European Medicines Agency

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ASSESSMENT REPORT
FOR

Aclasta

International non-proprietary name: zoledronic acid

Procedure No. EMEA/H/C/000595/II/0017

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

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INTRODUCTION

Zoledronic acid is a nitrogen-containing bisphosphonate and as such, inhibits osteoclast mediated bone resorption.

For the therapeutic indication of Paget's disease of the bone, zoledronic acid is approved worldwide under the trade name Aclasta as of 15 June 2007 in 61 countries and as Reclast in the United States.

In July 2007, Aclasta received a positive CHMP opinion for the treatment of post-menopausal osteoporosis (PMO) in women at increased risk of fracture, and in July 2008, the indication was further extended to include treatment of osteoporosis in post-menopausal women and men at increased risk of fracture, including those with a recent low-trauma hip fracture.

An intravenous formulation of zoledronic acid has been approved first in August 2000 and currently in over 96 countries worldwide, including Europe, under the trade name of Zometa. It is used in several oncology indications, including tumour-induced hypercalcaemia, treatment of patients with multiple myeloma, and treatment of bone metastases from solid tumours.

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

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

The purpose of the current submission for a Type II variation for Aclasta was to seek approval for an extension of indication to include treatment and prevention of glucocorticoid-induced osteoporosis, a secondary form of osteoporosis, in both men and women.

DEVELOPMENT PROGRAMME/COMPLIANCE WITH CHMP GUIDANCE/SCIENTIFIC ADVICE

Written scientific advice from the CHMP for the treatment and prevention of GIO was given in March 2004. The study design of study 2306 was discussed and the opinion given by the CHMP was that a placebo-controlled study design would be preferred. However, it was considered by the CHMP that an active-controlled trial focusing on the non-inferiority for BMD as primary endpoint might also be acceptable.

The study recruited patients with GIO in two subpopulations: “treatment” and “prevention”. The “treatment” subpopulation included those patients who at baseline had received glucocorticoid treatment for >3 months at a prednisone-equivalent daily dose of at least 7.5 mg. The “prevention” subpopulation included those patients at baseline with glucocorticoid treatment of ≤ 3 months at a prednisone-equivalent daily dose of at least 7.5 mg. The 3-month cut-off for separation of the two subpopulations of patients was also used in the two placebo-controlled risedronate studies and is recommended elsewhere for the assessment of therapies in GIO. Based on CHMP scientific advice, non-inferiority margins and analyses for the treatment and prevention indications were assessed separately for each indication. A non-inferiority design with BMD as an endpoint was considered acceptable, although a placebo controlled trial would have been preferred.

GENERAL COMMENTS ON COMPLIANCE WITH GMP, GLP, GCP

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

NON-CLINICAL ASPECTS

Pharmacokinetics

The disposition of zoledronic acid in rats and dogs is outlined in the Scientific Discussion for the initial Marketing Authorisation and shows the following characteristics:

1) a high and persistent affinity for bone tissue;
2) rapid elimination from the circulation and most soft tissues;
3) no evidence of biotransformation; and
4) accumulation in bone which is proportional to the cumulative dose.

In rats, approximately 60% of the dose is excreted with the urine within 12 months. The remaining portion of the dose is predominantly bound to the bone tissue, from where it is slowly eliminated.
Based on non-clinical studies in rats, the apparent half-life of zoledronic acid in the whole skeleton appears to be longer than 360 days.

Reproductive toxicity

In reproductive toxicity studies previously submitted for the initial MA, two species (rats and rabbits) were evaluated utilising s.c. administration of zoledronic acid. Teratogenicity was observed in rats at doses ≥ 0.2 mg/kg/day over 9 consecutive days of dosing between Day 6 – 15 of gestation. It was manifested by external, visceral and skeletal malformations. The total dose delivered was equivalent to approximately 3 times the human dose of 5 mg based on the comparison of estimated AUCs of free zoledronic acid in rat and human. This estimate takes into consideration the difference between rat and human in the percentage of drug bound to plasma proteins. Dystocia was observed at the lowest dose (0.01 mg/kg body weight) tested in rats. No teratological or embryo/foetal effects were observed in rabbits, although maternal toxicity was marked at 0.1 mg/kg due to decreased serum calcium levels. These observations are already reflected in the Product Information.

CLINICAL ASPECTS

In contrast to primary osteoporosis, in which age and/or menopause are the two main determinants of osteoporosis (e.g. PMO), glucocorticoid-induced osteoporosis is a secondary form that shows slightly different characteristics compared to the primary form.

The association between glucocorticoid therapy and increased risk of fractures is well established and even doses as low as 2.5 mg prednisolone daily have been shown to increase the risk of fractures. This risk increases with increasing dose of glucocorticoids. The risk rapidly increases during the first 3 – 6 months after initiation of steroid therapy (*van Staa et al. 2000a*). Glucocorticoids suppress protein synthesis in many cell types, including osteoblasts and osteoclasts. These effects lead to a suppression of bone formation and increased bone resorption. The trabecular bone is especially affected by the glucocorticoid induced disturbances in the bone mineral matrix. Vertebral fractures seem to occur at a higher bone mineral density (BMD) in GIO than in postmenopausal osteoporosis (PMO). Many diseases for which glucocorticoids are used also have an inherent increased risk of fracture (e.g. asthma, inflammatory bowel disease, rheumatoid arthritis, chronic obstructive pulmonary disease).
Measures against corticosteroid-induced osteoporosis should therefore be instituted as soon after the commencement of glucocorticoid therapy as possible *(Van Staa et al 2000b).*
Zoledronic acid is proven to show an effect to preserve the bone architecture (*Recker et al 2007*) and thus, initiating treatment with zoledronic acid as soon as possible after the start of glucocorticoid therapy could preserve bone architecture and reduce the incidence of fractures in patients with GIO.

Only a minority of patients on glucocorticoids are at present receiving prophylaxis medication to prevent bone loss. Existing medical prevention therapy for this condition are certain bisphosphonates (nationally authorised) and teriparatide.

The goal of (primary) osteoporosis therapy is prevention of fractures in susceptible patients. According to the EMEA guideline on the evaluation of new medicinal products in the treatment of primary osteoporosis, "the clinical significance of osteoporosis lies in the fractures that occur". This statement can be considered valid also for other forms of osteoporosis.

In contrast to PMO, there is no CHMP guideline for treatment or prevention of GIO. There are however recommendations for the registration of agents to be used in the prevention and treatment of GIO, issued by the Group for the Respect and Excellence in Science (GREES). These guidelines were updated in 2005 (*Abadie et al 2005*).

PHARMACOKINETICS

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

In humans, the mean urinary excretion of zoledronic acid over the first 24 hours post dose was 44 ± 18% of the injected dose, with very low urinary concentrations of drug thereafter. Since less than 3 % of an intravenous dose is found in the faeces, this indicates that >50% of the administered zoledronic acid dose may be taken up by bone. Zoledronic acid, like other bisphosphonates, remains in the skeleton for a very long time. Using an estimated human half-life of 10 years, the fraction remaining after one and three years would be approximately 93% and 81%, respectively.

CLINICAL PHARMACOLOGY

The dose finding study 0041 has been assessed in the AR for EMEA/H/C/595/II/10, which lead to the approval of Aclasta 5 mg once a year in "Treatment of osteoporosis in post-menopausal women at increased risk of fracture". The same dose is suggested for the ongoing variation 595/II/16, based on the results from the clinical study 2310 in patients who had suffered a low energy trauma hip fracture.

Phase II data for zoledronic acid had shown that after one year of treatment, all of the five studied doses (0.25 mg every third month, 0.5 mg every third month, 1 mg every third month, 2 mg every six month and 4 mg once a year) led to similar increases in lumbar spine BMD but at month 12 only a relatively small reduction for resorption markers was seen for the 4 mg yearly dose. This contributed to the assumption that a higher dose than the studied doses would be needed to provide sufficient inhibition of bone turnover over 12 months and thereby secure an antifracture effect. Therefore the higher dose of 5 mg yearly was chosen for the phase III Aclasta program for non-oncology indications.

The dose and method of dosing of zoledronic acid used in the pivotal study for this extension of the indication are those approved for Aclasta for use in postmenopausal osteoporosis.

CLINICAL EFFICACY

Study 2306 was a randomised 12 month double-blind double-dummy active controlled phase III study in glucocorticoid-induced osteoporosis (GIO).

Study design

The primary efficacy endpoint, study duration as well as main inclusion and exclusion criteria were chosen based on previous studies with risedronate in GIO, for comparison (*Cohen et al. 1999*). The

study was conducted in 54 study centres in 16 countries in 4 continents, during the period June 2004 to April 2007. The design of Study 2306 is summarised in Table 1.

Table 1: Summary of active-controlled trial 2306

Study No.	Study objective/ Population	No. of patients[1]	Study duration	Medication, dosing scheme	Primary efficacy endpoint(s)
2306	Phase III, randomised, double-blind, double-dummy, stratified, active controlled parallel group efficacy / safety study in GIO	833 patients (545 in the treatment subpopulation and 288 in the prevention subpopulation)	12 months	1 x 5 mg zoledronic acid (as single 15 min i.v. infusion) Risedronate 5 mg p.o./once a day	Percent change in lumbar spine BMD at 12 months relative to baseline

[1] Randomised
Key: i.v. = intravenous, p.o. = per os (by mouth), BMD=bone mineral density, GIO=glucocorticoid-induced osteoporosis
Note: Dual x-ray absorptiometry (DXA) was used to measure BMD.

Study participants

Males and females 18 to 85 years of age and treated with at least 7.5 mg of oral prednisone or equivalent systemic corticosteroid daily and expected to continue on corticosteroids for at lest one year were included in the study. Study participants were recruited to one of the following two subpopulations:

A. Patients on high dose glucocorticoid therapy for 3 months or less, "prevention subpopulation"
B. Patients on high dose glucocorticoid therapy for more than 3 months, "treatment subpopulation"

Treatments

The active control design was chosen because a placebo controlled study was thought to have been unethical, as these patients on high dose glucocorticoids were believed to be at high risk of fracture and because of the availability of several approved therapies for this category of patients. Study participants received 5 mg of zoledronic acid or placebo, administered as a slow infusion of 100 ml over 15 minutes, in sufficiently hydrated patients. Risedronate and matching oral placebo capsules were taken daily at least 30 minutes before the first food or drink of the day (except plain water).

Elemental calcium 1000 mg daily and vitamin D in a dose of between 400 and 1200 IU daily were taken daily by the study patients.

Primary objectives

The primary objective for the treatment subpopulation was to demonstrate that the % change in lumbar spine BMD at month 12 relative to baseline in males and females treated with one i.v. zoledronic acid 5 mg dose at randomisation was noninferior to the % change in lumbar spine BMD at month 12 compared to baseline in those patients treated with oral risedronate 5 mg daily.

The primary objective for the prevention subpopulation was to demonstrate that the % change in lumbar spine BMD at month 12 relative to baseline in males and females patients treated with one iv zoledronic acid 5 mg dose at randomisation was not inferior to the % change in lumbar spine BMD at month 12 compared to baseline to those patients who were treated with oral risedronate 5 mg daily.

Secondary objectives

The following objectives were evaluated separately in the treatment and prevention subpopulations, with the exception of the morphometric vertebral fractures and clinical fractures which were evaluated overall:

- To assess the % change in lumbar spine BMD at month 6 relative to baseline in patients treated with zoledronic acid compared to patients treated with risedronate.
- To assess the % change in BMD at the total hip, femoral neck, trochanter, and distal radius at month 6 and month 12 relative to baseline in patients treated with zoledronic acid compared to patients treated with risedronate.
- To assess changes in biochemical markers of the bone turnover at day 10, month 3, month 6 and month 12 relative to baseline in patients treated with zoledronic acid compared to patients treated with risedronate.
- To assess the change in height at month 6 and month 12 in patients treated with zoledronic acid compared to patients treated with risedronate.

