SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion and scientific discussion on procedures, which have been finalised before 4 June 2003. For scientific information on procedures after this date please refer to module 8B.

1. Introduction

Zometa with the active ingredient zoledronic acid is a biphosphonate intended for tumour induced hypercalcaemia. [the additional indication: *prevention of skeletal related events in pateints with advanced malignacies involving bone,* is examined in section 6 of the present EPAR]. Zometa has high binding affinity for divalent cations and accumulates in bone. The drug inhibits bone reabsorption by osteoclasts.
Cancer is one of the most common causes of hypercalcaemia. Tumour-induced hypercalcaemia (TIH) is considered as an emergency situation in clinical oncology because of the often-severe symptoms. Dehydration, renal failure, mental confusion, nausea, vomiting, anorexia and ECG abnormalities may evolve rapidly with increasing levels of serum calcium. TIH is seen in many types of malignancies with or without bone metastases. At least two mechanisms of hypercalcaemia seem to be involved in cancer. The tumour cells may produce humoral factors that increase bone resorption and some tumours may cause bone destruction through local osteolytic mechanisms.

Regardless of the mechanisms the first treatment principle in TIH aims at restoring normal hydration, as these patients often are severely dehydrated. Hydration consists of IV isotonic saline with replacement of potassium and magnesium. Concomitant use of loop diuretics requires close monitoring especially when the extracellular fluid volume is decreased (worsening of dehydration) or during vigorous hydration (risk of pulmonary oedema). A reduction in serum calcium will result in improvement in symptoms and many patients can be discharged from hospital.

There is general agreement that potent bisphosphonates (i.e. pamidronate and ibandronate both approved in the EU) given intravenously are the calcium-lowering agents of choice in severe TIH. These agents have a higher inhibitory effect on bone resorption than on bone mineralisation.

Thus, a bisphosphonate such as pamidronate is an appropriate comparator for the evaluation of any new biphosphonate like zoledronic acid. One might argue that comparative studies are of lesser importance for efficacy assessment because rapid normalisation of serum calcium is a valid surrogate for clinical benefit. Placebo-controlled studies are excluded for ethical reasons. One problem in the comparison of two bisphosphonates is the establishment of dose equipotency. The dosing scheme for pamidronate with regard to absolute dose, infusion time, and dosing intervals in relation to serum calcium levels has been adjusted several times since marketing. For the clinical development of zoledronic acid Novartis has selected the highest recommended single dose of pamidronate (90 mg as an 2-hour i.v. infusion) as comparator versus two different dose levels for zoledronic acid.

2. Chemical, pharmaceutical and biological aspects

Composition

Zometa is a lyophilisate presented as a powder for solution for infusion. The container is a clear, uncoloured glass vial (class I, Ph. Eur) with a butyl rubber stopper. A 4% overage is filled to the vials to permit withdrawal of the labelled amount from the vials. An ampoule with 5 ml water for injection is included for each vial of lyophilisate. Prior to administration the lyophilisate is reconstituted with water for injections and further diluted with infusion media (0.9% w/v sodium chloride or 5% w/v glucose solution for infusion.

Zometa is also presented as a concetrate for solution for infusion, in 5 ml transparent plastic vials with a rubber stopper. Each vial contains 4.264 mg of zoledronic acid monohydrate as the active ingredient, equivalent to 4 mg of anhydrous zoledronic acid.

Active substance

The active substance, zoledronic acid, is synthesised in a multistep process using well-established chemical reactions.

Specifications on all starting materials, solvents and reagents and of intermediates are provided and are acceptable.

Elemental analysis, UV, IR, 1H-NMR, 13C-NMR, MS, X-ray Powder Diffraction and X-ray structure analysis have proved the structure.

Related substances and a number of inorganic impurities formed during the synthesis have been identified. The impurity limits in the specifications are qualified by the toxicology studies.

Batch analysis results from production size batches (9 at Novartis Basel Pharma AG and 3 at the defined site for commercial production Novartis Stein Pharma AG, Switzerland) are presented. Data comply with specifications.

The stability data support a retest period of 36 months at up to 30°C, for the substance stored in double PE bags in metallic barrels.

Other ingredients

The excipients used in both formulations are commonly used in parenteral formulations and comply with PhEur. and are routinely tested for bacterial endotoxins (PhEur). The choice of excipients including the amounts used and specifications of these are justified.

Product development and finished product

- *Zometa powder for solution for infusion*

The qualitative composition has not changed during development and clinical trials. In phase I and II studies 0.1 mg, 1 mg and 4 mg dosage strengths of zoledronic acid have been used. Different relative amounts of excipients were used for each of these strengths, although these differences are not expected to have significant impact on efficacy or safety of the product intended for marketing.

The formulation is for parenteral use as the active substance is poorly absorbed after peroral administration.

Due to incompatibility of the bulk solution with pharmaceutical glass of hydrolytic class I, no heat sterilisation in the final container can be performed. Therefore the sterilisation method chosen is an aseptic process with sterile filtration before lyophilisation.

Zometa 4 mg powder for solution for infusion is manufactured by a standard aseptic procedure. Excipients and zoledronic acid are dissolved in water for injection. The solution is pre-filtered, sterile filtered and filled into washed, sterilised, depyrogenised glass vials. The vials are pre-stoppered with washed, sterilised butyl rubber stoppers. Afterwards they are freeze-dried in a lyophilyser under controlled conditions. After lyophilysation the vials are closed and sealed with aluminium flip-off caps.

The product is manufactured in a facility that holds the necessary Manufacturing Authorisation.

The control tests and specifications for the finished product are adequately drawn up and considered to be relevant for a product of this type. The impurity limits in the product specifications are justified by toxicology studies.

Specifications for sterility and bacterial endotoxins for the finished product are included in the release and shelf life specifications and conform to the requirements of PhEur.

Substances of animal origin covered by the scope of the TSE guideline (EMEA/CPMP/BWP/1230/98/rev. 1) are not included in, or used during the manufacture of Zometa.

- *Zometa concetrate for solution for infusion*

The liquid formulation in the plastic vial is of the same composition as the already licensed pharmaceutical form in glass vials after reconstitution with 5 ml water for injections, thus no additional clinical trials have been performed.
During development, the compatibility of the bulk solution with the filters and tubing material has been studied and has been found satisfactory. Chemical and physical stability during sterilisation of the concentrate for solution for infusion has also been found to be satisfactory. The compatibility of the finished product with the packaging material has been demonstrated by stability studies. For the compatibility of the preparation with infusion media (5% glucose solution and 0.9% saline solution) and different infusion devices the Marketing Authorisation Holder refered to studies performed with the already aproved pharmaceutical form (powder for solution for infusion), which, after reconstitution with 5 ml water for injections, had the same composition/concentration.
As part of the container/closure integrity test a microbiological challenge test with the primary packaging materials was performed. Results from storage in upright and inverted position show no evidence of growth.

The manufacturing method of the finished product consists of the following process steps. In the beginning the excipients are dissolved, under stirring, in water for injections. Then the active substance is added and dissolved. After final weight adjustment the bulk solution is filtered before filling into plastic vials. The closed vials are subsequently steam sterilised.
Validation has been carried out on 3 production scale batches. All batches met the acceptance criteria for the release of the final product and all pre-defined quality and performance specifications established in the approved validation protocol was met.

Specifications for sterility, bacterial endotoxins, pH, particulate matters and visible foreign particles are included in the release and shelf life specifications for the finished product and conform to the requirements of Ph.Eur.

Stability of the product

- *Zometa powder for solution for infusion*

The applicant has provided results from production batches, which have been stored according to ICH requirements in the packaging applied for.

No changes are seen for any of the tested parameters at any of the tested conditions, except for a minor increase in a leachable at 40°C/75%RH. The finished product is very stable.

Miscibility with physiologic saline and glucose:

Zometa was reconstituted with 5 ml water for injection and further diluted to 20ml and 50ml with 0.9% w/v NaCl solution or 5% w/vglucose solution. After storage at 2-8°C in 24 hours the solutions were in all cases clear.

Compatibility with infusion devises:

Zometa in 50ml 0.9% NaCl solution or 5% glucose solution stored for 24 hours at 2-8°C was found compatible with devices made from PVC, PE, PP or glass. No decrease in active ingredient was observed.

Stability of reconstituted solution:

Reconstituted vials stored upright or upside down at room temperature over 24 hours, show no change in the tested quality parameters.

A shelf life of 36 months is acceptable. There is no special storage condition specified. The reconstituted solution is chemically and physically stable for 24 hours at room temperature. From a microbiological point of view the product should be used immediately after further dilution, of the reconstituted solution, with 50 ml 0.9% sodium chloride solution for infusion or 5% glucose solution for infusion. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. The total time between reconstitution, dilution, and storage in refrigerator at 2-8°C and end of administration must not exceed 24 hours.

Solvent

Sterilised water for injection Ph. Eur. is used as a solvent. It is manufactured by Nycomed GmbH, St.-Peter Strasse 25, A-4010 Linz, Austria. It is produced from water for injection in bulk which is sterile filtered, filled into sterilised and depyrogenized ampoules and sterilised by autoclaving at 121°C for 15 min.

The final product is tested for sterility by the membrane filtration method according to PhEur and validated according to the requirements therein.

The glass ampoules used (packaging) consist of 5 ml colourless borosilicate glass (type 1, PhEur).

Results on production batches comply with the specification. Stability is satisfactory.

- *Zometa concetrate for solution for infusion*

Three pilot batches have been stored at 25°C/60%RH and 30°C/70%RH for 18 months and at 40°C/75% RH for 6 months in the packaging applied for. In addition to the conditions mentioned above, results at some time points are available for the following conditions: -20°C, 5°C, 50°C and 50°C/75%RH. As suggested by the stability results obtained with all batches, the proposed shelf life for the unopened commercially packaged product under the conditions specified in the SPC, is acceptable, as no changes were seen at neither long term nor accelerated conditions.
Furthermore special studies have been performed testing the photostability and the freeze and thaw cycle test stability of the finished product as well as the presence of extractables. There were no changes observed for any of the tested parameters at any of the tested conditions.

Discussion on chemical, pharmaceutical and biological aspects

Zometa is manufactured using a conventional, aseptic manufacturing process. The chemical-pharmaceutical dossier is well documented and guarantees the quality of the active substance and finished product, both initially and throughout the shelf life. The proposed specifications are suitable. A number of quality points were not resolved at the time of the CPMP opinion. However, these were considered to be minor, without any impact on the efficacy or safety of the product, and are indicated to be addressed post-approval.

3. Toxico-pharmacological aspects

Pharmacodynamics

In vitro studies

Cultures of murine calvarial bones, stimulated with a variety of naturally occurring agents, have been employed to demonstrate the efficacy of zoledronic acid in inhibiting calcium release; the effect was 100 times that of pamidronate. The potency of the inhibition of calcium release and calcium incorporation in murine calvarial cultures was compared with reference compounds. Zoledronic acid had the highest ratio for IC50 (calcium release)/IC50 (calcium incorporation) which indicates a potential for inhibition of bone resorption without affecting bone mineralisation.

