appropriate physical activity, non-smoking and healthy diet
- Patient information pack

The patient information pack should be provided and contain the following key messages:

- Package leaflet
- Contraindication in pregnancy and in breast-feeding women
- Need for adequate calcium & vitamin D supplementation, appropriate physical activity, non-smoking and healthy diet
- Key signs and symptoms of serious adverse events
- When to seek attention from the health care provider

The MAH has in addition to previous pharmacovigilance activities committed to perform an epidemiological study on bone and cardiovascular safety and a study to explore adherence to calcium and vitamin D supplementation and incidence of hypocalcaemia. Moreover, the SPC was amended in variation II-14, which was adopted in parallel to this procedure, with information about the incidence rates for atrial fibrillation in Study 2301.

II. OVERALL CONCLUSIONS AND RISK/BENEFIT ASSESSMENT

Non-clinical pharmacology and toxicology

The CHMP considered that additional non-clinical bone safety studies were unlikely to provide significant new information on bone safety. While the toxicological and pharmacological profile of bisphosphonates seems overall qualitatively similar there are considerable differences in potency. In relation to the extension of the indication, the known toxicity of zoledronate, in particular renal toxicity, and the fact that biochemical markers do not reliably detect renal injury, needed to be considered.

The additional studies performed since 2004 confirm the earlier findings and have increased the understanding of the mechanisms of action of zoledronate. No new problems or worries have emerged from these studies.

Efficacy

For time to first hip fracture, the risk reduction was 41%. Similar results for hip fractures were shown for those 20% receiving other concomitant anti-osteoporotic treatment (excluding bisphosphonates). The results for hip-fractures, however, were not consistent across all sub-groups and in patients with previous use of bisphosphonates, the risk for hip fracture was actually increased. It could not be evaluated if this was a chance finding or not and therefore it needs to be discussed further. Also in patients ≥ 75 years of age, the risk reduction was only marginal.

However, the CHMP agreed that the overall results on hip and other clinical fractures were convincing but it was considered likely that zoledronic acid has less effect at sites where cortical bone is present compared with the vertebrae where trabecular bone predominates. The non-significant results with regard to e.g. wrist fractures could support this. Less efficacy could also be expected in involutional

osteoporosis as compared with postmenopausal osteoporosis. The CHMP further pointed out that the mean age of the patients with previous bisphosphonate use compared with the bisphosphonate-naïve patients is not known at this time.

Results with regard to BMD data and biomarkers were consistent with fracture data, however, the CHMP considered it possible that similar or better efficacy could have been achieved with a different dosing, e.g. using a lower dose at a more frequent interval. The results indicate that zoledronic acid is non-inferior to oral alendronate, although there was a trend for larger increases in BMD with alendronate at 12 months and furthermore, a more stable suppression of biomarkers was observed with alendronate over the same period. The annual dosing, however, can be expected to be of a major benefit to many patients.

Due to the data on fracture rates in different age categories presented above, the CHMP concluded that Aclasta is efficacious also in the elderly.

In conclusion, Zoledronic acid 5 mg once per year reduced bone resorption to the lower half of the premenopausal range and provided consistent anti-fracture efficacy across all osteoporotic fractures. The relative reduction in vertebral and non-vertebral fractures was better than that seen for oral drugs like alendronate and risedronate, which induce stable reduction of bone turnover. The MAH considered the slight increases in bone turnover between dosing beneficial, because it may secure some repair of microdamage, should it occur. Nevertheless, bone resorption activity remains in the lower half of the premenopausal range, where, based on previous analyses, maximum anti-fracture efficacy should be secured.

Safety

Results from the large, long-term pivotal study in osteoporosis reveal in general no new or alarming adverse reactions to zoledronic acid. Adverse reactions were mainly post-infusion reactions, such as pyrexia and influenza-like illness, occurring within 3 days after infusion and were most prominent at day 2. The rate of post-infusion reactions overall was twice that compared with placebo and for individual symptoms, 2-5 times more frequent. For individual symptoms such as pyrexia, the rate was 16% compared with 2% in the placebo group. These reactions were most prominent after the first infusion but decline in frequency with repeated infusions. Administration of paracetamol/ibuprofen reduced these reactions by about 50%. The SPC was updated to reflect these AEs and the effect of administration of paracetamol/ibuprofen.

Overall, the critical side effects were:

- Atrial fibrillation. Unexpectedly high rate of serious atrial fibrillation was observed in the zoledronic acid group. As outlined above, Variation II-14 is adopted in parallel to reflect this adverse event in section 4.8 of the SPC.
- Renal adverse events. Zoledronic acid infusions were associated with transient increases in serum creatinine and in rare instances, acute renal failure and transient glomerulonephritis. The rare and transient episodes of acute deterioration of renal function were considered similar to those reported for the indication Paget's disease.
- Osteonecrosis of the Jaw (ONJ). Osteonecrosis was rare and was not more frequent in the zoledronic acid group. Particularly, there was one case of osteonecrosis of the jaw in the zoledronic acid group compared with 1 possible case in the placebo group. These results are reassuring but it is important that all cases of osteonecrosis continue to be monitored. What appears clear is that the incidence of ONJ is definitely lower than that reported among malignant patients.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

Risk/benefit assessment

The efficacy and safety of Aclasta in the treatment of postmenopausal osteoporosis have been well characterised for up to three years of treatment. The clinical studies have essentially been performed in accordance with what is recommended in the current CHMP guidelines. A clearly significant beneficial risk reduction of new vertebral fractures as well as of hip fractures during a three year study period was demonstrated in study 2301. The fracture prevention effects appear to be at least as good as for currently approved oral bisphosphonate regimens. The once a year i.v administration can be expected to increase control of patient compliance and also to reduce the risks of oesophageal side effects, as compared to oral bisphosphonate treatment.

In study 2301, there was an increased risk of serious AEs from atrial fibrillation in the Aclasta treatment group and also an increase for stroke related death was observed. However, in absolute numbers the increase was low. Whether these are class effects for bisphosphonates remains to be clarified.

There are also still concerns for bone safety as there are no long time data available on alendronate once yearly i.v. treatment. The risk for ONJ associated with zoledronate treatment extending over three years for postmenopausal osteoporosis must be regarded as insufficiently characterised. That appropriate follow up measures with regard to long term bone safety to which the MAH committed is a prerequisite for approval of zoledronic acid for an osteoporosis indication.

The increased risk for renal impairment after infusion of Aclasta is of concern and the drug should therefore not be administered to patients with a calculated glomerular filtration rate below 40 ml/min.

Taken together, the total benefit of 5 mg zoledronic acid iv yearly for the treatment of postmenopausal osteoporosis is considered to outweigh the risks of the treatment.

Since there was a clearly significant beneficial effect on risk reduction of new vertebral fractures as well as of hip fractures during a three year study period in study 2301, the total benefit of 5 mg zoledronic acid i.v. yearly for the treatment of postmenopausal osteoporosis is considered to outweigh the risks of the treatment. However, the SPC states that an increased risk of serious events of atrial fibrillation has been seen in clinical studies on postmenopausal osteoporotic women. Furthermore, the question of cardiovascular safety for bisphosphonates has to be discussed further by the CHMP.

II CONCLUSION

On 19 July 2007 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 subject to the additional commitments undertaken.