The following objectives were evaluated separately in the treatment and prevention subpopulations and overall:

- To explore changes from baseline in the total score of the health-related quality of life (QOL) questionnaire (EQ-5D) and its subcomponents over time in patients treated with zoledronic acid compared to patients treated with risedronate.
- To assess differences in bone histomorphometry parameters, as well as bone architecture, 3D microtomographic and bone histopathology parameters in a subset of patients for zoledronic acid compared to risedronate.
- To perform exploratory pharmacogenetic assessments to examine whether individual genetic variation in genes relating to drug metabolism, osteoporosis and the drug target pathway confer differential response to zoledronic acid.

Sample size

Initially 760 patients were planned to be included (504 in treatment and 252 in prevention group) but as the drop out rate exceeded the presumed 10 %, the sample size was reassessed (in accordance with the study protocol) and reset to 810 patients. A total of 833 patients were included in the study, 545 in the treatment and 288 in the prevention subpopulation.

Demographic data

Demographic characteristics in the “treatment” subpopulation were comparable for the two treatment groups. The majority of patients were Caucasian (93.4%) and female (67.5%). The mean weight (72.7 kg) of the patients in the zoledronic acid and risedronate groups was nearly identical. The median age was 53 years (range: 18 to 83). The majority of all patients were from Western and Eastern Europe (80%).

Overall, the two treatment groups in the treatment subpopulation were similar with respect to baseline disease characteristics including standardised lumbar spine and femoral neck BMD, and prednisone-equivalent corticosteroid dose. The median prednisone-equivalent corticosteroid dose taken by all patients at baseline was 10.0 mg/day. In the treatment subpopulation, less than half of the patients were osteoporotic or osteopenic (femoral neck T-score < -1.5). There was a lower percentage of patients in the zoledronic acid group with a femoral neck T-score > -1.5 compared to the risedronate group (52.9% vs. 59.3%, respectively) but the difference between treatment groups was not statistically significant.

Menopausal status was comparable between treatment groups for female patients in the treatment subpopulation. Most female patients were postmenopausal (63.9%), 80% of whom were postmenopausal for more than 5 years. The median number of years since menopause was 13.

Demographic characteristics of patients in the "prevention" subpopulation were comparable for the two treatment groups. The majority of patients were Caucasian (95.1%) and female (69.4%). The mean weight of all patients was 72.7 kg. The median age was 58 years (range: 19 to 84). The majority of all patients were from Western and Eastern Europe (79.2%).

Overall, the two treatment groups in the prevention subpopulation were similar with respect to baseline disease characteristics including standardised lumbar spine and femoral neck BMD, femoral neck T-score categories, and prednisone-equivalent corticosteroid dose. There were furthermore no significant differences between male and female standardized femoral neck BMD or femoral neck T-score in study 02306.

Menopausal status was comparable between treatment groups for female patients in the prevention subpopulation. Most female patients were postmenopausal (69.0%), 84.1% of whom were postmenopausal had been in the state for more than 5 years. The median number of years since menopause was 15.

The median prednisone-equivalent corticosteroid dose taken by all patients at baseline was 10.0 mg/day. In the prevention subpopulation, less than half of the patients were osteoporotic or osteopenic (femoral neck T-score < -1.5). There was a lower percentage of patients in the zoledronic acid group with a femoral neck T-score > -1.5 compared with the risedronate group (60.4% vs. 66.7%, respectively) but the difference between treatment groups was not statistically significant.

In the overall treatment subpopulation 30/545 (5.5%) patients permanently stopped steroid therapy and 30/288 (10.4%) in the prevention subpopulation. Within the treatment subpopulations 6.3% vs. 4.8% for the zoledronic acid and risedronate groups stopped corticosteroid treatment, while in the prevention subpopulation the percentage was 10.4% vs. 10.4% for the zoledronic acid and risedronate groups respectively.

Participant flow

In the treatment subpopulation, major protocol violations excluding a patient from the per protocol population were 13.6 % for the zoledronic acid group and 15.8 % for the risedronate group. A more than 1 % difference between treatment groups was seen for several major protocol deviations and in all cases the incidence was lower in the zoledronic acid group. The patient dispositions in this subpopulation are shown in table 2 below.

Table 2. Patient disposition in Treatment subpopulation, intent-to-treat (ITT) population.

Disposition/reason	**Zoledronic acid**	**Risedronate**	**Total**
	(N=272)	**(N=273)**	**(N=545)**
	n (%)	**n (%)**	**n (%)**
Completed	256 (94.1)	255 (93.4)	511 (93.8)
Discontinued	16 (5.9)	18 (6.6)	34 (6.2)
Adverse Event (s)	3 (1.1)	3 (1.1)	6 (1.1)
Protocol deviation	0 (0.0)	1 (0.4)	1 (0.2)
Subject withdrew consent	6 (2.2)	5 (1.8)	11 (2.0)
Lost to follow-up	3 (1.1)	2 (0.7)	5 (0.9)
Death	3 (1.1)	3 (1.1)	6 (1.1)
Not stated	1 (0.4)	4 (1.5)	5 (0.9)

In the prevention subpopulation, major protocol violations excluding a patient from the per protocol population were 22.2 % for the zoledronic acid group and 19.4 % for the risedronate group. A more than 1 % difference between treatment groups was seen for several major protocol deviations and in all cases the incidence was higher in the zoledronic acid group. The patient dispositions in this subpopulation are shown in table 3 below.

Table 3. Patient disposition in Prevention subpopulation, ITT population.

Disposition/reason	Zoledronic acid	Risedronate	Total
	(N=144)	(N=144)	(N=288)
	n (%)	n (%)	n (%)
Completed	129 (89.6)	131 (91.0)	260 (90.3)
Discontinued	15 (10.4)	13 (9.0)	28 (9.7)
Adverse event (s)	6 (4.2)	3 (2.1)	9 (3.1)
Subject withdrew consent	5 (3.5)	5 (3.5)	10 (3.5)
Lost to follow-up	3 (2.1)	4 (2.8)	7 (2.4)
Death	1 (0.7)	0 (0.0)	1 (0.3)
Not stated	0 (0.0)	1 (0.7)	1 (0.3)

Comorbidities

The most commonly reported active medical conditions in the *treatment subpopulation* (≥ 10.0% of all patients) were the following: hypertension (33.5% zoledronic acid; 41.0% risedronate), rheumatoid arthritis (43.8% zoledronic acid; 41.8% risedronate), systemic lupus erythematosus (15.1% zoledronic acid; 16.1% risedronate), osteoarthritis (11.4% zoledronic acid; 16.5% risedronate) and hypercholesterolemia (12.1% zoledronic acid; 8.1% risedronate). More risedronate-treated than zoledronic acid-treated patients in this group had active hypertension at baseline, 34.2 % versus 43.2 %.
The 3 most commonly-reported medical conditions which may have led to patients taking long-term corticosteroid treatment were rheumatoid arthritis, systemic lupus erythematosus and asthma.

The mean prednisone-equivalent dose at baseline of patients was 12.6 mg/day (median 10.0 mg/day). Mean lumbar spine T-score was -1.37.

In this subgroup, the mean prednisone-equivalent dose at baseline of all patients was 17.6 mg/day (median 10.0 mg/day), and the mean lumbar spine T-score was - 0.93.

The most commonly reported active medical conditions in the *prevention subpopulation* (≥ 10.0% of all patients) were: hypertension (35.4% zoledronic acid vs. 43.1% risedronate), rheumatoid arthritis (38.9% zoledronic acid; 36.8% risedronate), polymyalgia rheumatica (20.1% zoledronic acid; 20.1% risedronate) and osteoarthritis (14.6% zoledronic acid; 12.5% risedronate). The 3 most commonly reported medical conditions which may have led to patients taking long-term corticosteroid treatment were rheumatoid arthritis, polymyalgia rheumatica and systemic lupus erythematosus.

Concomitant medication

Use of the following medications was prohibited throughout the duration of the trial: any treatment for osteoporosis (bisphosphonates other than study drug, PTH, Hormone Replacement Therapy (HRT), SERMs, sodium fluoride, strontium, calcitriol, calcitonin, tamoxifen, tibolone, ipraflavone, DHEA, medroxyprogesterone), anabolic steroids. For HRT, low-dose vaginal estrogen such as 17-β estradiol ≤ 0.2 mg/day or estropitate ≤ 1.5 mg/day was permitted.

Overall, the three most commonly used concomitant medications other than calcium or vitamin D supplementation were prednisone, methylprednisolone, and methotrexate, all of which were used comparably in the two treatment groups.

Concomitant medication in the treatment subpopulation

General medications

Overall, the distribution of concomitant medication use (which may have been started prior to first study drug administration or at anytime during the conduct of the study) in the treatment

subpopulation was similar between the treatment groups. The three most commonly used concomitant medications other than calcium or vitamin D supplementation were prednisone, methylprednisolone, and methotrexate, all of which were used comparably in the two treatment groups.

Medications for osteoporosis

Data on the use of osteoporosis medications prior to the first infusion for the treatment subpopulation. showed that the two treatment groups were evenly matched with respect to their use in (5.5% for both treatment groups). Few patients took osteoporosis medications concomitantly (3 patients or 1.1% zoledronic acid vs. 2 patients or 0.7% risedronate).

NSAIDS or ACE inhibitors

Since the monitoring of renal function is important in understanding the potential effect an annual 5 mg dose of zoledronic acid may or may not have, the use of commonly used drugs known to affect renal function, e.g., non-steroidal anti-inflammatory medications (NSAIDs), angiotensin converting enzyme inhibitors (ACE), and cyclooxygenase-2 (COX2) inhibitors, were reviewed.

Patients in the two treatment groups used these compound classes similarly, including the drugs within each class. The most commonly used NSAIDs (i.e., ≥ 5% of patients) were acetylsalicylic acid, ibuprofen, and diclofenac.

The percentages of patients in the treatment subpopulation who took both an NSAID and an ACE-inhibitor were 14.3% for zoledronic acid and 16.1% for risedronate.

Concomitant medication in the prevention subpopulation

General medications

Overall, the distribution of concomitant medication use (which may have been started prior to first study drug administration or at anytime during the conduct of the study) in the prevention subpopulation was similar between the treatment groups The three most commonly used concomitant medications other than calcium or vitamin D supplementation were prednisone, methylprednisolone, and methotrexate, all of which were used comparably in the two treatment groups.

Medications for osteoporosis

Few patients had a prior use of osteoporosis medications (2 patients or 1.4% for zoledronic acid vs. 1 patient or 0.7% for risedronate), and few patients took osteoporosis medications concomitantly (3 patients or 2.1% zoledronic acid vs. 1 patients or 0.4% risedronate).

NSAIDS or ACE inhibitors

Patients in the zoledronic acid group took NSAIDs more frequently than patients in the risedronate group (42.4% vs. 36.1%, respectively). The most commonly used NSAIDs (i.e., more than 5 % of patients) were acetylsalicylic acid, ibuprofen, and diclofenac. ACE inhibitors and ARBs were taken less frequently in the zoledronic acid group than in the risedronate group (25.7% vs. 36.1%, respectively). The percentage of patients in the prevention subpopulation who took both an NSAID and an ACE-inhibitor was 17.4% for both treatment groups

Baseline fracture risk

The following baseline fracture risk factors were analysed: history of hyperthyroidism, height and weight, history of falls in past 12 months, sites of most recent fractures and mother with hip fracture after age of 50. All these factors were comparable between treatment groups, in the treatment as well as in the prevention subpopulation.

Primary efficacy results

For the primary efficacy data, the results of the analysis in the PP population were consistent with those in the MITT population in both study subpopulations.

Treatment subpopulation

Both treatment groups increased lumbar spine BMD at month 12 compared to baseline and the criterion for non-inferiority was met as the lower bound of the two-sided 95 % confidence interval for the difference of % change from baseline in lumbar spine BMD at month 12 was greater than – 0.70 which was the pre-set non-inferiority requirement. As non-inferiority for zoledronic acid was demonstrated, superiority was tested and was demonstrated by showing that the lower bound of the confidence interval was > 0 and that the p-value for the comparison between the two treatment groups was lower than 0.05.

Subgroup-by-treatment interactions were tested for region, gender, menopausal status, mean prednisone-equivalent dose and age category for the % change from baseline in lumbar spine BMD in the treatment subpopulation at month 12. The only treatment-by-factor interaction which was shown to be statistically significant was age (p-value = 0.0307).