Zoledronic acid was toxic in vitro (induced DNA fragmentation and apoptosis) in human myeloma cell lines, human epithelial carcinoma cell line and human breast cancer cell lines and it exhibited anti-angiogenic effects in vitro and in vivo.

In vivo studies

Two models have been used, inhibition of hypercalcaemia in thyroparathyroidectomized (TPTX) rats and inhibition of bone loss in ovariectomised (OVX) rats.

$1,25(OH)_{2vitaminD3}$ induces hypercalcaemia in TPTX rats. Zoledronic acid dose-dependently inhibited the acute hypercalcaemia, achieving normalisation of serum calcium in all animals studied at a dose of 1.5 µg/kg/day s.c. for 4 days. In this system zoledronic acid was about 850 times more active than pamidronate.

The effects of zoledronic acid in OVX rats were investigated in both short-term (3 weeks) and long-term studies (12 months). The OVX-induced bone loss could be completely prevented by zoledronic acid given both daily or intermittently. Similar findings were reported in OVX rhesus monkeys (16-month study).

Furthermore, zoledronic acid inhibited the systemic osteopenia in rats and rabbits with experimental inflammatory arthritis. In general, zoledronic acid increased primary spongiosa in the metaphyses of long bones in growing animals at nearly all doses (e.g. up to 0.01 mg zoledronic acid/kg/day given to rats for 12 months) and a significant increase in density, and improvement of the mechanical properties of trabecular bone, after i.v. treatment of dogs for 6 months, particularly at 0.03 mg/kg.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been performed.

General and safety pharmacology programme

Zoledronic acid has no CNS effects in mice at doses of up to 10-mg/kg i.v. In isolated guinea pig atria and ileum, only minor effects were observed at the highest concentration tested (246 μM). No cardiovascular effects were observed in anestesthetized cats at doses up to 3-mg/kg i.v. (30 mg/kg was lethal). In conscious rats zoledronic acid (1 mg/kg) had no significant effect on urinary volume or electrolyte secretion. Higher intravenous doses (1.5-50 mg/kg) dose-dependently increased the serum urea concentration in rats.

Pharmacokinetics

Disposition studies were performed with radiolabelled zoledronic acid. Concentrations in plasma and urine were analysed by a radioimmunoassay with the limit of quantification being 0.4 ng/ml and 10 ng/ml for plasma and urine determinations. A HPLC method was developed to separate zoledronic acid from potential metabolites in the urine of rats. Most studies were performed in rats and dogs.

In both rats and dogs radiolabelled i.v. Zoledronic acid (0.15 mg/kg) was cleared rapidly in a multiexponential manner from blood and plasma. Very low residual levels (about 0.1% of the concentration 5 minutes post-dose) persisted in blood and plasma for several days. This pattern is similar to the PK data obtained from patients. The studies suggest linear pharmacokinetics.

The radioactivity in plasma represented predominantly if not exclusively parent zoledronic acid. In rats zoledronic acid was almost completely bioavailable after s.c. administration.

The binding to plasma proteins shows species differences, 96% in rats, 22% in humans and only 9% in dogs. In growing rats 60% of a dose of 0.1 mg/kg was retained in the skeleton. The apparent half-life in the whole skeleton appeared to be longer than 360 days. This finding is similar to data for other bisphosphonates.

Except for the kidney, where a low temporary retention of zoledronic acid has been observed, no tissues other than bones seems to accumulate the drug.

Zoledronic acid not retained in the skeleton is mainly excreted via the kidney. About 30% of the administered dose is excreted within the first 24 hours. No evidence of metabolites was found in the urine of rats.

No data are available on the distribution of zoledronic acid in pregnant animals. However, it can be expected that the compound will cross the placental barrier and be taken up into foetal bones.

Plasma concentrations were measured at different times in the toxicology studies. These results are used to compare the systemic exposure in animals and humans. The upper anticipated human dose is 8 mg as a single i.v. infusion. The safety margins for AUC are about 16 (2 week rat study at dose of 0.6 mg/kg every third day) to 25 (3 month dog study at doses o.1-0.2 mg/kg once daily).

Toxicology

Single dose toxicity

In acute parenteral studies in mice, rats and dogs, the compound produced marked toxicity already at doses of 6 mg/kg and above. In rats a single i.v. dose of 1.6 mg/kg was well-tolerated with no mortality, the only clinical sign being local irritation at the injection site. At higher doses death

occurred most likely due to cardiac arrest (calcium sequestration by zoledronic acid) or in case of delayed mortality, deaths due to renal effects.

Repeat dose toxicity

Repeated dose toxicity studies were performed with duration of treatment from 10 days to 52 weeks in mice, rats and dogs. Parenteral administration is most relevant to the therapeutic indication, but data following oral and subcutaneous administration has also been submitted. The most frequent finding consisted of increased primary spongiosa in the metaphyses of the long bones in growing animals at nearly all doses. This effect is in line with the compound's pharmacodynamic antiresorptive activity.

Zoledronic acid induced renal tubular necrosis with elevated BUN and creatinine values in both rats and dogs. The NOAEL (mg/kg) for this effect were 1.6 mg/kg (rat, single i.v. dose), 0.6 mg/kg every third day for 6 doses (rats), 2 mg/kg (dog single dose), 1 mg/kg/day for 10 days (dog), 0.2 mg/kg daily for 1 month (dog), 0.01 mg/kg daily for 3 months (dog) and 0.005 mg/kg alternating days for 16 weeks, every third day through week 52 (dog).

As can be seen from these results, zoledronic acid can cause renal toxicity. The animal data suggest that the renal safety margins narrow with long-term exposure and the compound should only be given to humans as single doses.

High doses (specify dose) can cause hepatic injury with elevation of ALAT and ASAT, and degeneration, inflammation and necrosis of liver cells in individual cases, inflammation, haemorrhage and erosions of the gastrointestinal tract, severe local skin reactions at injection sites.

Both the renal and hepatic effects have been observed with other biphosphonates in preclinical studies.

As expected the most common changes in clinical chemistry consist of hypocalcaemia, other electrolyte imbalances, decreased bone alkaline phosphatase levels.

Genotoxicity

Zoledronic acid was not mutagenic in the standard genotoxicity battery.

Carcinogenicity

Oral carcinogenicity studies with duration of 104 weeks have been performed in mice and rats.

Except for an increase in Harderian gland adenoma/adenocarcinoma in male mice (0.1-1 mg/kg) and female mice ($\geq$3 mg/kg) no sign of carcinogenicity was observed. These findings were not considered of relevance for the human situation.

Reproduction Toxicity

Teratology and fertility studies have been performed with doses up to 0.1 mg/kg.

Many treated female rats and rabbits died or were sacrificed while moribund at parturition due to difficulty in delivery (dystocia).

In the teratology study conducted zoledronic acid caused skeletal malformations and dose-related poor skeletal ossifications in rats at doses over 0.2 mg/kg.

Local Tolerance

Local tolerance studies were carried out in rabbits and guinea pigs with treatment duration of 5 to 25 days. Zoledronic acid was shown to be intravenously irritating and to induce dermal irritation after repeated administration.

Environmental Risk Assessment

An assessment of the environmental risk was performed and no significant risk to the environment related to the use of zoledronic acid is anticipated.

Impurities/Metabolites

Two major by-products were identified in the batches used in toxicology and clinical studies. Their presence was not considered toxicologically important.

Discussion on toxico-pharmacological aspects

The antiresorptive effects on osteoclasts have been documented. In comparative pharmacodynamic studies zoledronic acid has a considerably higher potency than pamidronate, the currently most used bisphosphonate for the treatment of TIH. The thyro-parathyroidectomised rat model and the ovariectomised rat model have been used in most studies. No animal models of TIH have been included. In response to the List of Questions, which queried the lack of studies in animal models of TIH, the applicant argued that it had been demonstrated that zoledronic acid inhibits osteoclastic bone resorption. This effect can be translated into a lowering of serum calcium in animals with experimental hypercalcaemia and increased osteoclastic activity regardless of underlying disease plays a major role in the development of hypercalcaemia. Data from the new murine model that were presented in abstract form in response to the List of Questions support that zoledronic acid potently inhibits osteolysis induced by bone metastases, although the direct effects on hypercalcaemia have not been investigated in neoplastic animal models. However, it is still regrettable that the specific situation of tumour invasion was not studied. This is only justified because there are sufficient clinical data to support the indication TIH.

Zoledronic acid produced toxicological effects in the kidney, liver, osseous skeleton, and gastrointestinal tract and is a local irritant. The renal NOAEL in rat and dog studies compared with the highest intended human dose of 8 mg varied within narrow limits (between 8 and 1 times the human dose). At higher i.v. doses the toxic effects included inflammation, haemorrhage and erosions in the gastrointestinal tract; hepatocellular necrosis, haemorrhage and inflammation; severe local skin inflammation at the injection site. In both species studied zoledronic acid caused expected dose-dependent alterations in bones with increased primary spongiosa in the metaphyses of long bones in growing animals and a signficant increase in density and improvement of the mechanical properties of trabecular bone after i.v. treatment of dogs for 6 months. Hypocalcaemia and hypomagnesiaemia combined with lowered bone alkaline phosphatase were the most prominent laboratory findings.

The total systemic exposure to the highest dose in rats and in dogs was respectively about 1-8 and 6-28 times the highest expected human exposure (8 mg).

Zoledronic acid causes foetal skeleton malformations. Like other bisphosphonates, zoledronic acid should not be used in pregnant women. This is reflected in the SPC.

Zoledronic acid is not mutagenic or carcinogenic.

4. Clinical aspects

Clinical pharmacology

Zoledronic acid is being evaluated mainly in oncology indications, namely treatment of TIH, and treatment of bone metastases. Two studies of Paget's disease of bone are also included for the evaluation of pharmacodynamic properties of zoledronic acid. The studies were conducted in compliance with GCP. Studies in healthy volunteers have not been performed.

Overview of trials presenting pharmacokinetic and/or pharmacodynamic data is given in the table below:

	Study	Objective	Number of patients	Dose (intravenous)
TIH treatment studies	CJ/HC1	Assess non-toxic dose level able to induce normocalcaemia; effect on serun and urinary calcium Dose finding study	N=35, 5 treatment groups	0,002 mg/kg, 0,005 mg/kg, 0,01 mg/kg, 0,02 mg/kg, 0,04 mg/kg
	036	Single dose (and retreatment) safety and efficacy; effect on corrected serum calcium, serum and urinary markers on bone resorption	N=149; 3 treatment groups	4 mg, 8 mg Comparator: Pamidronate 90 mg
	037	Single dose (and retreatment) safety and efficacy; effect on corrected serum calcium, serum and urinary markers on bone resorption	N=138; 3 treatment groups	4 mg, 8 mg Comparator: Pamidronate 90 mg
Bone metastasis treatment studies	003	Dose ranging study; safety, tolerability, effect on serum and urinary biochemical markers of bone resorption of 4 consecutive doses given every 4 weeks	N=59, 8 treatment groups	0,1 mg, 0,2 mg, 0,4 mg, 0,8 mg, 1,5 mg, 2 mg, 4 mg, 8 mg
	007	Safety, tolerability, efficacy, and changes in markers of bone resorption and formation of zoledronic acid given every 4 weeks for 9 months	N=280, 4 treatment groups	0,4 mg, 2 mg, 4 mg Comparator: Pamidronate 90 mg
	035	Dose ranging study; safety, tolerability, effect on serum and urinary biochemical markers of bone resorption of single doses	N=44, 5 treatment groups	1 mg, 2 mg, 4 mg, 8 mg, 16 mg
PK/PD studies in patients with bone metastases	J001	Safety of escalating doses of zoledronic acid. Effects of escalating doses of zoledronic acid on bone resorption parameters. Zoledronic acid pharmacokinetics	N=9, 3 treatment groups	2 mg, 4 mg, 8 mg
	0503	Safety of escalating doses of zoledronic acid. Effects of escalating doses of zoledronic acid on bone resorption parameters. Zoledronic acid pharmacokinetics	N=23, 4 treatment groups	4 mg 5 min infusion, 4 mg 15 min infusion, 8 mg 15 min infusion, 16 mg 15 min infusion
Paget's disease treatement studies	001	Dose ranging study; safety, tolerability on urinary biochemical markers of bone resorption of single dose	N=16, 4 treatment group	0,024 mg, 0,072 mg, 0,216 mg, 0,400 mg
	002	Assess minimum and maximum tolerated single dose; effect on serum and urinary biochemical markers of bone resorption of single dose	N=175, 5 treatment groups	0,05 mg 0,1 mg, 0,2 mg, 0,4 mg Placebo

Pharmacodynamics

As Zometa inhibits osteoclastic bone resorption by binding to calcified bone matrix, its pharmacodynamic effects were evaluated by investigating how it affected biochemical markers of bone resorption, such as serum or plasma (albumin corrected) calcium, bone specific alkaline phosphatase, PTH, and PTHrP.

In TIH patients urine N-telopeptide (NTX)/creatinine ratio, urine calcium/ creatinine ratio, urine(deoxy)pyridinoline/ creatinine ratio, and urine hydroxyproline/ creatinine ratio all decreased significantly from baseline after a single infusion of zoledronic acid, consistent with the drug's inhibitory effects on bone resorption. Serum bone specific alkaline phosphatase tended to increase but the changes were not significant for this marker of bone formation. The differences were not dose-dependent.

Pharmacokinetics

All known bisphosphonates are characterised by a very low bioavailability after oral administration. For the treatment of TIH, only bisphosphonates formulated for i.v. use are of interest. There is a rapid disappearance of drug from the systemic circulation after i.v. administration reflecting binding to mineralised bone and renal excretion. This is followed by very low concentrations of zoledronic acid representing small amounts of drug being released from bones over weeks to months and eliminated almost exclusively by the kidney. A more complete evaluation of the pharmacokinetics (PK) would therefore require quantitative urine sampling over several weeks. PK studies in patients with TIH were not performed due to the anticipated difficulties in completing the required sampling schedule in this population. Zoledronic acid pharmacokinetics were studied in patients with bone metastases without TIH.

Zoledronic acid was determined in plasma and urine using a specific radioimmunoassay with the lower limits of quantification being 0.4 ng/ml and 10 ng/ml for plasma and urine determinations, respectively.

Two studies have been submitted, study J001 conducted in Japan (9 patients) and study 0503 conducted in the USA (23 patients). Pooled data from these studies with a total of 32 patients were analysed using a validated, population pharmacokinetic approach.

Maximal plasma concentrations of zoledronic acid were observed immediately post-end infusion. The concentration versus time curves showed a rapid decline followed by phases of slower decline. Low plasma concentrations of zoledronic acid were found up to 29 days post dose, indicating prolonged disposition from a storage compartment, presumably bone.

In the pooled evaluation of plasma concentration versus time data, a three-compartment model was chosen for the final fitting of the data. The half-lives for the triphasic decline of the plasma concentrations 0.23 hours, 1.75 hours and 167 hours reflect the high k (into bone)/k (out of bone) ratio of 48$\pm$ 20 and a much larger volume of distribution of the bone compartment, of 381 l to the combined volumes of the central and non-osseous peripheral compartments, of about 15 l.

Zoledronic acid plasma concentrations in both studies are consistent with dose proportionality.

Pharmacokinetic data indicate that AUC and Cmax increased proportionally with increasing doses of zoledronic acid. In the Japanese J001 trial, there were no dose-dependent differences in the results of bone metabolism marker studies, which were used as the major efficacy parameters. In the US trial 503 there is indication that the amount of zoledronic acid retained in the body at 24 hours post infusion correlates to changes in some bone markers (creatinine adjusted calcium and bone alkaline phosphatase). The more zoledronic acid retained in the body, the lower the urinary calcium excretion, and the higher the serum bone alkaline phosphatase level.

Plasma-clearance seemed to be almost independent of dose (2-16 mg) and infusion time (5 vs 15 minutes). The clearance of drug is unaffected by patient's age (range studied of 45-80 years). The plasma clearance is proportional to creatinine clearance.

Plasma protein binding is low, about 22%.

Biotransformation of zoledronic acid in animals and human is negligible.

Both studies used quantitative urine sampling 0-24 h (503) and 0-48 h (J001) post dose. Study 503 also included spot urine days 8, 15, 29 post dose. The urinary excretion of zoledronic acid was rapid over the first 6 hours which parallels the rapid decline in plasma concentrations. The percentage of drug excreted was not affected by dose or infusion rate.

Gender had no effect on total plasma clearance.

Based on data from 16 Caucasians, 7 black Americans and 9 Japanese there is no effect on total plasma clearance by race.

Interaction studies

No targeted studies have been performed. The low serum protein binding (22%), the lack of biotransformation, and the very low potential of reversible or irreversible inhibition of major human P450 enzymes in liver microsomes (CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6,

CYP2E1, CYP3A4/5 or CYP4A9/11) of zoledronic acid are all factors that justify the absence of formal drug-drug interaction studies.

Like other bisphosphonates, zoledronic acid should not be mixed with calcium-containing i.v. infusions because of its propensity to form insoluble calcium complexes. This is reflected in the SPC section 6.6.

Concomitant administration of anticancer agents, diuretics, antibiotics and analgesics in the clinical trials did not indicate the occurrence of drug-drug interactions. The SPC (section 4.5) cautions the co-administration with aminoglycosides, since both agents may have an additive effect, resulting in a lower serum calcium level for longer periods than required.

Special populations

In the US study 503 the mean age was 58 years (range 45 to 80 years). The results indicate that age has no effect on total plasma clearance of zoledronic acid.

Data in severe renal impairment are not available. In the 32 pharmacokinetic patients creatinine clearance ranged from 25 to 144 ml/min. As expected, the renal clearance of zoledronic acid was proportional to the creatinine clearance. The individual creatinine clearance is probably the most important covariate for total plasma clearance of zoledronic acid. Since zoledronic acid is exclusively administered as single dose infusions and at least one week should elapse before retreatment is considered, there are no recommendations for dose adjustment in patients with mild to moderate renal impairment.

Zoledronic acid is not metabolised and the liver plays no role in the overall clearance of the drug. Studies in liver insufficiency have, therefore, not been conducted.

Clinical efficacy

The clinical efficacy and safety studies were conducted according to GCP. The design, duration, the number of patients and the demographic characteristics of these patients are given below:

Study	Study design and treatment duration	Number of patients enrolled/completed	Dose (intravenous) zoledronic acid
CJ/HC1	Open, non-comparative, multicenter, dose finding, single dose study Single iv infusion	N=35, 5 treatment groups	0,002 mg/kg, 0,005 mg/kg, 0,01 mg/kg, 0,02 mg/kg, 0.04 mg/kg
036	Double blind, double dummy, randomised, active controlled, multicenter trial with parallel groups In stage 1 patients were treated with zoledronic acid or comparator, in stage 2 patients who were refractory or had relapsed on either therapy were retreated with zoledronic acid. A single dose was given in both stages	N=149; 3 treatment groups	4 mg, 8 mg Comparator: Pamidronate 90 mg
037	Double blind, double dummy, randomised, active controlled, multicenter trial with parallel groups In stage 1 patients were treated with zoledronic acid or comparator, in stage 2 patients who were refractory or had relapsed on either therapy were retreated with zoledronic acid. A single dose was given in both stages	N=138; 3 treatment groups	4 mg, 8 mg Comparator: Pamidronate 90 mg

Dose-response studies and main clinical studies

Dose response study (CJ/HC1)

The primary end-point was to determine with a dose escalation schedule (giving a single 30-minute infusion to each patient) two non-toxic dose levels, each able to induce normocalcaemia in 4 or 5 out of 5 patients with TIH.

The doses tested were established from toxicological studies in animals using zoledronic acid, and extrapolation to experience with pamidronate.

Overall, 37 patients were included. Four did not actually receive the drugs, three other were excluded because not eligible (1) or for early deaths (2), leaving 30 evaluable cases.

The table below summarises the results:

	Dose (mg/kg)				
	0.002	0.005	0.01	0.02	0.04
Range of actual doses (mg)	0.09-0.14	0.2-0.36	0.52-0.7	0.92-1.6	1.54-3.52
Baseline CSC (range mmol/l)	2.94-2.99	3.17-3.37	2.98-3.91	2.96-3.46	2.75-3.62
Patients with normocalcaemia (≤2.60 mmol/l) (n/N - %)	1/3 (33)	1/3 (33)	1/4 (25)	5/5 (100)	14/15 (93)

Other secondary endpoints (days of normalization and duration of action) described the rapidity and duration of drug action. The day of normalisation of the corrected serum calcium was day 2 or day 3 for most patients. The duration of action (i.e., time until hypercalcaemic relapse, computed from the day when the patients achieved normocalcaemia), is not a valid criterion because of the small number of patients recruited and as most patients were actually not evaluable: eight patients died, two were lost or non-compliant. In addition, at the effective doses (0.002 and 0.04 mg/kg) only one patient per level actually relapsed (the duration of drug action was, respectively, 17 and 16 days).

Main studies (036, 037)

Both pivotal studies in patients with TIH (any cancer and corrected serum calcium (CSC) ≥ 3.00 mmol/l) have been submitted. Both used a randomised double blind, double-dummy design comparing 4 mg or 8 mg zoledronic acid (5 minute i.v. infusion) with pamidronate 90 mg (2 hour infusion). The dummy consisted of equal amount of 0.9% NaCl (50 ml/5 min for patients randomised to pamidronate; 250 ml/2 hours for patients randomised to zoledronic acid). The pamidronate dose is the highest recommended in the current approved SPC. Both treatment arms included i.v. hydration with a third infusion of 250 ml saline after active drug + dummy infusion. Both studies comprised two stages. In stage I patients were randomised to initial treatment of TIH with zoledronic acid (4 or 8 mg), or pamidronate. In stage II, patients with refractory or relapsed TIH could be retreated with open-label 8 mg zoledronic acid.