Prevention subpopulation

Both treatment groups increased lumbar spine BMD at month 12 compared to baseline: the LS mean increase in lumbar spine BMD was 2.37 % in the zoledronic acid group compared to 0.31 % in the risedronate group. The criterion for non-inferiority was met as the lower bound of the two-sided 95% confidence interval for the difference of % change from baseline in lumbar spine BMD at month 12 was > -1.12 % which was the non-inferiority limit set at the start of the study. As non-inferiority was demonstrated, superiority of zoledronic acid relative to risedronate was tested and was demonstrated as the lower bound of the confidence interval was > 0 and that the p-value for the comparison between the two treatment groups was < 0.05.

Subgroup-by-treatment interactions were tested for region, gender, menopausal status, mean prednisone-equivalent dose and age category for the % change from baseline in lumbar spine BMD in the prevention subpopulation at month 12. There were no significant such treatment-by-factor interactions.

Disease factors (menopausal status, femoral neck T-score, prednisone dose during the study)

The only subgroup-by-treatment interaction which was shown to be statistically significant for the primary efficacy endpoint was baseline femoral neck T-score in the prevention sub-population (p-value = 0.0707). There was a greater difference between the treatment groups with increased T-score except for patients with a baseline femoral neck T-score ≤-2.5 where the zoledronic acid group (n=12) experienced an unusually large mean increase in lumbar spine BMD which was more 2% greater than the average increase observed in any other zoledronic acid subgroups. There was no other evidence of any significant subgroup-by-treatment interactions (all interaction p-values >0.10).

The mean treatment difference was comparable in both postmenopausal women and premenopausal women, although statistical significance was only achieved in postmenopausal women due to a larger available sample for the comparison. The treatment differences in both subgroups were consistent with the results from the overall treatment subpopulation.

Secondary efficacy variables

Treatment subpopulation

For the secondary efficacy results, a 13-step closed testing procedure was used to control the type I error rate. Testing for statistical significance was performed in each subpopulation and continued as

long as each test showed statistical significance at the 0.05 level. In the treatment subpopulation, requirements for the success of the first 6 endpoints were met, but not for the 7th, and it is at this point that the closed testing procedure stopped.

Bone resorption markers

In the treatment population, the reduction of bone resorption marker serum beta-CTx was significantly higher in the group that received zoledronic acid, with a marked drop after the first injection, compared to the risedronate group which showed a lower reduction of beta-CTx levels over time (figure 1). A similar pattern could be observed for the prevention subpopulation (figure 2)

Figure 1. Relative mean change from baseline of serum beta-CTx (ng/ml) over time, Serum bone marker population in the treatment subpopulation (at day 10: Secondary efficacy endpoint 2).

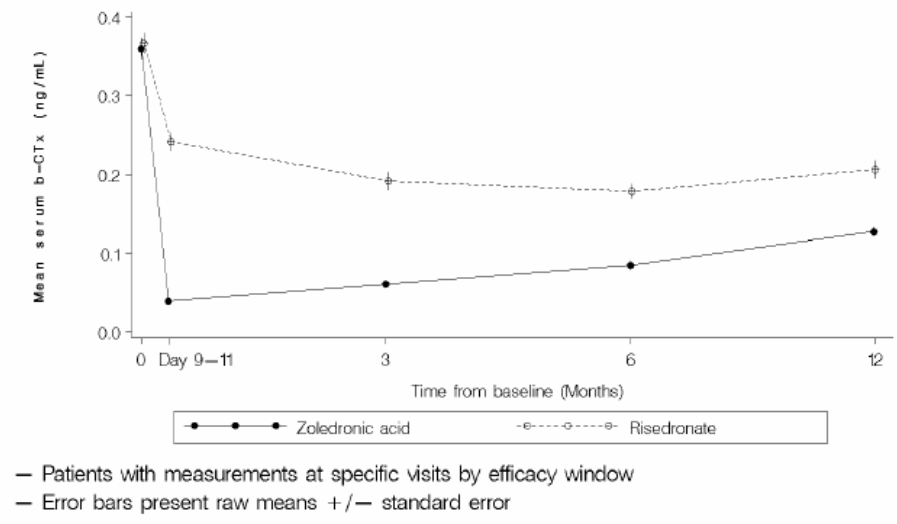
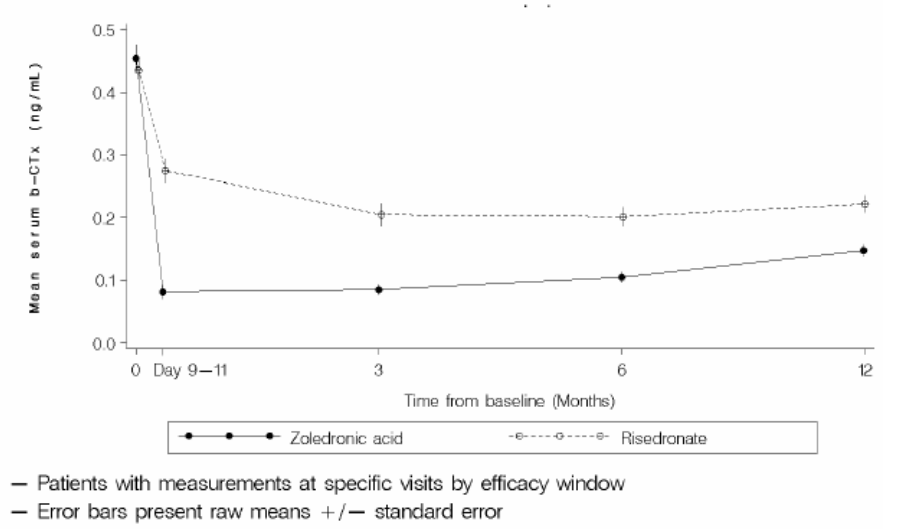


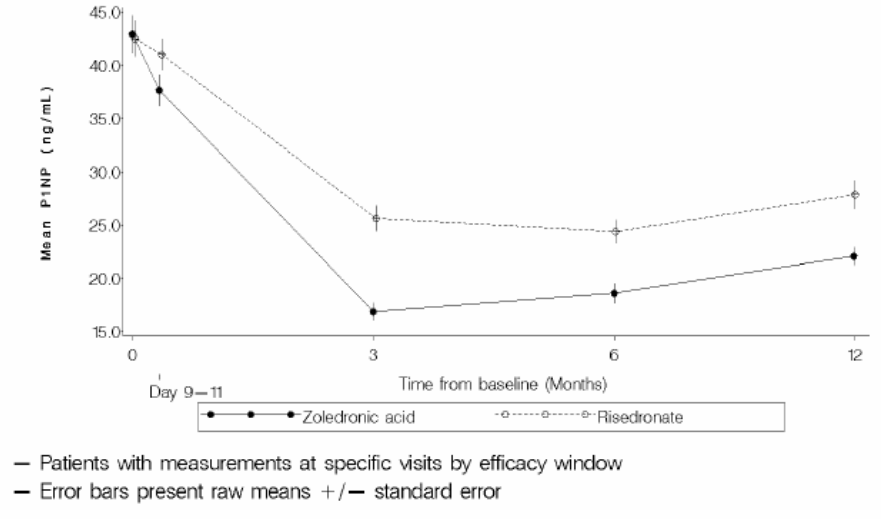
Figure 2. Mean change from baseline of serum beta-CTx (ng/ml) over time, Serum bone marker population in the prevention subpopulation (Relative % change at day 10: Secondary efficacy endpoint 2; at month 3: secondary efficacy endpoint 3).



Bone formation markers

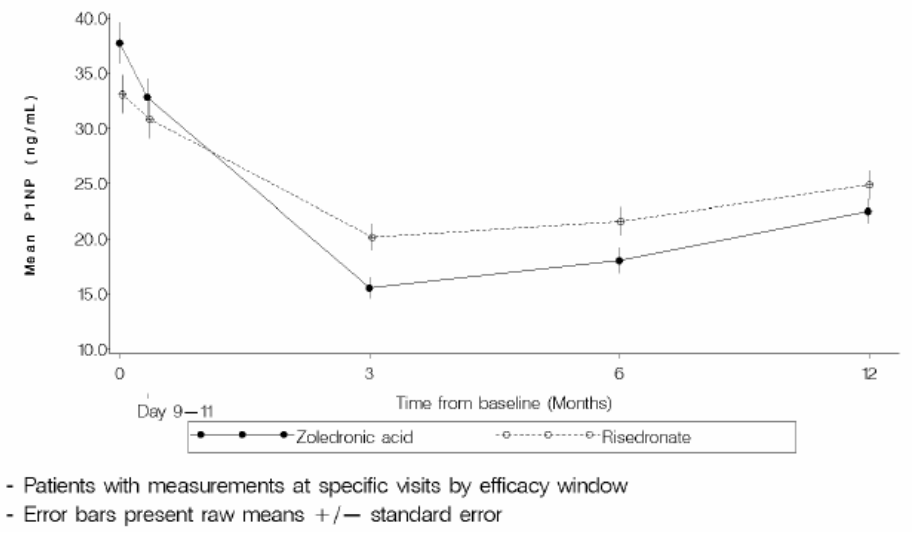
The level of amino-terminal propeptide of type 1 procollagen (P1NP), which is produced during the build-up of collagen 1 in osteogenesis and reflects osteoblast activity, dropped sharply after initiation of therapy for both substances in the treatment subpopulation. However, the initial reduction of P1NP after injection in the group that received zoledronic acid was significantly higher. The values started rising again after 3 (zoledronic acid), respective 6 months (risedronate) after injection (see figure 3).

Figure 3 Mean values of serum P1NP (ng/ml) over time, Serum bone marker population in the treatment subpopulation (Relative change from baseline at day 10: Secondary efficacy endpoint 4; relative change from baseline at month 3: Secondary endpoint 5).



A similar pattern, however with a slightly more pronounced initial drop of P1NP concentrations in the risedronate group could be observed for the prevention subpopulation (figure 4)

Figure 4. Mean values of serum P1NP (ng/ml) over time, Serum marker population in the prevention subpopulation (Relative % change at day 10: Secondary endpoint 4).



Additional secondary endpoints

The following additional secondary endpoints were analysed in this study without inclusion in the closed testing procedure:

- Percent change in trochanter, total hip and distal radius BMD at month 6 and month 12 relative to baseline
- Relative change from baseline in serum Urine N- telopeptides (u-NTx) and serum bone specific alkaline phosphatase (BSAP) at day 10 and months 3, 6 and 12
- Change in height at months 6 and 12 relative to baseline

The increases in BMD were significantly greater in the zoledronic acid-treated group at all sites including the femoral neck, total hip, trochanter and distal radius at 12 months compared to risedronate (all $p < 0.03$).

Both subpopulations combined

A between-treatment comparison of the change from baseline in stadiometer height showed no significant differences between the treatment groups at month 6 or month 12 in either subpopulation.

Fractures

Fracture rate was also a secondary endpoint. Over 12 months, new morphometric vertebral fractures occurred in 5/379 (1.3%) of zoledronic acid-treated patients compared to 3/381 (0.8%) of risedronate-treated patients. The relative risk was 1.68 with an odds ratio of 1.60 (95% CI: 0.38, 6.79) (p=0.5156). Over 12 months, 8/416 (1.9%) zoledronic acid-treated patients and 7/417 (1.7%) risedronate treated patients had at least one clinical fracture. The 1-year event rates based on Kaplan-Meier estimates were 3.31% and 2.70% for the zoledronic acid- and risedronate groups, respectively. The estimated hazard ratio was 1.14 (95% CI: 0.41, 3.16, p=0.8055).

Of the male subjects participating in the study who had both an evaluable baseline and postbaseline X-ray, 2/114 (1.75%) of zoledronic acid-treated subjects and 1/117 (0.85%) of risedronate-treated subjects experienced a new morphometric vertebral fracture (p=0.5447).

Of the female subjects participating in the study who had both an evaluable baseline and postbaseline X-ray, 3/265 (1.13%) of zoledronic acid-treated subjects and 2/264 (0.76%) of risedronate-treated subjects experienced a new morphometric vertebral fracture (p=0.7417).