In both studies only patients with a histologically or cytologically confirmed diagnosis of cancer and a corrected serum Calcium (CSC) level ≥ 3.00 mmol/l (12.0 mg/dl) were included. Patients with previous bisphosphonate therapy for hypercalcaemia within last 90 days or for other reasons within last 30 days, treatment with calcitonin, mithramycin or gallium nitrate within last 72 hours, 7 or 14 days respectively, change in antineoplastic chemotherapy or hormonal therapy within last 7 days, serum creatinine > 400 μmol/l (4.5 mg/dl) or hyperparathyroidism, vitamin D intoxication, "milk alkali syndrome", sarcoidosis or granulomatous disease, adrenal insufficiency, multiple endocrine neoplasia syndromes were excluded from the studies.

The primary efficacy parameter was the incidence of complete response (CR) defined as corrected serum calcium ≤ 2.70 mmol/l (10.8 mg/dl) within 10 days after treatment. Secondary efficacy parameters included time to relapse of TIH, duration of CR, change from baseline CSC level, and % patients with refractory TIH.

Patients achieving CR were followed until day 56 in Stage I or CSC ≥ 2.90 mmol/l, whichever occurred first. Also patients with an incomplete response but CSC < 2.90 on day 10 were followed until day 56 or until CSC equal to or above 2.90 mmol/l. In stage II, patients received retreatment with 8 mg zoledronic acid if their TIH was refractory to initial treatment, or if the TIH relapsed as defined by a CSC of ≥ 2.90 mmol/l. If retreatment resulted in a CR by day 10, the patient was followed in stage 2 for 4 weeks or until relapse, whichever occurred first. Patients who did not achieve CR upon retreatment were discontinued from the trial.

Within each treatment group, the 95% confidence interval for the proportion of completed responders by Day 10 was calculated using the normal approximation to the binomial distribution. Time to relapse and duration were presented by Kaplan-Meier plots with descriptive statistics including 95%

confidence limits on the median. Additionally, secondary analyses were performed on between-treatment comparisons. These analyses are considered secondary, because the studies were not powered to detect differences between-treatment groups. The proportion of complete responders by Day 4, 7 and 10, the change from baseline in CSC at Day 4, 7 and 10, and the time to relapse were analysed using Cochran-Mantel-Haenszel test controlling for baseline CSC, analysis of covariance including baseline CSC as covariate, and Cox regression including baseline CSC as covariate respectively.

Efficacy analyses were performed on both the per protocol (PP) population and the intent-to-treat (ITT) population. The PP population, which consisted of all randomised patients who received the i.v.infusion at, visit 1 (baseline) and satisfied the admission criteria for TIH was considered as the primary data set for efficacy analysis. The ITT population consisted of all randomised patients who received the i.v. infusion at visit 1 (baseline) of Stage I of the trial.

Safety analyses were based on the ITT population.

In terms of baseline demographic characteristics the three treatment groups in 036 were generally well balanced. The mean baseline CSC levels (mmol/l) were 3.50, 3.39 and 3.51, respectively. Renal function and hydration state were similar in the three treatment groups. In study 037 the three treatment groups were similar with regard to baseline demographic characteristics including CSC levels, renal function and hydration status. There were relatively more patients with breast or haematological cancer in the 4 mg zoledronic acid group as compared to more patients with lung cancer in the 8 mg zoledronic acid and pamidronate groups. The patients in the 4 mg zoledronic acid groups had a longer duration of cancer as compared to the two other treatment groups. Finally, there was a greater percentage of patients with bone metastases in the two zoledronic acid groups.

For the primary efficacy parameter, incidence of complete response (CSC≤ 2.70 mmol/l (10.8 mg/dl)) within 10 days of treatment the results are shown in table below:

	036			**037**		
PP population	Zoledronic acid 4 mg	Zoledronic acid 8 mg	Pamidronate 90 mg	Zoledronic acid 4 mg	Zoledronic acid 8 mg	Pamidronate 90 mg
No. CR	41	43	37	35	35	32
Estimate (%)	89.1	89.1	74.0	87.5	83.3	65.3
95% CI	80.1-98.1	80.9-98.2	61.8-86.2	77.3-97.8	72.1-94.6	52.0-78.0
P-value[1]	<0.001	<0.001	0.519	<0.001	<0.020	0.490

[1]Test of H0 p=0.70 vs p different from 0.70.

In study 036 the between-group differences in CR rates at Day 10 were not significant, but the zoledronic acid treated patients achieved CR more rapidly than the pamidronate group. CR rates appeared to be independent of the CSC baseline level for zoledronic acid 4 mg group, and with the exception of baseline PTHrP all other baseline characteristics appeared to have little if any effect on CR rates. Patients with PTHrP level above 2.0 pmol/l had somewhat lower CR rates.

In study 037 The between-group difference in CR rate at Day 10 was significantly higher in the 4 mg zoledronic acid group compared the pamidronate group (p=0.018). There was no clear dose response with zoledronic acid. CR rates appeared to be independent of the baseline severity of TIH.

For the secondary efficacy parameter, duration of response the results are shown below:

	036			037		
	Zoledronate 4 mg	Zoledronate 8 mg	Pamidronate 90 mg	Zoledronate 4 mg	Zoledronate 8 mg	Pamidronate 90 mg
Time to relapse (median days)	36 days	40 days	20 days	29 days	40 days	16 days
95% CI for the median	[24, not reached]	[21, not reached]	[11,42]	[22, not reached]	[21, not reached]	[6, 23]
Hazard ratio compared to pamidronate (95% CI)	0.56 [0.33, 0.96]	0.70 [0.42, 1.19]	-	0.49 [0.28, 0.85]	0.50 [0.29, 0.86]	-
P-value	p= 0.036	p=0.187	-	p= 0.011	p= 0.013	-

The mean change from baseline in corrected serum calcium level (mmol/l) is shown below:

	036			037		
	Zoledronate 4 mg (N=46)	Zoledronate 8 mg (N=48)	Pamidronate 90 mg (N=50)	Zoledronate 4 mg	Zoledronate 8 mg	Pamidronate 90 mg
Corrected Day 4	-0.76[1]	-0.76[1]	-0.65	-0.70[1]	-0.62	-0.57
Corrected Day 7	-0.99	-1.01[1]	-0.87	-0.95[4]	-0.89	-0.78
Corrected Day 10	-1.05[2]	-1.06[3]	-0.88	-0.93[1]	-0.94[1]	-0.79

[1] p<0.05 vs pamidronate 90 mg; [2] p=0.014 vs pamidronate 90 mg; [3]p=0.01 vs pamidronate 90 mg,
[4]p=0.007 vs pamidronate 90 mg

Of the 34 patients in study 036 who received retreatment with zoledronic acid 8 mg, 23 had achieved CR in stage 1 of the trials, the remaining 11 were either refractory to treatment or had less than CR. CR was achieved by Day 10 in 19 (55.9%) patients. Patients with a prior CR in stage 1 had a CR rate of 74% whereas refractory or failing patients on initial therapy only had a CR rate of 18%.

Of the 35 per-protocol patients re-treated in 037, 24 previously had CR in Stage 1 of the study and were retreated because of relapsing TIH. Their CR rate in Stage 2 was 58%. The remaining 11 patients had either refractory TIH, partial response or were unclassified. In this group, the response rate in Stage 2 was only 27%. The overall CR rate after retreatment with 8 mg zoledronic acid was 48.6% (17 patients).

Discontinuation rates due to death (before day 56) were similar in the 3 treatment groups, whereas the dicontinuation rate due to unsatisfactory therapeutic effect was higher in the pamidronate group (13 in pamidronate group, 4 in zoledronic acid 4 mg group and 5 in zoledronic acid 8 mg group). The same was seen in where 7 discontinued in the pamidronate because of unsatisfactory therapeutic effect, where the same number for the 4 mg and 8 mg zoledronic acid groups was 3 and 1 respectively.

Pre-planned analysis performed across trials.

A prospective metaanalysis from the two studies 036 and 037 was performed since the individual trials were not powered for statistical comparisons between treatments. Given the known variability in response in patients with TIH to bisphosphonates a difference of 10% is considered acceptable. Thus, assuming an one-sided equivalence range of 10%, an expected response rate of 90% after pamidronate and of 92% after zoledronic acid 4 or 8 mg, 90 patients per treatment arm are necessary to show *non-inferiority* of either dose compared to pamidronate with a two-sided test on the 5% level (one-sided test on the 2.5% level) and a power of 80%.

Again, the primary efficacy variable was CR in the per protocol population defined as CSC $\leq$ 2.70 mmol/l (10.8 mg/dl) by Day 10 (Stage 1 – initial treatment). Patients who discontinued or died prior to Day 10, and never had a CR, were considered as non-responders.

Although there were some differences in baseline cancer characteristics as reflected by the individual trials, the treatments groups were comparable with respect to baseline demographic characteristics, severity of TIH, renal function and hydration status.

Assignment of patients to analysis populations (Stage 1 = initial treatment)

	Zoledronic acid 4 mg	**Zoledronic acid 8 mg**	**Pamidronate 90 mg**
ITT population	86 (100%)	98 (100%)	103 (100%)
PP population	86 (100%)	90 (92%)	99 (96%)

Both doses of zoledronic acid (4 mg and 8 mg) were declared non-inferior to pamidronate 90 mg, since the 95% CI of the difference between zoledronic acid and pamidronate in the percentage of CR was not only above the –10% preset non-inferiority limit but also above 0%. This indicates that both zoledronic acid doses are statistically superior to pamidronate. The results are shown in table below:

Summary of between-treatment analysis of complete responders

	Difference Zol 4 mg – Pam 90 mg	**Difference Zol 8 mg – Pam 90 mg**	**Difference Zol 8 mg – Zol 4 mg**
Estimate (%)	18.7	17.0	-1.7
95% CI	7.4-30.0	5.5-28.4	-11.5-8.1
P-value	0.002	0.015	0.674

Summary of within-treatment analysis of complete responders

	Zoledronic acid 4 mg	**Zoledronic acid 8 mg**	**Pamidronate 90 mg**
No. of complete responders	76	78	69
Estimate (%)	88.4	86.7	69.7
95% CI	81.6-95.2	79.6-93.7	60.6-78.8
P-value	<0.001[1]	<0.001[1]	0.948

Test of the H_0 p=0.70 vs. ≠0.70 [1] denotes statistical significance at the 0.05 level, two sided test

There were no indications that 8 mg zoledronic acid is more effective than 4 mg zoledronic acid in specific subgroups of patients.

For the secondary parameters number of patients with complete response by study day and treatment group, the mean change in baseline in corrected serum calcium levels and the time to relapse of TIH, duration of response and the duration of the complete response are shown in the tables below.

Number of patients with complete response by study day and treatment group (PP population)

	Number of patients with complete response n(%)			**p-values for comparison against pamidronate**	
	Zoledronic acid 4 mg (N=86)	Zoledronic acid 8 mg (N=90)	Pamidronate 90 mg (N=99)	Zoledronid acid 4 mg vs Pamidronate	Zoledronic acid 8 mg vs Pamidronate -
Day 4	39 (45.3)	50(55.6)	33(33.3)	0.104	0.021
Day 7	71(82.6)	75(83.3)	63(63.6)	0.005	0.010
Day 10	76(88.4)	78(86.7)	69(69.7)	0.002	0.015

Mean change from baseline[1] in corrected serum calcium levels (PP population)

	Mean change from baseline CSC n(%)			p-values for comparison against pamidronate	
	Zoledronic acid 4 mg (N=86)	Zoledronic acid 8 mg (N=90)	Pamidronate 90 mg (N=99)	Zoledronic acid 4 mg vs Pamidronate	Zoledronic acid 8 mg vs Pamidronate -
Day 4	-0.73 (-2.92)	-0.70 (-2.80)	-0.62 (-2.48)	0.005	0.051
Day 7	-0.97 (-3.88)	-0.96 (-3.84)	-0.83 (-3.32)	0.001	0.003
Day 10	-1.00 (-4.00)	-1.00 (-4.00)	-0.84 (-3.36)	0.001	0.001

If CSC was missing then the last non-missing value including baseline was carried forward

Time to relapse of TIH, duration of response and duration of complete response (PP population)

	Treatment group		
	Zoledronic acid 4 mg	Zoledronic acid 8 mg	Pamidronate 90 mg
Time to relapse (days) median[3]	30	40	17
95% Cl for median	25-NR	25-51	10-24
Risk ratio (95%Cl)	0.52 (0.36-0.77)[4]	0.59 (0.41-0.87)[4]	
Duration of response[1] (days) median[3]	33	43	22
95% Cl for median	25-NR	26-NR	18-39
Duration of complete response[2] (days) median[3]	32	43	18
95% Cl for median	25-NR	25-NR	12-36

[1] Time from occurrence of complete response to last corrected serum Ca level <2.90 mmol/l (11.6 mg/dl)
[2] Time from of occurrence of complete response to last corrected serum Ca level <2.70 mmol/l (10.8 mg/dl)
[3] Death counted as relapse
[4] Denotes statistical significance at the 0.05 level vs pamidronate 90 mg (Cox regression, model adjusting for baseline CSC group.

In the pooled analysis 69 patients received retreatment in Stage 2 of the protocol. Day 10 achieved CR in 36 patients (52.2%). Patients with a previous response to bisphosphonate had a higher CR rate (78.3%) than patients with initial refractory TIH (21.7%).

Clinical studies in special populations

No clinical studies have been performed in special populations.

Supportive studies

No supportive clinical studies in the indication applied for have been submitted.

Discussion on Clinical Efficacy

The more rigorous and extensive pharmacokinetic evaluations were possible only in the surrogate population of cancer patients with bone metastases, who would offer more definitive and reliable, as well as representative pharmacokinetic data. This would also allow assessment of PK/PD relationships and testing the influence of population covariates (intrinsic and extrinsic factors) on PK. From a clinical point of view it is therefore justified to perform PK studies in patients with cancer and bone metastases but without overt TIH.

No studies have been performed in specific populations, such as patients with renal or hepatic impairment. In patients with mild to moderate renal impairment dose adjustments are not considered necessary as only relatively small increases in AUC (on average only about 1.6-fold higher in patients with moderate renal impairment compared to patients with normal renal function) were seen in patients with increased serum creatinine representing mild to moderate renal impairment. The recommended clinical dose in treatment/retreatment for zoledronic acid allows for an adequate margin in renal impairment, since single doses up to 16 mg have been shown to be well tolerated. Only data in patients with mild and moderate renal impairment are available and a recommendation to monitor renal function is included in the SPC. Due to the lack of clinical data the applicant does currently not recommend the use of zoledronic acid in patients with severe renal impairment (i.e. serum creatinine values ≥ 400 μmol/l or ≥ 4.5 mg/dl). Lack of studies in patients with hepatic impairment is justified because the drug is not metabolised, experimental studies demonstrate low plasma protein binding, the absence of biotransformation and because there is no hepatic clearance of zoledronic acid. Pharmacokinetic drug – drug interactions related to protein binding and hepatic metabolic clearance processes are therefore not expected.

Formal drug-drug interaction studies were not conducted, but this is well justified.

The dose-finding study indicated that a dose of 2 to 4 mg maximum should be chosen for future phase II trials in patients with TIH. In the pivotal trials the applicant used an infusion time of 5 min for zoledronic acid was used. This shorter infusion time had been used in the trial 003 without safety problem. In response to the List of Questions the applicant argued that the dose selection for the pivotal trials had also been based on studies in non-TIH patients (i.e. phase II dose ranging studies in patients with bone metastases) as well as some extrapolation from pamidronate experience.

This is acceptable given the efficacy and safety results of pivotal trials, although the effective dose might be lower than the recommended 4 mg dose.

Due to concern about renal safety expressed by the CPMP in the List of Questions and emerging data from clinical trials in bone metastases the applicant has changed the recommended infusion time from 5 to 15 minutes. Although this change is not founded on the clinical experience in patients with TIH, the change is based on data from patients with bone metastases in whom renal safety was improved by lengthening the infusion time without losing efficacy.

The 8 mg dose recommended for retreatment had been tested without controls and 4 mg had not been tested. In response to the List of Questions the applicant argued that the choice of the 8 mg dose was based on clinical experience with pamidronate and with other bisphosphonates in the treatment of TIH, which showed that repeated administration at the same dose as initial treatment produces lower response rates. In addition, study 007 demonstrated that the efficacy of zoledronic acid 4 mg and pamidronate 90 mg appeared comparable. Therefore, the higher dose of zoledronic acid, 8 mg, was deemed to be the best dose for retreatment, since this dose would probably be at least as efficacious as the 4 mg zoledronic acid dose and the pamidronate 90 mg dose while offering patients initially treated with 8 mg zoledronic acid the greatest protection if the first dose did not result in a sustained or adequate response. Despite this, 52.2% of patients responded to the 8 mg dose when retreated. The SPC acknowledges this, but states that limited data are available regarding retreatment.The applicant committed to perform a clinical study to evaluate the efficacy of the retreatment in TIH patients comparing a dose of Zometa 4 mg and 8 mg.

The applicant has shown a consistent high activity of zoledronic acid (4 or 8 mg single dose) in the treatment of tumour-induced-hypercalcaemia.

In the preplanned metaanalysis zoledronic acid (4 or 8 mg) was shown to be not only non-inferior to, but also statistically significantly superior to pamidronate 90 mg for 3 important efficacy variables (proportion of complete responders at Day 90, change in CSC from baseline at Day 10, and time to relapse). The applicant considered it appropriate to switch the objective of the analysis from non-inferiority to superiority although not explicitly stated in the pooled analysis protocol for a number of reasons.

The justification is in concurrence with the CPMP Points to consider paper on this topic (CPMP/EWP/482/99). The factors that might be affected by the change in the objective such as appropriateness of comparator, power calculations, size of additional clinical benefit, choice of

analysis population, trial quality have all been addressed by the applicant. Additionally, the meta-analysis protocol was not done post hoc, but was preplanned. The clinical relevant difference was determined a priori and the results imply clinically relevant superiority.

Clinical safety

Patient exposure

The population evaluated for safety comprises patients from the 3 studies in the treatment of TIH (CJ/HC1, 036, 037), 3 studies in the treatment of bone metastases (003, 007, 035). Studies 007, 036 & 037 compare zoledronic acid with pamidronate.

The level of exposure is shown in table below:

Number of patients treated	< 4 mg	4 mg	8 mg	8 mg retreatm.	All
TIH	33	86	98	70	287
Bone metastases	168	65	17	50	300
All	201	151	115	120	587

Adverse events and serious adverse events/deaths

The incidence of AE is high in TIH trials as expected for endstage cancer patients. The most frequent reported AE were fever, progression of cancer, anaemia, constipation, nausea, and dyspnea.

The most frequent treatment related adverse events are given below:

	Zol < 4 mg	**Zol 4 mg**	**Zol 8 mg**	**Zol 8 mg retreatment**	**Pamidronate 90 mg**
Number of patients (N)	33	86	98	103	70
Adverse events					
Fever	10 (30.3)	6 (7.0)	10 (10.2)	10 (9.7)	2 (2.9)
Hypocalcaemia	4 (12.1)	5 (5.8)	6 (6.1)	2 (1.9)	1 (1.4)
Hypophosphataemia	7 (21.2)	3 (3.5)	3 (3.1)	1 (1.0)	0
Nausea	0	1 (1.2)	3 (3.1)	1 (1.0)	0
Skeletal pain	0	1 (1.2)	1 (1.0)	1 (1.0)	1 (1.4)
Conjuntivitis	0	0	1 (1.0)	1 (1.0)	0
Hypomagnesaemia	1 (3.0)	1 (1.2)	0	0	0
Chest pain	0	1 (1.2)	1 (1.0)	0	0
Pruritus	0	1 (1.2)	1 (1.0)	0	0
Erythematous rash	0	0	1 (1.0)	1 (1.0)	0
Headache	0	0	1 (1.0)	0	1(1.4)
Taste perversion	0	1 (1.2)	0	0	1 (1.4)
Thrombocytopaenia	0	0	0	1 (1.0)	1 (1.4)
Vomiting	0	1 (1.2)	1 (1.0)	0	0

The expected AEs following bisphosphonate treatment include an acute phase reaction (fever, arthralgia/myalgia), renal toxicity, infusion site reactions, electrolyte disturbances (calcium and phosphate levels) and rare ocular toxicities.

These specific symptoms and signs irrespective of causality are summarised below:

	Treatment groups				
	Zol < 4 mg	**Zol 4 mg**	**Zol 8 mg**	**Zol 8 mg retreatment**	**Pamidronate 90 mg**
No of patients (N)	33	86	98	70	103
Fever	17 (51.5%)	38 (44.2%)	34 (34.7%)	11 (15.7%)	34 (33%)
Arthralgia	0	7 (8.1%)	6 (6.1%)	2 (2.9%)	2 (1.9%)
Arthritis	0	0	1 (1.0%)	0	0
Myalgia	0	2 (2.3%)	0	0	1 (1.0%)
Hypocalcaemia	4 (12.1%)	5 (5.8%)	8 (8.2%)	1 (1.4%)	2 (1.9%)
Hypophosphat.	7 (21.2%)	11 (12.8%)	5 (5.1%)	2 (2.9%)	2 (1.9%)
Hypokalemia	1 (3.0%)	10 (11.6%)	12 (12.2%)	4 (5.7%)	16 (15.5%)
Hypomagnesemia	1 (3.0%)	9 (10.5%)	6 (6.1%)	0	5 (4.9%)
Renal failure acute	0	1 (1.2%)	1 (1.0%)	2 (2.9%)	0
Renal function abnormal	0	4 (4.7%)	3 (3.1%)	1 (1.4%)	1 (1.0%)
Uraemia	0	2 (2.3%)	4 (4.1%)	0	0
Any eye abnormality	0	5 (5.8%)	5 (5.1%)	2 (2.9%)	5 (4.9%)

Hypocalcaemia and hypophosphataemia were slightly more common among patients treated with zoledronic acid than in the pamidronate group.