Over 12 months, 8/416 (1.9%) zoledronic acid-treated patients and 7/417 (1.7%) risedronate-treated patients had at least one clinical fracture over the course of 12 months. Of the male subjects, 2/131 and 1/134 of zoledronic acid- and risedronate-treated subjects experienced a clinical fracture during the study. Of the female subjects, 6/285 and 6/283 of zoledronic acid and risedronate-treated subjects experienced a clinical fracture during the study.

Of the 180 pre-menopausal women included in the analysis of morphometric vertebral fractures, and out of 195 premenopausal women included in the ITT population for the evaluation of clinical fractures none of the patients experienced a new morphometric vertebral fracture during the 12-month double-blind period.

Bone biopsies

Bone biopsies were obtained from 23 patients, 21 from the treatment and 2 from the prevention subgroup. These patients were recruited from 7 centres in 5 European countries and one centre in Australia. Of these 23 biopsy cores, 16 (7 in the zoledronic acid and 9 in the risedronate group) were considered as adequate: they were comprised of two cortices and the trabecular network. Qualitative histopathological analyses of all evaluable biopsies showed that newly formed bone was of normal quality in terms of normal lamellar structure. There was no evidence of pathological findings. A total of 20 biopsies contained double tetracycline label in either trabecular or cortical bone.

The presence of tetracycline labelling in all technically adequate bone biopsies indicates ongoing remodelling and absence of excessive reduction of bone turnover. Normal mineralisation of newly formed bone was seen, but no marrow fibrosis, woven bone or osteomalacia after 12 months of treatment. The bone microarchitecture in the two treatment groups was similar.

Morphometric vertebral fractures

Over 12 months, new morphometric vertebral fractures occurred in 5/379 (1.3%) of zoledronic acid-treated patients compared to 3/381 (0.8%) of risedronate-treated patients. The relative risk was 1.68 with an odds ratio of 1.60 (95% CI: 0.38, 6.79) (p=0.5156).

Health-related QoL questionnaire (EQ-5D)

The objective was to measure change in health status over 1 year, using the EQ-5D at the baseline visit, after 3 months, after 6 months and at the last visit after 1 year. For the Treatment subpopulation, there were no significant differences between the treatment groups at any time point. For the prevention subpopulation, there were no significant differences between the treatment groups at any time point either.

Resource utilisation

• Treatment subpopulation: Five patients (1.8%) in the zoledronic acid group and no patient in the risedronate group were hospitalised during the study. None of the hospitalisations involved time spent in the Intensive Care Unit.
• Prevention subpopulation: No patient in the zoledronic acid group and one patient (0.7%) in the risedronate group was hospitalised during the study.

Patient preference questionnaire

At the end of the study, patients were asked to answer four questions to determine their preference for the different treatment modalities. A once-a-year infusion was preferred overall by 83.8% of all patients. A once daily pill was preferred by 10.1% of all patients. The belief that both treatments were equal was held by 6.1% of the patients overall.

Subgroup analyses

In the subgroup analysis, efficacy was seen for zoledronic acid for the primary efficacy variable in the premenopausal women in the study (see Table 5)

Table 5. Between-treatment comparison of % change from baseline in lumbar spine BMD with treatment-by-menopausal status interaction for the treatment sub-population by visit MITT lumbar spine population.

Visit	Menopausal status	Treatment	n	LS Mean (SE)	Treatment difference	95% CI of difference		Within subgroup p-value	Subgroup X treatment interaction p-value
Month 6	Post menopausal	Zoledronic acid	111	3.16 (0.45)	1.03	0.12,	1.94	0.0274	0.9546
		Risedronate	108	2.14 (0.44)					
	Pre menopausal	Zoledronic acid	63	2.77 (0.39)	1.05	0.03,	2.07	0.0443	
		Risedronate	60	1.72 (0.38)					
Month 12	Post menopausal	Zoledronic acid	111	3.68 (0.52)	1.37	0.31,	2.43	0.0118	0.9230
		Risedronate	108	2.31 (0.52)					
	Pre menopausal	Zoledronic acid	63	3.12 (0.56)	1.38	-0.08,	2.85	0.0636	
		Risedronate	60	1.74 (0.54)					

DISCUSSION ON CLINICAL EFFICACY

Overall, the risk of fracture has been demonstrated to increase at a relatively low dose of glucocorticosteroid therapy, below 7.5 mg daily, and already a short time after start of this therapy. In patients on glucocorticoids, fractures tend to occur at a higher BMD than in patients with postmenopausal osteoporosis and the population on glucocorticoids is also younger than the

population with postmenopausal osteoporosis. With this background, the CHMP agreed that fracture prevention is desirable in this population.

Trial design

The CHMP considered that the study design and endpoints for study 2306 are in accordance with the GREES recommendations for the registration of agents to be used in the prevention and treatment of glucocorticoids-induced osteoporosis.

The CHMP further agreed that in essence, the design of the trial 2306 was approved by the CHMP in a scientific advice in 2004. Two points however warrant comments.

1. The advice expressed a preference for a placebo-controlled trial although an active-controlled design was also considered acceptable. The lack of placebo has therefore to be accepted, although especially for fracture data, it would have been of value to have placebo comparison. As it turned out, the rate of fractures was very low in the study and in retrospect it seems that a 12-month study with a placebo control would not have been unethical. The CHMP highlighted in this respect that placebo-controlled studies have been performed with risedronate for the prevention and treatment of GIO (*Cohen et al.* [III] and *Reid et al.* respectively). In these studies, the placebo response was somewhat inconsistent, a decrease in BMD of –2.8% was observed in the prevention trial while BMD remained stable in the treatment trial. A possible explanation could be the natural course of GIO, i.e. bone loss is most prominent at start of glucocorticoid therapy and less with continued treatment.

2. The advice recommended separate trials for the separate indications, prevention vs. treatment of GIO. The MAH chose to rather perform a single trial, stratifying patients into 2 sub-populations; the prevention sub-population and the treatment sub-population. Since then, there has been a change in the view of the management of osteoporosis as regards differentiating between prevention and treatment of osteoporosis (see CHMP Guideline on clinical trials in primary osteoporosis).

The management of osteoporosis has also changed with the availability of the WHO Risk Assessment Tool (FRAX). Accordingly, an indication including both prevention and treatment of GIO was proposed as outlined in the section “Indication” below.

Indication

The management of osteoporosis has also changed with the availability of the FRAX Tool, which has been developed to aid decision making in osteoporosis, i.e. when to initiate treatment for osteoporosis based on the 10-year probability of a fracture. Thus, it is unlikely that nowadays the CHMP would request separate trials for these separate indications of treatment and prevention of osteoporosis, respectively, and stratification for the duration of corticosteroid use pre-study is therefore acceptable. Furthermore, and in line with the indication for post-menopausal osteoporosis, an indication for both prevention and treatment of GIO would not be justified.
Due to the above reasons the wording of the indication was therefore changed to reflect that Aclasta is indicated in the treatment of osteoporosis in post-menopausal women and in men at increased risk of fracture instead of using treatment and / or prevention claims.

While it is agreed that bone loss associated with high-dose glucocorticosteroid treatment is typically most prominent during first 3-6 months of treatment, anti-osteoporotic treatment is not indicated for short-term corticosteroid use (< 3 months) since bone loss is potentially reversible upon cessation of therapy. Considering that zoledronic acid is effective for one year, it is important that only patients intended for long-term treatment with corticosteroids receive Aclasta. This is also reflected in the pivotal Study 2306 where patients continued to receive corticosteroids throughout the 52 weeks of study duration, although patients had been stratified with respect to duration of corticosteroid use prior to randomisation. The median baseline corticosteroid dose was 10 mg of prednisone or equivalent baseline.

As treatment with corticosteroids should be as short as possible, the clinical relevance of treatment of patients at risk of fracture with bisphosphonates for 1 year was discussed during the procedure. The CHMP considered that corticosteroid treatment for more than one year is however not uncommon in clinical practice and therefore treatment of patients at risk of fracture for a period of 12 months is warranted.

Therefore, the indication now reflects use of Aclasta only for patients intended for chronic treatment with corticosteroids. The wording of the indication was further modified, in line with the wording of recently approved GIO indications for other products.

Pre-menopausal women

Although a small sub-set of pre-menopausal women treated with high-dose corticosteroids may experience fractures, in general the absolute risk is very low. Furthermore, the relationship between BMD and fracture risk in pre-menopausal women has not been established. The analyses and calculations for the sub-population of pre-menopausal women in Study 2306 also support this. At baseline this sub-population had a femoral neck T-score of –0,7, i.e. within the normal range of BMD according to the WHO classification. Bone density at the lumbar spine is not reported by the MAH. Fracture risk, using the FRAX tool, was also low and below the threshold for intervention with bisphosphonates according to WHO treatment Guidelines. The WHO FRAX tool applies only to patients > 40 years of age and therefore calculations for the younger patients in Study 2306 using the FRAX may have overestimated the risk.

The CHMP noted in this respect that high disease activity and a history of previous fracture resulted in a higher risk and in one country exceeded the threshold for intervention. The evidence that treatment with Aclasta prevents fractures in the sub-population of pre-menopausal females with multiple risk factors is lacking. Overall, fracture rates in this active controlled study were very low, and for this reason have not been presented for the different sub-groups. No fractures occurred in the group of pre-menopausal females, and it should be noted that risedronate is not indicated for GIO in pre-menopausal females.

Male Population

Aclasta has received approval for the treatment of osteoporosis in men at increased risk of fracture (see SPC) based on data from studies L2310 and M2308. Therefore, an effect in reducing fractures in men with GIO should be expected based on the concept of double-bridging which is described by the GREES group *(Compston, et al 2008).*

Dose used in the study

The CHMP considered that the arguments for using the same dose for glucocorticoid induced osteoporosis as the dose approved for postmenopausal osteoporosis can be accepted. Considering the positive benefit/risk demonstrated for this dose in the PMO and elderly population, the dose was found to be acceptable. The CHMP questioned whether the dose could be unnecessarily high in the younger GIO population. It was noted that there are no clinical data on the use of a lower dose of zoledronic acid in a glucocorticoid treated population. Zoledronic acid in the selected dose of 5mg once yearly has been effective in glucocorticoid induced osteoporosis as well as in osteoporosis in males and in postmenopausal women. From the dose finding study 0041(assessed in the ARs for Aclasta variations II/10 and II/16), it seems that a lower dose of the drug could also be effective. However, no other dose of zoledronic acid than 5 mg yearly has been explored for the non-malignant indications. As the adverse effects of this dose have been acceptable in all studied populations, the dose of 5 mg yearly was considered acceptable also for the GIO indication.

Patient Population

The relatively young age of the patients, the large proportion of pre-menopausal females and the under-representation of patients with osteoporosis at baseline (less than 10%) indicates that the patient population, apart from receiving high-dose corticosteroids, may have been at a low risk of fracture. The MAH therefore discussed the fracture risk of the study-population with reference to the FRAX tool as outlined in section "fractures" below.

The CHMP considered that the concomitant/underlying diseases observed and medications reflect a study population in a study for GIO. The majority of patients (about 40%) had rheumatoid arthritis as underlying disease and probable cause for glucocorticoid treatment. In the prevention group, 20% had polymyalgia rheumatica compared with only 5% of patients in the treatment group. Baseline morbidity was considerable, and comparable between groups. A majority of patients were Caucasian. About one third of the female patients included in the study were premenopausal.

There were no other significant differences with respect to demographic results or disease characteristics between the two sub-populations, apart from the duration of treatment with corticosteroids. Baseline corticosteroid dose was 10 mg, and thus it can be concluded that patients included were patients at risk for fracture.

Information as regards mean duration of corticosteroid treatment pre-randomisation in the treatment sub-population was provided. The median values for treatment duration pre-randomisation indicate that most patients had received glucocorticoids for less than 1 year (less than 6 months in the zoledronic acid group). The majority of the patients continued receiving corticosteroids during the study.

During the study, corticosteroids were tapered but the majority, however, continued to receive doses of ≥ 7.5 mg. At the end of study 23% in the prevention sub-population and 14% in the treatment sub-population received doses below 7.5 mg.

The study included both males (30%) and females (70%) and the two-thirds of females were post-menopausal. The proportion of pre-menopausal females, however, has to be regarded as relatively large, considering that pre-menopausal females have usually been under-represented in studies on GIO (n=133 [36%] and n=62 [31%] in the treatment and prevention sub-populations, respectively).

Compared with previous studies that have been assessed in type II variations, the study population in Study 2306 was considerably younger (mean age was 73 in the post-menopausal Study 2301 and 74.5 years in the hip fracture prevention Study 2310) and less osteoporotic. Actually, less than 10% were osteoporotic at baseline in Study 2306.

Furthermore, comparing the two sub-populations, the patients in the treatment sub-population were somewhat younger (mean age 53 vs. 58 years) but the proportion of patients that were osteopenic or osteoporotic was higher (44% vs. 36%) compared to the prevention sub-population. This is not unexpected as patients treated for osteoporosis would have been expected to be more osteopenic / osteoporotic compared with a population receiving treatment for the prevention of osteoporosis. Proportion of osteoporotic patients was, however, similar or 9.5% in both sub-populations. This overall low proportion of patients with osteoporosis baseline indicates that the patients in general in Study 2306 were at a low risk for fractures, as also discussed further below.

Discontinuation rate was no more than about 10 % in any of the subpopulations which is reasonable. More patients in the prevention than in the treatment subpopulation had protocol violations and about 10 % of patients in the prevention subpopulation were inadequately stratified.

Rather few patients seem to have had previous fractures, and the rate of low-trauma fractures in particular being low. The MAH further presented that overall the history of previous fracture at baseline was similar across both the treatment and prevention subpopulations. Of the patients

randomised to the treatment subpopulation, 35.0% (191/545) (35.0%) had a previous fracture prior to randomisation compared to 35.1% (101/288) of patients randomised into the prevention subpopulation. The incidence of previous fracture was similar as well across treatment groups with 36.4% and 33.7% of zoledronic acid- and risedronate-treated patients having experienced a previous fracture in the treatment subpopulation and 33.3% and 36.8% of zoledronic acid- and risedronate-treated patients having experienced a previous fracture, respectively in the prevention subpopulation. The arm and foot were generally the most common location of previous fracture in both subpopulations.

The CHMP agreed that the low rate of prevalent vertebral fractures at baseline (4% and 3% in the treatment and prevention population, respectively) confirmed that the patients included were patients at a low risk of fracture, which is expected considering that only 10% had osteoporosis at baseline.

In conclusion, the relatively young age of the patients, the large proportion of pre-menopausal females and the under-representation of patients with osteoporosis (less than 10%) indicates that the patient population, apart from receiving high-dose corticosteroids, have been at a low risk of fracture.

Discussion of efficacy results

In study 2306, an intravenous dose of 5 mg zoledronic acid was convincingly shown to increase the lumbar spine BMD from baseline to 12 months significantly compared to daily oral risedronate, in the prevention (on glucocorticoids 3 months or less) as well as in the treatment (on glucocorticoids for more than 3 months) subpopulations.

Primary efficacy variables

The CHMP agreed that zoledronic acid was shown to be superior to risedronate for the primary efficacy parameter "% change in lumbar spine BMD at month 12 relative to baseline" in the prevention as well as in the treatment subpopulation.

In both treatment groups, the percentage increase in BMD at 12 months was higher in the treatment sub-population compared with the prevention sub-population. Results for the risedronate arm are comparable to what has previously been published. Results for zoledronic acid in the treatment sub-population are comparable to previous results in females with PMO (Study 2301). The reason for less pronounced effect in the prevention group was considered to be related to the natural course of GIO, i.e. rapid loss of bone density at the start of treatment with corticosteroids may have counterbalanced the anti-resorptive effects of bisphosphonates. Consistent results of BMD increase in both populations support an indication independent of start of corticosteroid treatment.

The results for the sub-group analysis confirm the overall results for the primary efficacy endpoint and support an indication that is based on pharmacodynamics of zoledronic acid to increase bone mineral density. Similar percentage increases in BMD were obtained in both males and females, although in the prevention sub-population, BMD actually decreased in risedronate treated males.
Comparing pre-menopausal females with post-menopausal females, somewhat larger increases were shown for both treatments in the post-menopausal females.

Secondary efficacy variables

Zoledronic acid showed also superiority to the comparator for several secondary efficacy parameters, decreasing bone markers and increasing BMD also at other sites than the lumbar spine. The study was of 12 months duration and was not powered to demonstrate a difference in fracture incidence between treatment groups. Few patients had fractures in the study and there was no apparent difference between the treatment groups.

Overall, in the prevention study subpopulation, the pattern of decline for bone markers serum beta-CTx and serum P1NP were similar to that in the treatment subpopulation. The CHMP however noted

that in the treatment subpopulation, bone markers serum beta-CTx and serum P1NP were significantly more depressed in the zoledronic acid- than in the risedronate group through the study period.

Concerning the additional secondary endpoints, the CHMP considered that these analyses were not adjusted for multiplicity, as they were analysed in this study without inclusion in the closed testing procedure.

The CHMP noted also that bone biopsies, a majority of them from the treatment subpopulation, were normal in both treatment groups.

No difference was found between treatment groups for Quality of Life or for resource utilisation. A majority of patients preferred a once a year intravenous infusion regimen to a daily oral regimen.

The CHMP considered that the secondary results support the results for the primary endpoint with demonstration of superiority of zoledronic acid over risedronate with respect to percentage increase in BMD already after 6 months. At 12 months, the curves approached each other and this is consistent with previous study results where zoledronic acid was compared with oral alendronate, i.e. zoledronic acid results in a more profound effect on biomarkers initially following infusion while daily oral treatment results in a more steady suppression of markers over time. The effects on bone resorption markers is most pronounced at day 9-11 while effect on bone formation markers is most pronounced at month 3 with zoledronic acid. This is consistent with previous results in PMO.

As regards efficacy, it can therefore be concluded that the pivotal study met its endpoints demonstrating non-inferiority, and also superiority, of zoledronic acid compared with oral risedronate in increasing BMD at the lumbar spine over 12 months.

Fractures

Given the overall low incidence of fracture in both treatment groups, the incidence in male and female subjects were low in both treatment groups with no noticeable patterns in the incidence across genders.

This finding was not unexpected considering that all patients received active treatment. The study was not powered to show a difference in fracture rate.
The relatively young age of patients, relatively large proportion of pre-menopausal females and the fact that only about 10% were osteoporotic at baseline may also have influenced the fracture rate. There was no difference between the treatment groups, despite superiority of zoledronic acid for the primary endpoint of BMD change.

Fractures tend however to occur at higher BMD in glucocorticosteroid induced osteoporosis (GIO) than in postmenopausal osteoporosis. Regardless of the combination of risk factors for fracture, the MAH found that the most influential factors in determining an individual patient's fracture risk are decreasing BMD, age and existing rheumatoid arthritis.

The FRAX tool for assessing the 10-year fracture risk is designed to estimate the risk for individuals. The MAH presented an estimation of fracture risk based on the average profile of the treatment and the prevention population, respectively. The CHMP considered that the limitations of the FRAX tool are acknowledged since this tool has not been validated for the GIO population and considering the age range of the study population (18-85 years), which was outside the range for which the FRAX has been validated (40-89 years).

In summary, for the treatment population, the 10-year probability of an osteoporotic fracture was between 3.3% and 10% for the various countries and for the prevention population, the risk ranged from 3.5% to 13%. Thus, overall the patient population had a low risk of fracture. Sub-analyses confirmed that adding risk factors resulted in a higher10-year probability of a fracture. For the sub-group of patients with active RA, history of fractures and BMD T-score of < -1.5, the risk in the "northern" countries (UK, Sweden and US) exceeded the threshold for intervention according to WHO Guidelines.

In conclusion, these analyses support that treatment with Aclasta should only be given to patients at high risk of fractures, and the currently proposed indication reflects this.

BMD and fracture risk in the GIO population

The 1-year BMD increase demonstrated at the lumbar spine in study 2306 (4.1%) was somewhat higher than that seen in postmenopausal women (3.66%), thus the MAH considered that anti-fracture efficacy at the spine in GIO patients in a placebo-controlled trial, would be expected to be of similar magnitude to that seen in women with postmenopausal osteoporosis in study 2301 (60% and 70% after 1 and 3 years, respectively). In the risedronate and alendronate trials 1-year lumbar spine BMD increases of 4.7 % and 4.1%, respectively, were reported. The relative risk reductions for spine fractures were 89% and 60%, respectively.

The MAH presented two studies with risedronate, which closely mimic the design of Study 2306, including both males and females receiving corticosteroids and with a similar risk profile. These demonstrated changes in BMD of 0.6 and 2.9% for risedronate in a prevention and a treatment population, respectively. The figures are in line with the results for risedronate in Study 2306. The vertebral fracture rate in the prevention study was 17.3% in the placebo group and 5.7% in the risedronate 5 mg group (a reduction of 71%) and in the treatment study it was 15% in the placebo group and 5% in the risedronate 5 mg group (a reduction of 70%). Thus, it can be expected that in Study 2306, the risk reduction would have been around 70% for risedronate.
The CHMP further noted that for the studies in male osteoporosis and GIO presented by the MAH, the absolute number of fractures was low due to relatively small sizes of the studies, albeit significant results were obtained.

The translation of demonstrated effects of treatment with zoledronic acid on BMD in terms of overall fracture risk reduction was also discussed by the CHMP. The BMD results of the 2306 study can be considered of similar magnitude compared to the results in the 2301 pivotal PMO trial (assessed in variation II-10). The event rate reported for vertebral fractures in the SPC for risedronate was 6% in the prevention study and 5% in the treatment study, both of which are higher than the clinical fracture rate for risedronate observed in Study 2306.

In the PMO study 2301, zoledronic acid treated patients had a 40% reduction in the risk of hip fractures during the 36 month study period. Lumbar spine BMD increased 6.82 % from baseline in patients treated with zoledronic acid, compared to a 0.06 % decrease in placebo treated patients in study 2301. Fracture rates from studies in a PMO population can however not directly be transferred to a younger GIO population with other fracture risk factors. In study 2306, factors such as patient age, steroid dose, duration of steroid therapy and the prevalence of active rheumatoid arthritis in the population affect the fracture risk in the study population and these risk factors are very varying in different subgroups of the study population, making fracture risk calculations difficult.

Fracture prevention has not been shown in the glucocorticoid treated population but there are some indications of a fracture prevention effect: Significant improvement in BMD data, and positive trends for fracture data for the comparator in several clinical studies with risedronate. Based on BMD data, risedronate has been approved in the indication “To maintain or increase bone mass in postmenopausal women undergoing long-term (more than 3 months), systemic corticosteroid treatment at doses 7.5mg/day prednisone or equivalent”. The CHMP therefore considered that risedronate is an adequate comparator for clinical studies of osteoporosis in a population of glucocorticoid treated patients - with the exception of premenopausal women, as discussed under clinical safety.

CLINICAL SAFETY

The primary source of safety data is also the active controlled Study 2306.

Patient exposure

In the treatment subpopulation in study 2306, 270 patients were exposed to IV zoledronic acid, 267 to placebo infusion. Oral study medication was given to 272 patients in the zoledronic acid group (placebo) while risedronate was administered to 273 patients in the risedronate group. In the prevention subpopulation in study 2306, 143 patients were exposed to IV Aclasta, 141 to placebo infusion. In this study subpopulation, oral study medication was given to 144 patients in the zoledronic acid group (placebo) while risedronate was administered to 144 patients in the risedronate group.

Targeted assessment of fracture non-union and delayed union as well as avascular necrosis / Osteonecrosis of the Jaw (ONJ) was followed by expert adjudication Adverse events within the following further categories were adjudicated in a blinded manner: hypocalcaemia, arrhythmia SAEs, and primary cause of death.

An overview of the participation and withdrawals in the GIO safety population is shown for each of the treatment groups in Table 1-14.

Table 1-14 Study completion and reason for study discontinuation (GIO ITT population)

	Zoledronic acid N=416 n (%)	Risedronate N=417 n (%)
Completed	385(92.5)	386(92.6)
Discontinued	31(7.5)	31(7.4)
Adverse Event(s)	9(2.2)	6(1.4)
Protocol deviation	0(0.0)	1(0.2)
Patient withdrew consent	11(2.6)	10(2.4)
Lost to follow-up	6(1.4)	6(1.4)
Death	4(1.0)	3(0.7)
Not Stated	1(0.2)	5(1.2)

The CHMP noted that discontinuation rate was low and comparable in both treatment groups. The rate of discontinuation due to AEs was slightly higher.