A slightly greater proportion of patients in the zoledronic acid 4 mg and zoledronic acid 8 mg treatment groups had renal adverse events reported compared to the other treatment group pamidronate 90 mg. A higher incidence of patients classified as having abnormal renal function, uraemia, and urinary retention in these 2 groups accounted for most of this difference, which on further analysis of all Renal Adverse Event terms was determined not to be statistically significant.

Summary of all renal adverse events in TIH trials

	Treatment group				
	Zoledronic acid				Pam
	< 4 mg	4 mg	8 mg	8 mg retreatment	90 mg
Patients studied n(%)					
Total no. of patients	33 (100)	86 (100)	98 (100)	70 (100)	103 (100)
Total no. of patients with renal adverse events	4 (12.1)	14 (16.3)	14 (14.3)	4 (5.7)	10 (9.7)
Adverse Events					
Hyperuricemia	0	1 (1.2)	0	1 (1.4)	2 (1.9)
Anuria	0	0	1 (1.0)	0	0
Hematuria	0	1 (1.2)	2 (2.0)	1 (1.4)	2 (1.9)
Hydronephrosis	0	1 (1.2)	0	1 (1.4)	0
Micturition frequency	0	1 (1.2)	0	1 (1.0)	0
Obstructive uropathy	0	0	0	0	1 (1.0)
Oliguria	3 (9.1)	1 (1.2)	0	0	3 (2.9)
Pyelonephritis	0	1 (1.2)	0	0	0
Renal failure acute	0	1 (1.2)	1 (1.0)	2 (2.9)	0
Renal function abnormal	0	4 (4.7)	3 (3.1)	1 (1.4)	1 (1.0)
Uremia	0	2 (2.3)	4 (4.1)	0	0
Urethral disorder	0	0	1 (1.0)	0	0
Urinary retention	1 (3.0)	3 (3.5)	2 (2.0)	0	1 (1.0)
Urinary tract disorder	0	1 (1.2)	0	0	0

Although there are slightly more events in the zoledronic acid treatment group, the overall incidence is low, there is no dose-related trend in overall occurrence of renal events in the zoledronic acid groups, and there is a lower incidence after retreatment. A review of patient histories shows that the zoledronic acid groups included a higher proportion of patients with a prior medical history of renal dysfunction or conditions such as diabetes, hypertension, and hyperuricaemia, which predisposed them to renal dysfunction, as well as a history of co-administration of nephrotoxic medications. A review of the renal adverse event profile determined that none of the renal adverse event was ascribed to the study drugs by the investigator.

In response to the List of Questions the applicant listed all renal cases reported in the pivotal studies 036 and 037. There is no statistical significant difference with regard to the overall incidence of renal events among all treatment groups. On the other hand there were numerically slightly more events listed with acute renal failure, renal function abnormal and uraemia in the zoledronic acid treatment groups as compared to the pamidronate group.

Out of the 217 TIH patients treated, 58 (26.7%) died and 102 (47%) had serious AEs. Only in one case (confusion and hallucinations) did the investigator assess the AE to be related to the study medication.

The number of patients with SAEs irrespective of causality in the different treatment groups is given below.

	Treatment groups				
	Zol < 4 mg	**Zol 4 mg**	**Zol 8 mg**	**Zol 8 mg retreatment**	**Pamidronate 90 mg**
No of patients (N)	33	86	98	70	103
No. of patients who died	10 (30.3)	16 (18.6)	32 (32.7)	9 (12.9)	20 (19.4)
No. of patients with SAE	2 (6.1)	45 (52.3)	55 (56.1)	19 (27.1)	43 (41.7)
No of patients who discontinued due to SAE	0	0	0	0	1 (1.0)
No of patients with treatment related SAE	0	1	0	0	1 (1.0)

Six patients treated with zoledronic acid 4 mg, 1 patient treated with zoledronic acid 8 mg, 2 patients retreated with zoledronic acid 8 mg and 2 patients treated with pamidronate experienced serious renal SAEs. For none of these patients did the investigator consider the renal SAE to be related to the treatment.

Laboratory findings

A slightly higher frequency of low WBC and platelets (4.9% and 5.1% respectively) was seen in the zoledronic acid 4 mg group than in the 8 mg group (1.1% and 1.2% respectively), probably due to the more frequent use of chemotherapy in this group.

The most common grade 3 or 4 haematological values for each treatment group were in absolute lymphocyte count. Similarly, although abnormalities in liver function tests were common, there appeared to be no consistent or systematic effects or differences between the treatment groups in effect on the liver.

Hypocalcaemia and hypophosphataemia occurred more frequently following both doses of zoledronic acid than with pomegranate. No consistent effect of zoledronic acid was observed on serum magnesium, sodium or potassium levels.

Summary of patients with increase in serum creatinine in all TIH trials

	< 4 mg Zol	**4 mg Zol**	**8 mg Zol**	**Retreat 8 mg Zol**	**90 mg Pam**
Total no. of patients (N (%))	33	86	98	70	103
Number (%)of patients with serum creatinine values[1]	33 (100)	86 (100)	96 (98)	68 (97)	100 (97)
Serum creatinine >4.5 mg/dl or increase of 0.5 mg/dl from baseline	2 (6.1)	7 (8.1)	12 (12.5)	4 (5.9)	9 (9.0)
Grade 3 creatinine	0	2 (2.3)	3 (3.1)	1 (1.5)	3 (3.0)
Grade 4 creatinine	0	0	2 (2.1)	1 (1.5)	1 (1.0)

[1]Total number of patients with serum creatinine laboratory values at baseline and at least one post-infusion timepoint.

The overall incidences of increases in serum creatinine greater than 4.5 mg/dl or increases of 0.5 mg/dl from baseline ranged from 5.9% to 12.5 %. Grade 3 or 4 increases in serum creatinine ranged from 0 to 3.1 %.

Safety in special populations

In patients with bone metastases, the AEs reported were similar to those reported in the TIH studies. Rates of deaths and serious adverse events were lower reflecting that TIH patients had more advanced cancer. In patients with bone metastases the frequency of renal AEs was similar for zoledronic acid and pamidronate.

Discussion on Clinical Safety

The renal adverse events were numerically more frequently reported in the zoledronic acid treatment arms and in response to the List of Questions the applicant carried out a number of additional analyses pertaining to renal safety.

There was a numerical greater number and percentage of patients in the zoledronic acid treatment groups with a renal adverse event term 14/86 (16.3%) and 14/98 (14.3%) with zoledronic acid 4 and 8 mg, respectively) when compared to pamidronate (10/103 (9.7%)). There are, however, not any statistically significant differences in the number of patients who experienced a renal adverse event between the treatment groups as shown in the table below.

Study	< 4 mg Zol n (%)	4 mg Zol n (%)	8 mg Zol n (%)	90 mg Pam n (%)	P-Value+ <4 mg Zol vs. 90 mg Pam	P-Value+ 4 mg Zol vs. 90 mg Pam	P-Value+ 8 mg Zol vs. 90 mg Pam
Study 036	N/A	7 (15.2)	8 (15.7)	5 (9.6)	N/A	0.540	0.390
Study 037	N/A	7 (17.5)	6 (12.8)	5 (9.8)	N/A	0.355	0.753
Pooled 036, 037, CJ/HC1	4 (12.1)	14 (16.3)	14 (14.3)	10 (9.7)	0.744	0.194	0.386

+P-Value is from Fisher's Exact Test, two-sided, using a significance level of 0.05.
N/A: not applicable; < 4 mg Zol group only applies to CJ/HC1 stud for TIH

When analysing the narratives of the renal adverse events it was found that in none of these cases was the renal event considered to be study drug related by the investigator. The following conditions were repeatedly found, which could possibly explain the occurrence of the renal event: progression or complications of underlying disease or those of its treatment, concomitant conditions (e.g. infections, cardio-pulmonary failure, diabetes), concomitant potentially nephrotoxic medication, conditions that were present prior to study start (e.g. hyperuricemia, urethral stricture) or mechanical irritation during urinary catheterisation.

The proportion of patients with an increase in serum creatinine of 0.5 mg/dl from baseline or with serum creatinine >4.5 mg/dl in TIH studies showed a tendency to increase with increasing zoledronic acid dose. However, there were no significant differences across the treatment groups in the TIH trials with respect to serum creatinine increases. Another analysis was carried out classifying patients according to specified changes from baseline serum creatinine levels. Deterioration in renal function was defined as an increase of serum creatinine of 0.5 mg/dl (44.2 μmol/l) or more if the baseline serum creatinine level was normal (less than 1.4 mg/dl); an increase of serum creatinine of 1.0 mg/dl (88.4 μmol/l) or more if the baseline serum creatinine level was abnormal; or doubling the serum creatinine level from baseline regardless of baseline serum creatinine level. The results are shown in the table below.

Renal function deterioration in TIH trials

Study	Treatment	Number of patients	Number of patients with renal function deterioration
036	4 mg Zol	46	3
	8 mg Zol	51	9
	90 mg Pam	52	5
037	4 mg Zol	40	3
	8 mg Zol	47	4
	90 mg Pam	51	5
Pooled	Zol 4 mg	86	6
036/037	Zol 8 mg	98	13
	90 mg Pam	103	10

The statistical analysis of these data has not revealed any statistically significant differences between the treatment groups in the number of patients with increases in serum creatinine.

In the completed studies in the treatment of bone metastases there were no statistically significant differences in the number of patients with renal adverse events between the treatment groups. There were no significant differences in the number of patients with serum creatinine changes across the zoledronic acid and pamidronate treatment groups. However patients switched to zoledronic acid 8mg dose had a higher incidence in serum creatinine changes due to the fact that these patients were on the trial twice as long as the original treatment groups and there was a preponderance of multiple myeloma patients in this group.

Analysis of unblinded information on renal safety of ongoing studies in treatment of bone metastases confirm that the dose and infusion time adjustments made in the ongoing trials resulted in a safe use of zoledronic acid, also when chronically administered.

The applicant has committed to provide additional safety data especially regarding renal safety, from ongoing long-term studies testing Zometa 4 mg versus a control administered in a 15 minutes infusion and to provide post-marketing surveillance data accordingly.

When treating TIH patients with zoledronic acid, precautions should be taken to minimise risk factors for renal dysfunction, including rehydration and avoidance of co-administration of aminoglycosides or other nephrotoxic medications, as well as consideration of a more prolonged infusion time. This is reflected in the SPC.

5. Overall conclusions and benefit/risk assessment

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Preclinical pharmacology and toxicology

Overall, the primary pharmacodynamic studies provided adequate evidence that zoledronic acid has antiresorptive effects on osteoclasts and in comparative pharmacodynamic studies zoledronic acid was shown to have a considerably higher potency than pamidronate, the currently most used bisphosphonate for the treatment of TIH.

Overall, the toxicology programme revealed that zoledronic acid was not genotoxic and no tumour inducing effect was observed in the carcinogenicity studies.

In preclinical studies zoledronic acid has toxic effects on the kidney, liver, osseous skeleton, gastrointestinal tract and is a local irritant. The renal NOAEL in rat and dog studies compared with the highest intended human dose of 8 mg varied within narrow limits (between 8 and 1 times the human dose). At higher i.v. doses the toxic effects included inflammation, haemorrhage and erosions in the gastrointestinal tract; hepatocellular necrosis, haemorrhage and inflammation; severe local skin inflammation at the injection site. Hypocalcaemia and hypomagnesiaemia combined with lowered bone alkaline phosphatase were the most prominent laboratory findings.