Potential interactions

Glucocorticoids

AEs were analysed by mean prednisone-equivalent dose during study 2306 (lower, middle and upper tertiles (≤ 8.14 mg/day, > 8.14 mg/day - 10 mg/day and > 10 mg/day). There was no relationship between the incidence of AEs and the prednisone dose. Patients in the middle tertile experienced the lowest incidence of AEs (zoledronic acid group 70 %; risedronate group 60.1 %) relative to the lower tertile (zoledronic acid 81.1 %; risedronate 69.2 %) and the upper tertile (zoledronic acid 83.9 %; risedronate 75.8 %).

Adverse events

In both subpopulations, post-dose symptoms of pyrexia, myalgia and influenza-like illness were more common among zoledronic acid-treated patients. These symptoms occurred typically within the first 3 days after infusion. AEs in the *treatment subpopulation* were more common in the zoledronic acid group than in the risedronate group (77.6 and 68.1 %, respectively).

The greatest between-treatment difference in the percentage of patients with AEs was in the general disorders and administration site conditions primary system organ class (PSOC) (29.3% for the zoledronic acid group and 13.9% for the risedronate group). This difference was mainly driven by the AEs pyrexia and influenza-like illness, which had at least a twofold higher incidence in the zoledronic acid group compared to the risedronate group. There was a higher incidence of nervous system disorders in the zoledronic acid group (13.5%) relative to the risedronate group (8.6%), which was mainly driven by a higher incidence of headache in the zoledronic acid group (5.3%) relative to the risedronate group (2.4%). Headache is often one of the AEs associated with post-dose symptoms observed with i.v. and high dose oral bisphosphonates.

AEs with at least a twofold higher incidence in the zoledronic acid group than in the risedronate group were pyrexia and influenza-like illness, myalgia and vomiting. Eleven (4.0 %) of patients in the zoledronic acid group and 5 patients (1.8 %) in the risedronate group had AEs of arrhythmias. See below under Arrhythmia AEs.

In the prevention subgroup, 77.1 % of patients in the zoledronic acid group and 64.6 % in the risedronate group reported AEs. 33.3 % of zoledronic acid- patients and 15.3 of risedronate patients reported general disorders and administration site conditions. Pyrexia and influenza-like symptoms were at least twice as common in the zoledronic acid group as in the risedronate group. Ten patients (6.9 %) in the zoledronic acid group and 6 (4.2 %) in the risedronate group had arrhythmia AEs. Four cases of atrial flutter or fibrillation were reported (3 of them in the zoledronic acid group), none of them serious. Data on specific AEs in study 2306 are also given in section IV of the Risk Management Plan (Safety Specification).

The CHMP pointed out that the higher rates of pyrexia, myalgia and influenza-like illness reflect the post-dose symptoms associated with zoledronic acid. Gastrointestinal symptoms, such as nausea, abdominal pain and dyspepsia were more frequent with zoledronic acid compared with oral risedronate.

In general, safety data for this study did not differ from studies 2301 and 2310. As no general recommendation was given to patients in study 2306 to take prophylactic medication against post-dose influenza-like symptoms, there was a high frequency of such symptoms.
Like in the big postmenopausal osteoporosis study 2301- but in contrast to the smaller study 2310 in secondary fracture prophylaxis after hip fracture - more cases of arrhythmia events were reported in zoledronic-acid treated patients. The arrhythmia events were in general reported long time after the zoledronic acid infusion.

Serious adverse events and deaths

Six patients died in the treatment subpopulation, 3 zoledronic acid- and 3-risedronate-treated. 19 zoledronic acid-treated (7.0 %) and 15 risedronate-treated patients (5.5 %) discontinued the study due to AEs.

Only one patient died in the prevention subpopulation, a zoledronic acid-treated patient. 14 zoledronic acid-treated (9.7 %) and 7 risedronate-treated patients (4.9 %) discontinued the study due to AEs. Three cardiac-related deaths were confirmed by adjudication, all in the zoledronic acid group: 2 were due to myocardial infarction and one was due to pulmonary artery bypass procedure. 2/3 had a history of cardiac disease. In all three cases, the deaths occurred more than 5 months after zoledronic acid infusion.

In total seven patients died, four in the zoledronic acid group, and three patients in the risedronate group. For all patients, the causes of death were not suspected by the investigator to be related to study medication.

The CHMP noted that the overall death rate was low with no differences between the treatment groups. All cardiac events occurred in the zoledronic acid group, but due to the low number of deaths,

no conclusion can be drawn with respect to possible relationship to study drug. There were no cerebrovascular deaths.

Laboratory findings

No significant differences between treatment groups were seen for routine laboratory data. Sixteen patients in the zoledronic acid group (3.9%) and 15 patients in the risedronate group (3.6%) had renal events (renal function AEs and/or pre-determined laboratory abnormalities) that were sent to the adjudication committee for review. Of these, 9 patients in the zoledronic acid group (2.2%) and 7 patients in the risedronate group (1.7%) had confirmed clinically significant renal events.
Only one patient in each treatment group (0.2 %) had clinical events of hypocalcaemia. Only one of these events, in the zoledronic acid group, was adjudicated as a confirmed hypocalcaemia event. This patient was asymptomatic.

The overall incidence rate for increase in serum creatinine from baseline (> 0.5 mg/dl) was higher in the zoledronic acid group in Study 2306 (zoledronic acid 9, 2.2%; risedronate 3, 0.7%). In general, for other selected biochemistry parameters, no clinically relevant differences between treatment groups were observed.

Pregnancies

In spite of female patients of childbearing potential being requested to have a negative pregnancy test and to practice contraception during the whole study period, three pregnancies occurred, all of them in risedronate-treated patients. Two of these women chose abortion while the third woman delivered a healthy baby.

Ocular Adverse Events

Six patients in each treatment group (1.4%) had ocular events that were sent for expert review. All events were adjudicated as confirmed ocular events, and all but one (conjunctivitis which occurred in a zoledronic acid-treated patient) were considered to be unlikely to be related to study medication by the expert reviewer.

Hypocalcaemia

One patient in each treatment group (0.2%) had clinical events of hypocalcaemia that met the pre-specified criteria and were sent to the adjudication committee for review. Only the one patient in the zoledronic acid group was adjudicated to have experienced a confirmed event of hypocalcaemia; no symptoms were reported.

Avascular necrosis(AVN)

Two patients in the zoledronic acid group (0.5%) and three patients in the risedronate group (0.7%) had cases of potential AVN events that were sent to the adjudication committee for review. All but one patient had their events adjudicated as indeterminate, as no radiographs were provided. One zoledronic acid-treated patient was adjudicated as having a confirmed event, but in the adjudication committee comments it was noted that AVN was suspected prior to study enrolment.

Maxillofacial events

Five patients in the zoledronic acid group (1.2%) and four patients in the risedronate group (1.0%) had maxillofacial events that were sent to the adjudication committee for review. There were no patients who had events that were confirmed by adjudication.

Renal adverse events

The overall incidence rates for each of the three categories of renal laboratory criteria at any time were low and comparable for both treatment groups: increase in serum creatinine >0.5 mg/dl (8 patients [2.0%] zoledronic acid; 6 patients [1.5%] risedronate), creatinine clearance <30 ml/min (4 patients, [1.0%] zoledronic acid, 4 patients [1.0%] risedronate patients); and decrease in creatinine clearance (CrCl) ≥ 30% and ≤60 ml/min at baseline (1 patient [2.9%] zoledronic acid, 2 patients [5.0%] risedronate).

The incidence of clinically significant renal events (renal laboratory criteria confirmed by the adjudication committee) was low for each category, and there was a similar incidence in the zoledronic acid group relative to the risedronate group (2.2% vs. 1.4%, respectively), except for the category of increase in serum creatinine > 0.5mg/dl (zoledronic acid 9, 2.2%; risedronate 3, 0.7%).

The incidence of adverse events associated with a change in renal function based on the pre-specified MedDRA search criteria was 10 (2.4%) patients in the zoledronic acid group, and 8 (1.9%) in the risedronate group.

The incidence of adverse events associated with a change in renal function and confirmed by adjudication was slightly higher in the zoledronic acid group (7 [1.7%]) than in the risedronate group (4 [1.0%]).

The incidence of renal laboratory AEs was similar in both groups but slightly higher for clinical significant event of "increase in serum creatinine > 0.5 mg/dl" in the zoledronic acid group. The number of cases are however too few to draw any conclusions.

Cardiac/cardiovascular and stroke-related adverse events

There was a higher incidence of cardiac arrhythmia AEs in the zoledronic acid group (4.1%) than in the risedronate group (1.7%). A between-treatment comparison of time to first cardiac arrhythmia adverse event showed a statistically significantly higher incidence in the zoledronic acid group (p = 0.0411, Hazard ratio = 2.4, 95% CI: 1.0, 5.9).

Atrial fibrillation or atrial flutter was experienced by four patients, none of the events were serious (3 in the zoledronic acid group and 1 in the risedronate group). One of the patients in the zoledronic acid group never received study drug infusion, although the patient had been randomised and received the first dose of oral placebo study medication. Of note, more than twice as many patients in the zoledronic acid group (2.2%) as in the risedronate group (1.0%) had active atrial fibrillation/flutter at baseline.

Six patients (3 in the zoledronic acid group [supraventricular tachycardia, cardiac arrest, and atrioventricular block third degree] and 3 in the risedronate group [palpitations, tachyarrhythmia, and tachycardia]) had arrhythmia SAEs. In the zoledronic acid group, all three events were adjudicated as a confirmed event. No events were confirmed by adjudication in the risedronate group.

The number and percentage of all stroke-related AEs reported by investigators was low and similar between the treatment groups (3 [0.7%] of zoledronic acid-treated patients vs. 2 [0.5%] of risedronate-treated patients).

The overall incidence of arrhythmia was higher in the zoledronic acid group, 4.1 versus 1.7%. Three cases of arrhythmia SAE were confirmed by adjudication committee but none in the risedronate group. There were 3 cases of atrial fibrillation in the zoledronic acid group, but one patient had never received the study drug compared to none in the risedronate group. Furthermore, more patients in the zoledronic acid had AF at baseline.

Bone biopsies

Trans-iliac bone biopsies were obtained from 23 patients (12 in the zoledronic acid group and 11 in the risedronate group). Due to the small numbers of biopsies from the prevention group the two subpopulations were analysed together. The newly formed bone was of normal quality in terms of normal lamellar structure in all evaluable biopsies. There was no evidence of pathological findings, osteomalacia, marrow dyscrasia, marrow fibrosis or woven bone. The two treatments resulted in almost identical effects on static and dynamic histomorphometric parameters indicating normal osteoid formation and mineralisation of newly formed bone in both treatment groups. Bone remodelling capacity was preserved in patients treated with zoledronic acid over 12 months of treatment.

Bone turnover at the tissue level revealed lower values for activation frequency (Ac.F), bone formation rate (BFR/BS), and mineralising surface (MS/BS) in the zoledronic acid group compared with the risedronate group but the differences were not statistically significant. The low values reflect reduction in bone turnover, due to the decrease in activation frequency of new remodelling cycles, consistent with the known mode of action of bisphosphonates. The median formation period (FP) was similar in both treatment groups.
Histomorphometric analysis of bone structure such as trabecular number, trabecular thickness, and wall thickness did not reveal differences between the two treatments.

The CHMP noted that these findings are in line with previous results from Study 2313 comparing alendronate with zoledronic acid, in which transiliac bone biopsies were obtained in a subset of 25 patients at the end of the study. The study showed similar effects of zoledronic acid and alendronate on various histomorphometric measures, with no evidence of marrow fibrosis or mineralisation defects.

Discontinuation due to AES

The incidence of AEs causing discontinuation was 2.6% higher in the zoledronic acid treatment group (zoledronic acid, 7.9%; risedronate, 5.3%). The most frequently affected PSOC was gastrointestinal disorders, which also had the three most commonly reported AEs leading to discontinuation: diarrhoea (5 patients vs. 2 patients), vomiting (4 patients vs. 1 patient), and nausea (3 patients vs. 5 patients) for the zoledronic acid vs. risedronate treatment groups, respectively.

Post marketing experience

Post-marketing experience of Aclasta, based on a cut-off date of 30-Apr-2007, indicates an estimated exposure of 11,373 patient-years (01-Nov-2006 – 30-Apr-2007). An estimate of patient exposure is calculated based on worldwide sales volume in gram (g) of active substance sold during the review period divided by the defined dose (DD). The sales volume of Aclasta during the review period is 31.13 g and the DD is 5 mg (one unit). Aclasta 31.13 g is equal to 6,226 units. As indicated in the CDS, re-treatment with Aclasta may be considered 12 months after the initial dose, therefore, the estimated exposure is 6226 patient-years. Cumulative estimated exposure is 11,373 patient-years.

DISCUSSION ON CLINICAL SAFETY

In general, safety data for this study did not differ from studies 2301 and 2310. As no general recommendation was given to patients in study 2306 to take prophylactic medication against post-dose influenza-like symptoms, there was a high frequency of such symptoms.

Safety data analysed separately for elderly patients and for premenopausal women showed that there were few AEs in the zoledronic acid group which occurred at more than a two-fold greater incidence in the ≥ 65 years sub-group than the pre-menopausal sub-group (back pain, constipation, oedema peripheral, contusion), most of which may be expected to occur at a greater incidence in an elderly

population. There were few AEs in the zoledronic acid group which occurred at more than a two-fold greater incidence in the pre-menopausal sub-group than the ≥ 65 years sub-group (rheumatoid arthritis, bone pain, asthenia, upper respiratory tract infection, weight increased).

The CHMP considered that the differences seen could most probably be attributed to diseases and symptoms being related to old age for the ≥ 65 years group and to rheumatoid arthritis for the premenopausal group.

Arrhythmia and atrial fibrillation

Like in the large postmenopausal osteoporosis study 2301- but in contrast to the smaller study 2310 in secondary fracture prophylaxis after hip fracture - more cases of arrhythmia events were reported in zoledronic-acid treated patients. The arrhythmia events were in general reported long time after the zoledronic acid infusion. The CHMP pointed out that the results of this study could indicate a higher risk for arrhythmia, but in this relatively small study, the number of cases was too low to draw any conclusions and does not warrant any changes in the current RMP.

The elderly have in general a high risk of developing cardiac arrhythmias especially atrial fibrillation (AF), either at baseline or during the course of therapy. Data on Aclasta showed that treated patients have higher risk for developing cardiac arrhythmias. The overall incidence of arrhythmias was significantly higher in the zoledronic acid group, 4.1 versus 1.7%. Three cases of arrhythmias SAE were confirmed by adjudication committee but none in the risedronate group. Four cases of atrial flutter or fibrillation were also reported (3 of them in the ZOL group). The arrhythmia events were in general reported long time after the zoledronic acid infusion.

Atrial fibrillation is included in the RMP as a potential risk and the MAH has committed to perform a 5-year Scandinavian registry study (protocol CZOL446H2422) including the end-points arrhythmias and cardio- and cerebrovascular disorders. The protocol has been expanded to include men and women treated with zoledronic acid who are receiving chronic glucocorticoid treatment. In addition, patients entering the placebo controlled 6 and 9 year extension studies of Study 2301 in PMO are being monitored for AF.

The cardiac arrhythmia events observed in study 2306 were distributed amongst a variety of different PTs belonging to the HLTs Cardiac conduction disorders, Rate and rhythm disorders NEC, Supraventricular arrhythmias, Ventricular arrhythmias and cardiac arrest and Cardiac signs and symptoms NEC. Atrial fibrillation is already included as a common adverse drug reaction in the SPC. No additional amendment to the SPC concerning cardiac arrhythmias is considered needed at present.

Gastrointestinal symptoms

Based on the available data, the CHMP considered that a yearly intravenous dose of zoledronic acid does not cause gastrointestinal symptoms like those often linked to the intake of oral bisphosphonates. The i.v. dosing schedule is also considered to increase patient compliance.

Laboratory data and renal events

Laboratory data and renal events did not significantly differ between treatment groups. The concomitant treatment with glucocorticoids and zoledronic acid could theoretically increase the risks of renal adverse events as steroids increase calciuria.

Overdose

Limited information on overdose in single oncology patients is now available, however there is no information on overdose of zoledronic acid from any clinical studies in any non-oncology indication.
Some of the patients experienced adverse events, such as transient hyperthermia, paresthesia and abnormal liver function tests. In controlled clinical trials in the oncology indication, zoledronic acid 8

mg was associated with an increased risk of renal toxicity compared to zoledronic acid 4 mg when given as a 15-minute i.v. infusion.

Pregnancies and use in pre-menopausal females

The CHMP highlighted that three pregnancies occurred in the study, in spite of patients being requested to practice contraception during the study period.

Zoledronic acid is currently contraindicated during pregnancy and considering the once yearly dosing and long-standing effect special care has to be taken if pre-menopausal women are to be given zoledronic acid, considering that during the year following infusion pregnancies may occur without the possibility to discontinue treatment.

After infusion of zoledronic acid, plasma concentrations of the active drug substance increases rapidly, followed by a rapid decline to < 10% of peak after 24 hours, with a subsequent prolonged period of very low concentrations not exceeding 0.1% of peak levels. Intravenously administered zoledronic acid is rapidly distributed to bone, and like other bisphosphonates localises preferentially at sites of bone resorption.

The CHMP highlighted that teratogenicity has been well confirmed in the rat and thus the current contraindication during pregnancy and during breast-feeding should remain unchanged.
Aclasta, being a once yearly infusion, can however not be discontinued in case of pregnancy.
The CHMP pointed out that it is evident that the plasma concentration of zoledronic acid decreases rapidly and reaches undetectable levels within 28 days. However, animal and human data clearly demonstrate that more than 50% of the administered dose is taken up by bone and that zoledronic acid, like other bisphosphonates, remains in the skeleton for a very long time. Using an estimated human half-life of 10 years, the fraction remaining after one and three years would be approximately 93% and 81%, respectively.

Thus, the skeleton represents an endogenous reservoir, from which zoledronic acid may be mobilised by states of increased bone turn-over, which occurs especially during pregnancy.

The MAH could not present any clinical data to support a 12 month period for practising contraception after the last dose of Aclasta. Furthermore the CHMP considered that a potential risk remains for a very long time after an infusion. The CHMP also considered that there is a potential risk that zoledronic acid may be mobilised from the skeleton during pregnancy and exhibit a substantial risk for a developing foetus. Applying principles of precaution, the CHMP considered consequently that women of childbearing potential should be excluded from the indication.

The CHMP further considered that the inclusion of bone distribution data in the Product Information should be considered by the MAH and that the MAH should commit to further discuss this point.

User testing

User testing was performed in English. The PL was tested in two test rounds, with a total of 20 test persons (60 % patients with bone disease, age 32-74, 85 % women). The questionnaire covered the key safety issues of the PL although these were not identified prior to making the questionnaire. Each interview lasted between 25 and 35 minutes, depending on the age and ability of the interviewee.

The methodology followed the readability guideline. Revisions of the PL were made following the pilot round and the first test round. All questions met the criteria of at least 16 out of 20 being able to find and understand each question, although one question scored below 90 % in finding.

At the time of the testing the indication was Paget's disease only, but it was anticipated that the product would be approved thereafter in post-menopausal osteoporosis. Considering that in the combined populations women would form the vast majority of treated patients therefore the MAH

accepted to have an over-representation of women. In conclusion, the CHMP considered that the submitted test results were judged acceptable.

However, for future tests the CHMP recommends that only the PL that is included in the application is tested. If there are major changes during the procedure or if an older version of the PL has been tested, it may be necessary to retest the whole document or focus test on specific sections. However, in this matter the PL is found acceptable and rewordings made by the MAH are endorsed.

PHARMACOVIGILANCE PLAN AND RISK MANAGEMENT PLAN (RMP)

The elements of the proposed risk management plan (RMP) are consistent with the recommendations made in the ICH E2E Guideline on Pharmacovigilance and the CHMP Guideline on Risk Management Systems for Medicinal Products for Human Use (November 20, 2005). The CHMP considered that the structure of the RMP was satisfactory, and the current version follows the template for EU RMP (September 2006).

The RMP has been updated with information on studies 2306 as discussed within this report, and study 2308 as currently discussed in variation EMEA/H/C/595/II/16.

Summary of the risk management plan for Aclasta

A summary of safety concerns, Pharmacovigilance activities and Risk minimisation activities is presented below.

Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimisation activates (routine and additional)**
Important identified risks		
Post dose symptoms	Routine pharmacovigilance	Detailed information in section 4.8 of the CDS. Guide for healthcare professionals and patients (EU). Patient and healthcare professional education initiative.
Renal dysfunction	Routine pharmacovigilance Targeted follow-up of all serious post-marketing and clinical trial reports, using a targeted questionnaire/checklist. Cumulative analysis in PSUR. Adjudication of clinical trial cases meeting pre-identified criteria*.	Detailed information in section 4.4 of the CDS. Guide for healthcare professionals and patients (EU). Patient and healthcare professional education initiative.
Ocular adverse events	Routine pharmacovigilance Targeted follow-up of all serious post-marketing and clinical trial reports, using a targeted questionnaire/checklist. Cumulative analysis in PSUR. Adjudication of clinical trial cases*.	Listed in ADR section 4.8 of the CDS.

Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimisation activates (routine and additional)**
Hypocalcaemia	Routine pharmacovigilance Targeted follow-up of all serious post-marketing and clinical trial reports, using a targeted questionnaire/checklist. Cumulative analysis in PSUR. Post US approval voluntary registry study (Study ZOL446K2401) Adjudication of clinical trial cases meeting pre-identified criteria*.	Detailed information in sections 4.4 and 4.8 of the CDS.
Osteonecrosis of the jaw	Routine pharmacovigilance Targeted follow-up of all post-marketing and clinical trial reports, using a targeted questionnaire/checklist. Cumulative analysis in PSUR. Special 15-day expedited reporting of ONJ regardless of seriousness, listedness and causality will be provided to EEA and USA Health Authorities for the two first years after launch of the osteoporosis indication in the EU. Adjudication of post-marketing cases of purported ONJ and clinical trials reports in phase III trials. Study ZOL446H2413 Scandinavian Registry study (ZOL446H2422) Extension studies ZOL446H2301E1 and ZOL446H2301E2	Detailed information in section 4.4 of the CDS.
Anaphylactic reaction	Routine pharmacovigilance Targeted follow-up of all post-marketing and clinical trial reports, using a targeted questionnaire/checklist. Cumulative analysis in PSUR	Detailed information in section 4.4 of the CDS.
Important potential risks		
AVN/fracture nonunion and/or delayed union	Routine pharmacovigilance Targeted follow-up of all post-marketing and clinical trial reports, using a targeted questionnaire/checklist. Cumulative analysis in PSUR. Adjudication of clinical trial cases*. Scandinavian Registry study (ZOL446H2422) Extension studies ZOL446H2301E1 and ZOL446H2301E2	Currently available data do not support the need for risk minimisation.
Cerebrovascular AEs	Routine pharmacovigilance Targeted follow-up of all post-marketing and clinical trial reports, using a targeted questionnaire/checklist. Cumulative analysis in PSUR. Scandinavian Registry study (ZOL446H2422) Extension studies ZOL446H2301E1 and ZOL446H2301E2.	Currently available data do not support the need for risk minimisation.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activates (routine and additional)
Atrial fibrillation	Routine pharmacovigilance Targeted follow-up of all post-marketing and clinical trial reports, using a targeted questionnaire/checklist. Cumulative analysis in PSUR. Adjudication of serious clinical trial cases in phase III trials. Scandinavian Registry study (ZOL446H2422) Extension studies ZOL446H2301E1 and ZOL446H2301E2.	Listed in ADR section 4.8 of the CDS.
Gastrointestinal AEs	Routine pharmacovigilance	Detailed information in section 4.8 of the CDS.
Potential interactions		
Products that can significantly affect renal function	Routine pharmacovigilance Drug interactions will be monitored through post-marketing on a case-specific basis for suspected interactions, with targeted follow-up as appropriate.	Warning in Section 4.5 of the CDS
Paracetamol/ acetaminophen	Routine pharmacovigilance Drug interactions will be monitored through post-marketing on a case-specific basis for suspected interactions, with targeted follow-up as appropriate.	None as the effects are mild, transient and not clearly related to Zoledronic acid 5 mg
#Additional activities may have been agreed with Health Authorities in other countries *For studies H2301E1 and H2301E2 only		

Discussion of the RMP

The MAH has submitted an updated RMP (version 006) and has amended the safety specification with newly completed clinical trial data. No new safety concerns have been added to the safety specification since the last RMP. Long-term follow-up (beyond 12 months) is not available in the population with GIO. Long-term therapy with bisphosphonates as well as concomitant therapy with corticosteroids are considered as risk factors for the development of ONJ, AVN and impaired fracture healing. The MAH is therefore currently addressing the possibility of an increased risk of negative skeletal effects with long term zoledronic acid treatment in combination with high doses of corticosteroids: Men and women treated with Aclasta and receiving chronic corticosteroid treatment will be included in the 5 year Scandinavian registry study. This study protocol has been assessed within the Follow-Up Measures (FUMs) FU2 016.3, 017.4 and 019.2.