The total systemic exposure to the highest dose in rats and in dogs was respectively about 1-8 and 6-28 times the highest expected human exposure (8 mg).

Zoledronic acid causes foetal skeleton malformations. Zoledronic acid is contraindicated in pregnant women. This is reflected in the SPC.

Efficacy

The data provided support the claim that doses of 4 mg is effective in the treatment of tumour-induced hypercalcaemia and at least as effective as the highest recommended dose of pamidronate. The results are corroborated by a preplanned metaanalysis of the data from the two pivotal studies, which shows that zoledronic acid is statistically superior to pamidronate.

At a dose of 4 mg as single i.v. infusion, zoledronic acid consistently normalised the serum calcium level in about 90% of the patients treated. The results of the secondary parameters (mean change in corrected serum calcium levels, time to relapse of TIH, duration of response and duration of complete response) are similar to the results of the primary parameter.

No studies have been performed in patients with renal impairment. Dose adjustments are not considered necessary in patients with mild to moderate renal impairment and the use in patients with severe renal impairment is not recommended. This is reflected in the SPC.

Safety

The incidence of AEs is high in TIH trials as expected in this population. The most frequent reported AE were fever, progression of cancer, anaemia, constipation, nausea, and dyspnea. Overall, the safety profile of Zometa including SAEs did not differ from that of pamidronate.

The renal adverse event profile of zoledronic acid and pamidronate is similar. There was no difference between the treatment groups with regard to increases in serum creatinine. Zoledronic acid is renally excreted and therefore could be associated with renal dysfunction, especially in patients with pre-existing renal impairment, a medical history of pre-disposing conditions or concomitant, potential nephrotoxic medications.

The applicant has committed to provide additional safety data especially regarding renal safety, from ongoing long-term studies testing Zometa 4 mg versus a control administered in a 15 minutes infusion, and to provide post-marketing surveillance data accordingly.

Benefit/risk assessment

The overall benefit/risk assessment is considered to be positive considering that

- the clinical efficacy is established compared to the chosen bisphosphonate reference treatment
- zoledronic acid was shown in the pivotal studies to be at least as effective and in the preplanned metaanalysis to be statistically superior to pamidronate, this difference was shown to be clinically relevant.
- The renal adverse event profile of zoledronic acid is comparable to that of the chosen bisphosphonate reference treatment.

Thus, the overall risk/benefit balance for Zometa is positive.

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Zometa in the treatment of tumour-induced hypercalcaemia was favourable and therefore recommended the granting of the marketing authorisation.

6. <u>Additional indication</u>: Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in pateints with advanced malignacies involving bone.

Zometa was authorised on 20 March 2001 for the indication of tumour –induced hypercaliaemia as described in sections 1-5 of this EPAR. Subsequently, the Marketing Authorisation Holder applied for a Type II variation introducing an additional indication for the treatment of osteolytic, osteoblastic, and mixed bone metastases of solid tumours and osteolytic lesions of multiple myeloma, in conjunction with standard antineoplastic therapy.
The recommended dose of Zometa in the treatment of bone metastases and treatment of osteolytic lesions of myeloma is 4 mg reconstituted and further diluted with 100 ml 0.9% w/v sodium chloride or 5% w/v glucose, solution for infusion given as 15 minute intravenous infusion every 3 to 4 weeks.

6.1. Introduction

The development of bone metastases is a common event for cancer patients, in particular for those patients suffering from cancers in the breast, lung or prostate. Pain, pathologic fractures, and neurologic deficits resulting from spinal cord compression are symptoms and complications caused by bone metastases. A central role in the pathogenesis of bone metastases is played by osteoclasts, specialised bone cells which erode mineralised bone by secreting acids and lysosomal enzymes. The disruption of normal bone remodeling seen in this setting develops because tumour cells synthesise and release soluble factors (e.g. PTHrP, growth factors, and cytokines) that stimulate osteoclastic activity. This increased osteoclastic activity leads to focal destruction of bone at the site of osteolytic metastases. Bone metastasis characterised by increased radiographic density is called osteoblastic metastasis. Occasionally, patients might have metastases with a mixed osteolytic and osteoblastic pattern. It appears that osteoblastic metastases are also dependent on osteoclastic activity because the local formation of abnormal new bone is preceded by local osteoclastic resorption.

Bisphosphonates are effective inhibitors of osteoclastic bone resorption and have demonstrated therapeutic efficacy (in terms of reducing skeletal events and/or controlling bone pain) in the treatment of lytic bone disease associated with multiple myeloma, lytic and blastic bone metastases associated with breast cancer, and in controlling bone pain in blastic bone metastases associated with prostate cancer. However, no currently available bisphosphonate has been demonstrated to significantly reduce skeletal events in patients with predominantly blastic metastases. Newer more potent bisphosphonates might be useful in the treatment of bone metastases of prostate cancer.

6.2 Quality aspects: N/A

6.3. Toxico-pharmacological aspects

Additional pharmacological data on zoledronic acid monohydrate were reported from studies done since the initial application for the treatment of TIH. The new data indicated that zoledronic acid is effective against the bone resorption induced by lytic bone metastases arising from malignant tumour cells, as it was in benign models of elevated bone turnover. These effects are probably shared by other bisphosphonates too. It was also suggested that zoledronic acid has anti-tumour and anti-angiogenic properties, both *in vitro* and *in vivo*. Further investigations are needed to confirm the additional pharmacological effects, to establish whether similar properties are shared by other bisphosphonates or are unique to zoledronic acid, and to clarify the mechanism of action.
Zoledronic acid was well tolerated in all the *in vivo* experiments up to the highest dose tested of 250 μg/kg/day. The main issue regarding the additional pharmacological effects of zoledronic acid, and possibly other bisphosphonates, is the different concentration required. The 50% inhibition of viability and growth of endothelial cells appears at 2-7, μM i.e., 130 – 460 times higher than that needed to inhibit osteoclasts (15 nM in a particular murine model, for instance). Moreover, except for human bladder cancer cells, the 50 % inhibition of growth of other tumour lines is observed at much higher concentrations (13-30 μM) than in normal endothelial cells.

6.4. Clinical aspects

Clinical Pharmacology

Pharmacodynamics and pharmacokinetics were evaluated in 64 cancer patients with bone metastases from different primary tumours, enrolled in three PD/PK studies (Table 1).

Table1

Study	Population/design	Treatment	PK and/or PD objective
J001	n=9 cancer patients with bone metastases Parallel group	Zometa: 2 mg, 4 mg, 8 mg single dose; 5 min infusion Single dose	PK: Plasma and urine after single dose PD: Serum and urine markers of bone resorption after single dose
503	n = 36 cancer patients with bone metastases Parallel group	Zometa: 4 mg, 5 min infusion; 4 mg, 8 mg, 16 mg,15 min infusion Single dose	PK: Plasma and urine after single dose PD: Serum and urine markers of bone resorption after single dose
503 E	n = 12 cancer patients with bone metastases Parallel group	Study 503 patients continued on same dose as initial treatment. 2 additional doses	PK: Plasma and urine after 2nd and 3rd dose of Zometa
506	n = 19 cancer patients with bone metastases and with varying degrees of renal impairment.	Zometa: 4 mg, 15 min infusion 3 doses q 4 weeks	PK: Plasma and urine after 3 doses PD: Serum and urine markers of bone resorption after 3 doses

Pharmacodynamics

The effect of zoledronic acid on serum and urinary markers of bone formation and resorption was studied in J001, 505/503E and 506. In view of a large interpatient and interstudy variability in the bone marker data, no clear-cut dose-response and duration-response relationships could be established. In earlier dose ranging studies in patients with Paget's disease of bone and patients with cancer and bone metastases described in the original application, low single and multiple doses (0.1 mg to 0.4 mg) produced no or only marginal inhibitory effects, while higher doses resulted in significant decreases of serum and urinary markers of bone resorption from baseline. The dose seemed to affect the duration of the effect too, as the earlier dose ranging studies, as well as studies J001, 503, and 506 showed, that doses ≥ 4 mg strongly inhibited bone markers up to >3-4 weeks, whereas doses ≤ 2 mg did not have a prolonged effect. When the drug was administered chronically q 3-4 weeks, doses ≥ 4 mg provided the most consistent effect, reducing bone markers of bone resorption throughout the period of treatment.

Pharmacodynamic studies also evaluated renal safety. Renal toxicity seemed to be dose-related. Single zoledronic acid doses of 4 mg to 16 mg had no immediate (24-hour post-dose) renal effect on serum creatinine. Long-term monitoring of serum creatinine (in study 503) revealed no clinically important changes in the 12 patients in the 4 mg q 4 weeks 5-min and 15-min infusion groups. However, 2 out of 12 patients in the 8 mg q 4 weeks group, and 3/12 patients in the 16 mg q 4 weeks group, all with multiple myeloma, showed serum creatinine increases >0.5 mg/dL. Data from study 506 confirmed the lack of deleterious renal effect of three monthly 4-mg doses, irrespective of baseline renal function.

Pharmacokinetics

The pharmacokinetics of zoledronic acid were described in the original application based on studies J001 and 503. The present application included an extension of one of those studies (503E) and study 506. The first addressed the effect of different infusion times; the second the effect of various degrees of renal impairment. Zoledronic acid underwent rapid biphasic disappearance from the systemic circulation, followed by a gradual elimination phase. The longer infusion (15 min vs 5 min) of the 4 mg dose gave an approximately 30% decrease in the post-end-infusion concentrations (C_{end}) but no significant differences in the partial area under the curve (AUC_{0-24h}). The plasma concentrations (C_{max} and AUC_{0-24h}) were essentially dose-proportional in the range of 4-16 mg. Approximately 40% of the dose was excreted in the 24-h urine, with very low urinary excretion thereafter regardless of the dose and duration of infusion. Renal clearance of zoledrenate correlated significantly with creatinine clearance after the first intravenous dose. Accumulation was low after repeated doses.

In patients with mild and moderate renal impairment AUC_{0-24h} was respectively 26-36% and 27-41%, and C_{max} 11-15% and 0-17% higher than normal (these differences were not statistically significant). Within 24 h after infusion 30% to 40% of zoledronic acid was excreted in urine. The differences from patients with normal renal function were small (-19 to 17%) and not significant. There was no accumulation of zoledronic acid in renal impairment. Pharmacokinetics in severe renal impairment was not studied.

Clinical trials

Four pivotal studies were presented (table 2). These are double – blind multicenter to study safety and efficacy of Zometa (iv). All studies were conducted according to GCP.