As part of the type II variation EMEA/H/C/595/II/16, the SPC, section 4.8 was amended with information on the observed post marketing reports of hypersensitivity reactions including rare cases of bronchoconstriction, urticaria and angioedema and very rare cases of anaphylactic reaction/shock (based on a recent change in the CCDS).

The CHMP considered that pharmacovigilance and risk minimisation activities should also be addressed for the identified risk of hypersensitivity reactions, the potential risk of gastrointestinal AEs and the missing information concerning use in children/ adolescents and use in patients with severe renal impairment (<30 ml/min). The MAH has satisfactorily specified these points during the procedure as outlined in the table above.

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

Data on bone safety beyond 12 months is not available in the zoledronic acid treated patients with GIO. Both long-term therapy with bisphosphonates and concomitant therapy with corticosteroids are considered to be risk factors for the development of osteonecrosis and impaired fracture healing.

The MAH has committed to perform a long term follow up of skeletal and cardiovascular adverse events following treatment of patients with Aclasta. A 5 year registry study in Scandinavia is planned to monitor diagnoses pertaining to cardiovascular and bone diseases in patients treated with Aclasta and compare them to diagnoses registered for patients treated with oral bisphosphonates and to untreated matched controls. The current trial protocol version includes only women but it will be expanded to include all men and women treated with Aclasta and receiving chronic corticosteroid treatment (This study protocol has been assessed in FUMs 016.3, 017.4 and 019.2).

PRODUCT INFORMATION

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

Changes were also made to Annex II in section "Conditions or restrictions with regard to the safe and effective use of the medicinal product" to reflect the new indication and that educational material will be made available following the launch of the new indication. The section "other conditions" was updated to reflect the current version number of the RMP.

During the procedure, variation II-16 received a positive Opinion and consequently these changes were included in the final Product Information.

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

SPC:

Section 4.1 Therapeutic Indications
This section was revised to reflect the current state of scientific knowledge on osteoporosis treatment taking into account the WHO FRAX tool and the CHMP Guideline on clinical trials in primary osteoporosis to reflect that the indication focuses on treatment of osteoporotic patients at increased risk of fracture. As discussed above the indication was also revised to include only for patients intended for chronic treatment with corticosteroids. The wording of the indication was further modified in line with the wording of recently approved GIO indications for other products and to reflect that premenopausal women are not included in the indication.

Section 4.2 Posology and method of administration
The revised indication was reflected in this section stating that for the treatment of post-menopausal osteoporosis, osteoporosis in men and the treatment of osteoporosis associated with long-term systemic glucocorticoid therapy, the recommended dose is a single intravenous infusion of 5 mg Aclasta administered once a year.

Section 4.6 Pregnancy and lactation
This section was revised to include a statement that Aclasta is not recommended in women of childbearing age to reflect the revised indication and the above discussions on teratogenicity in humans.

Section 4.7 Effects on ability to drive and use machines
As the adverse event "dizziness" listed in section 4.8, this section was revised to reflect that dizziness may affect the ability to drive or use machines, though no studies on this effect with Aclasta have been performed.

Section 4.8 Undesirable effects
The adverse events following the evaluation of safety data including study 2306 and those observed post marketing were included in one common table in the sense of the current SPC guideline, the term hypocalcaemia was included in the table, as well as a footnote to indicate which adverse events were observed in patients taking concomitant glucocorticosteroids.

Section 4.9 Overdose
Based on the safety information provided for this procedure the text was revised to reflect that clinical experience with acute overdose is limited.

Section 5.1 Pharmacodynamic properties
The sub-section "Pharmacodynamic effects" was updated to include additional information on the molecular mechanism and the binding of zoledronic acid to the bone.

The proposed sub-sections "Clinical efficacy in osteoporosis associated with systemic glucocorticoid therapy" and "Effect on bone mineral density (BMD)" were amended to reflect the new indication focusing on long-term glucocorticoid therapy in postmenopausal women and men.

Information on the duration of glucocorticoid therapy, the mean age of males and females and the incidence of fractures in study 2306 was included in line with the above discussions. A previously proposed paragraph on bone histology was removed, as the results from a limited group of patients in study 2306 were comparable to similar results from other studies already included in this section.

PL

The PL was further updated to reflect the revised indication and to translate some the term "infusion" in more patient-friendly language. A statement concerning symptoms of ONJ and an advice concerning dental treatment was included to better reflect the information in the SPC. The sub-section "Driving and using machines" and section 4 "Possible side effects" were amended in line with the SPC changes discussed above.

ENVIRONMENTAL RISK ASSESSMENT

The MAH did not submit an abbreviated ERA report with this procedure, but committed to submit modified Follow-Up Measures as previously committed for EMEA/H/C/595/II/16 (FUM 021) taking into account the population of the indication of this procedure. The CHMP agreed to this approach.

BENEFIT/RISK ASSESSMENT

The risk of fracture has been demonstrated to increase at a relatively low dose of glucocorticoid therapy, below 7.5 mg daily, and already a short time after start of this therapy. In patients on glucocorticosteroids, fractures tended to occur at a higher BMD than in patients with postmenopausal osteoporosis and the population on glucocorticoids was also younger than the population with postmenopausal osteoporosis. With this background, the CHMP considered that treatment of osteoporosis patients at risk of fracture is desirable in this population.

The CHMP estimated that only a minority of patients on glucocorticoids are at present receiving prophylaxis medication to prevent bone loss. Existing medical prevention therapy for this condition are certain bisphosphonates (nationally approved) and teriparatide.

Benefit

Overall, the pivotal study met its endpoints demonstrating non-inferiority, and also superiority, of zoledronic acid compared with oral risedronate in increasing BMD at the lumbar spine over 12 months.

The study was adequately sized and performed. Zoledronic acid was also significantly superior to the comparator for a number of secondary efficacy parameters, decreasing bone markers and increasing BMD also at other sites than the lumbar spine. The study was of 12 months duration and was not powered to demonstrate a difference in fracture incidence between treatment groups. Few patients had fractures in the study and there was no apparent difference between the treatment groups. A yearly intravenous dose of zoledronic acid did not cause gastrointestinal symptoms like those often linked to the intake of oral bisphosphonates and the IV dosing schedule is considered to increase patient compliance.

The IV dosing schedule is considered to increase patient compliance and furthermore Aclasta is not associated with local irritating effects on the oesophagus associated with oral bisphosphonates

In study 2306, an intravenous dose of 5 mg zoledronic acid was convincingly shown to increase the lumbar spine BMD from baseline to 12 months significantly better than daily oral risedronate, in the prevention (on glucocorticoids 3 months or less) as well as in the treatment (on glucocorticoids for more than 3 months) subpopulations.

In a CHMP Scientific advice in 2004, separate trials for the separate indications, prevention vs. treatment of GIO, were recommended. Since then, however, there has been a change in the view of the management of osteoporosis as regards differentiating between prevention and treatment of osteoporosis (see also CHMP Guideline on clinical trials in primary osteoporosis). The management of osteoporosis has also changed with the availability of the WHO Risk Assessment Tool (FRAX). The MAH therefore agreed to change the wording accordingly by avoiding separate treatment and / or prevention claims.

Furthermore, the indication now reflects use of Aclasta only for patients intended for chronic treatment with corticosteroids. The wording of the indication was therefore further modified, in line with the wording of recently approved GIO indications.

Fractures tend to occur at higher BMD in GIO than in postmenopausal osteoporosis. Other factors than BMD for fracture risk in this condition were considered to be age and existing rheumatoid arthritis.
The translation of the effects on BMD into fracture reduction was discussed above and the MAH provided satisfactory justifications in this respect. Fracture prevention has not been shown in the glucocorticoid treated population but significant improvement in BMD data, and positive trends for fracture data for the comparator in several clinical studies with risedronate provide strong indications for a fracture prevention effect.

The relatively young age of the patients, the large proportion of pre-menopausal females and the under-representation of patients with osteoporosis baseline (less than 10%) indicates that the patient population, apart from receiving high-dose corticosteroids, may have been at a low risk of fracture. The MAH discussed the fracture risk of the study-population with reference to the FRAX tool and addressed the fracture risk in pre-menopausal females. The CHMP agreed that a small sub-set of pre-menopausal women treated with high-dose corticosteroids may experience fractures, but in general the absolute risk is very low and the evidence of benefit for the majority of pre-menopausal women is lacking.

Concerning the male population, Aclasta has received approval for the treatment of osteoporosis in men at increased risk of fracture (variation II-16, see SPC) based on data from studies 2310 and 2308. The MAH further presented that no difference could be found in fracture data and demographic data on femoral neck BMD between males and females in study 2306. An effect in reducing fractures in

men with GIO can therefore be expected based on the concept of double-bridging described by the GREES group as discussed above.

Therefore, an effect in reducing fractures in men with GIO can be expected based on the concept of double-bridging described above.

Fracture rates were similar and very low in both active treatment groups. The fact that fracture reduction has not been demonstrated for zoledronic acid in GIO is now reflected in section 5.1 of the SPC.

Risks

The previously identified safety issues could be confirmed in study 2306. Like in study 2301, but in contrast to study 2310, there is a tendency to more arrhythmia events in the zoledronic acid treatment group, but numbers were too low to draw any conclusions. This adverse event will however be sufficiently followed up by the MAH in on-going studies, which is also reflected in the RMP. In addition, atrial fibrillation is already listed in the Product Information.

The risks of post dose influenza-like symptoms, renal toxicity and ONJ do not seem to differ from the risks in earlier studies in osteoporosis indications. The current data do not warrant any further changes neither to the SPC nor in the RMP concerning arrhythmia or atrial fibrillation.

The safety concern for the subgroup of premenopausal women in the study population in this study remains as zoledronic acid is contraindicated in pregnancy and lactation due to potential teratogenic effect. As a precautionary measure, the CHMP considered that the indication should not include premenopausal females. Teratogenicity has been well confirmed in the rat and thus the current contraindication during pregnancy and during breast-feeding should remain unchanged.

Benefit/Risk Balance

While there in general might be need for bisphosphonate treatment in a small sub-group of pre-menopausal females receiving chronic treatment with high-dose corticosteroids, the evidence of benefit for the majority of pre-menopausal women is lacking. Based on a review of available data presented by the MAH, a teratogenic effect of zoledronic acid in humans can not be excluded. For Aclasta specifically, there is a concern that treatment cannot be discontinued in case of pregnancy, and that bisphosphonate may be released at a higher rate from the bone during pregnancy. As a measure of precaution, zoledronic acid should not be administered to women of childbearing potential. Therefore, premenopausal women should be excluded from the indication.
Taken together, the data on efficacy and safety are supporting a positive benefit/risk balance in the remaining populations reflected in the new indication “treatment of osteoporosis associated with long-term systemic glucocorticoid therapy in post-menopausal women and in men at increased risk of fracture” is considered favourable.

CONCLUSION

On 23 April 2009 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.