Table 2 Clinical trials

Study No.	Population	No. of patients randomized	Efficacy Measure (Primary)
Active-controlled trials			
007	Patients with bone metastases breast cancer or multiple myeloma.	Total: 280 Zol 0.4 mg: 68 Zol 2 mg: 72 Zol 4 mg: 67 Aredia: 73	Proportion of patients having radiation to bone.
010	Patients with bone metastases breast cancer or multiple myeloma.	Total: 1648 Zol 4 mg: 564 Zol 8/4 mg:526 Aredia:558	Proportion of patients having at least one SRE (excluding TIH)
Placebo-controlled trials			
011	Patients with any cancer with bone metastases other than breast cancer, multiple myeloma or prostate cancer.	Total: 773 Zol 4 mg: 257 Zol 8/4 mg:266 Placebo:250	Proportion of patients having at least one SRE (excluding TIH)
039	Prostate cancer patients with metastatic bone lesions.	Total: 643 Zol 4mg: 214 Zol 8/4 mg:221 Placebo:208	Proportion of patients having at least one SRE (excluding TIH)

SRE: skeletal-related event, i.e. pathologic bone fractures, spinal cord compression, surgery to bone, radiation therapy to bone (including the use of radioisotopes), or change in antineoplastic therapy to treat bone pain (latter specific to 039).

Dose-response

One active-controlled (pamidronate) dose-finding study (007) was conducted. Patients were randomised to 0.4, 2, or 4 mg zoledronic acid (5-min infusion), or pamidronate 90 mg given as a 2-hour IV infusion every 4 weeks for 9 months. The study tested whether the proportion of patients requiring radiation to bone in each group was significantly less than 30%. All treatment groups but zoledronic acid 0.4 mg met this criterion. The doses used in efficacy trials (4-8 mg) were higher than the minimum effective dose identified in 007. The infusion time tested (5 min) had to be prolonged to 15 min in order to minimise the renal toxicity that appeared in several patients exposed to these dosages.

Efficacy / Safety

Pivotal efficacy data were provided by one non-inferiority trial vs pamidronate (010), and two superiority trials vs placebo as illustrated in table 2:

The primary efficacy variable in each study was the proportion of patients experiencing at least one skeletal-related event (SRE), which included radiation therapy to bone, surgery to bone, pathological bone fractures, spinal cord compression, or change of antineoplastic therapy to treat bone pain (only in study 039). Secondary endpoints were: time to progression of disease; time to progression of bone lesions; objective bone lesion response from radiological studies; pain score (Brief Pain Inventory);

analgesic score; ECOG performance scores; bone mineral density; and biochemical markers of bone turnover. TIH was included as an SRE for some secondary efficacy analyses.
In view of the increased incidence of renal adverse events the MAH amended ongoing trials and increased the initial infusion time for zoledronic acid from 5 min to 15 min, and the infusion volume from 50 mL to 100 mL. Following further safety analysis in studies 039, 010, and 011 (then ongoing), the Data Safety Monitoring Board (DSMB) and an independent board composed of nephrologists, recommended that all patients randomised to 8 mg zoledronic acid be switched to 4 mg in June 2000. These subsets of patients, referred to as "8/4 mg groups", were not included in the primary analyses of the relevant trials, but results are reported for this group as well.

Study 010

The company sought scientific advice from European health authorities on the design of 010. On the basis of this advice, the MAH designed the statistical non-inferiority parameters of zoledronic acid 4 mg compared to pamidronate 90 mg so that 'the upper bound of a two-sided 95% confidence interval for the difference on the primary endpoint is below the non-inferiority margin of 8%. The 8% margin was chosen, since the intention was to establish the safety and efficacy of zoledronic acid in the treatment of bone metastases across a broad spectrum of patients (5-6% had conversely been suggested by the health authorities). Pamidronate was chosen as a comparator since it is considered standard treatment for breast cancer and MM patients with cancer-related bone lytic lesions. Superiority tests were 2-sided (5% level).
The treatment groups were well matched at baseline for demographic and disease characteristics. Patients treated with zoledronic acid 4 mg had fewer SRE than those treated with pamidronate (-2%, 95% CI -7.9% to 3.7%), (Table 3) and the upper limit of the 95% CI of the difference was less than the specified non-inferiority margin of 8%.

TABLE 3 Proportion of patients with any SRE at 13 months excluding TIH

		95% C.I. for the difference in SRE	
	Proportion of patients with at least 1 SRE	Zometa 4 mg	Zometa 8/4 mg
Excluding TIH			
Pamidronate 90 mg	257/555 (46%)	(-7.9%, 3.7%)	(-6.1%, 5.8%)
Zometa 4 mg	248/561 (44%)	-	(-3.9%, 7.9%)
Zometa 8/4 mg	242/524 (46%)	-	-
Including TIH			
Pamidronate 90 mg	260/555 (47%)	(-8.1%, 3.6%)	(-6.4%, 5.5%)
Zometa 4 mg	250/561 (45%)	-	(-4.1%, 7.7%)
Zometa 8/4 mg	243/524 (46%)	-	-

The proportion of patients experiencing at least one skeletal related event (SRE), excluding tumour-induced hypercalcemia (TIH), up to Month 13 is shown in Table 4. The proportions were 44% and 46% for the ZOMETA 4 mg group and the AREDIA 90 mg group, respectively.

TABLE 4 Proportion fof Ptients with any SRE at 13 months including TIH at 13 months

		95% C.I. for the difference	
Stratum	Proportion	Zol 4 mg	Zol 8/4 mg
Multiple myeloma			
AREDIA 90 mg	82/167 (49%)	(- 12.6%, 8.4%)	(- 10.6%, 11.1%)
Zol 4 mg	86/183 (47%)	-	(- 8.2%, 13.0%)
Zol 8/4 mg	79/160 (49%)	-	-
Breast cancer with chemotherapy			
AREDIA 90 mg	78/181 (43%)	(- 9.0%, 11.6%)	(- 7.0%, 13.8%)
Zol 4 mg	79/178 (44%)	-	(- 8.3%, 12.6%)
Zol 8/4 mg	80/172 (47%)	-	-
Breast cancer with hormonal therapy			
AREDIA 90 mg	97/207 (47%)	(- 15.0%, 4.3%)	(- 13.4%, 6.1%)
Zol 4 mg	83/200 (42%)	-	(- 8.1%, 11.5%)
Zol 8/4 mg	83/192 (43%)	-	-
Total			
AREDIA 90 mg	257/555 (46%)	(- 7.9%, 3.7%)	(-6.1%, 5.8%)
Zol 4 mg	248/561 (44%)	-	(-3.9%, 7.9%)
Zol 8/4 mg	242/524 (46%)	-	-

In the stratum of breast cancer patients receiving hormonal therapy, the difference between ZOMETA 4 mg and AREDIA was –5.4%, which was the largest difference observed in any of the 3 strata in this study. The median time to first occurrence of any SRE (including TIH) was also similar between treatment groups. The mean SMR of any SRE (including TIH) up to month 13 was slightly lower for the ZOMETA groups than for the AREDIA 90 mg group, but differences between treatments were not statistically significant. The specific SRE that mostly accounted for the observed tendency to reduction was "radiation therapy" which may depend on subjective decisions and, though important itself, is less so than other endpoints such as fractures. The proportion of patients with spinal cord compression, surgery to bone, and hypercalcemia was very small in all treatment groups.

TABLE 5	Zol 4 mg	Zol 8/4 mg	Aredia
Type of SRE	N=561	N=524	N=555
Proportion of pathological fracture	200/561 (36%)	179/524 (34%)	203/555 (37%)
Proportion of vertebral fracture	109/561 (19%)	84/524 (16%)	108/555 (19%)
Proportion of non-vertebral fracture	145/561 (26%)	135/524 (26%)	148/555 (27%)
Proportion of spinal cord compression	11/561 (2%)	12/524 (2%)	16/555 (3%)
Proportion of radiation therapy to bone	85/561 (15%)	112/524 (21%)	112/555 (20%)
Proportion of surgery to bone	21/561 (4%)	15/524 (3%)	31/555 (6%)
Proportion of hypercalcemia	7/561 (1%)	5/524 (1%)	12/555 (2%)

No clinically or statistically significant differences between treatment groups were observed for all secondary efficacy endpoints, including the composite pain score, the analgesic score and the quality of life assessment.
217 out of 1643 patients (13.2%) died. Mortality did not differ significantly in the treatment groups. Drug-related SAE were more frequent in the zoledronic acid 8/4 group than with zoledronic acid 4 mg and pamidronate 90 mg (4.6% vs. 1.8 and 1.4%). Renal SAE were somewhat different even in patients randomised after the infusion amendment: 1.9% in the zoledronic acid 8/4 mg group (acute renal failure being the most common, 1.3%) compared with 0.5% with 4 mg and 0.2% with pamidronate. Renal function deterioration measured by serum creatinine levels was more frequent in the zoledronic acid groups (13.2 and 20.4 %) than with pamidronate (6.7%). After the 15-minute infusion amendment, proportions of those experiencing deterioration were similar with 4 mg and pamidronate (8.8 vs. 8.2%), though still higher in the 8/4 mg group (18.6%).

Study 039
The use of placebo in the control arm is considered appropriate. The treatment groups were well matched in terms of demographic variables and for most disease variables, but there were some

indications of slightly more severe disease in the 8/4 mg zoledronic acid group, namely higher baseline serum levels of prostate-specific antigen (PSA), and slightly higher percentages of patients with ECOG scores over 2 and higher analgesic scores. The zoledronic acid 8/4 mg group also had a greater percentage of patients with abnormal renal function (serum creatinine ≥ 1.4 mg/dL) at baseline (21.6% *versus* 19.2% in the zoledronic acid 4 mg group and 15.9% in the placebo group).

As shown in Table 6, zoledronic acid (4 mg) was more effective than placebo in preventing SRE. In this study, only two patients experienced TIH, and both of them also had other SRE; analyses of SRE including and excluding TIH are therefore identical. The difference in SRE rates between zoledronic acid 4 mg and placebo was evident after only three months of treatment, a clinically important finding.

Table 6: SRE excluding TIH		95% C.I. for the difference	
	Proportion n/N	Zometa 4 mg	Zometa 8/4 mg
Placebo	92/208 (44%)	(-20.3%, -1.8%)	(-15.1%, 3.6%)
Zometa 4 mg	71/214 (33%)	-	(-3.7%, 14.3%)
Zometa 8/4 mg	85/221 (38%)	-	-

It is noteworthy that zoledronic acid 8/4 mg did not achieve the same advantage as the 4 mg dose. This lack of consistency was surprising as one would expect the higher doses to produce better efficacy, though possibly more toxicity.
The incidence of all SRE (including pathological, vertebral, and non-vertebral fractures) was consistently lower with zoledronic acid 4 mg than placebo (Table 7).

Table 7 Incidence of SREs in study 039	Zol 4 mg	Zol 8/4 mg	Placebo
SRE	(N =214)	(N =221)	(N=208)
Pathologic fracture[1] n (%)	28 (13%)	33 (15%)	46 (22%)
Vertebral fracture n (%)	8 (4%)	17 (8%)	17 (8%)
Non-vertebral fracture n (%)	22 (10%)	22 (10%)	33 (16%)
Spinal cord compression n (%)	9 (4%)	11 (5%)	14 (7%)
Radiation to bone n (%)	49 (23%)	53 (24%)	61 (29%)
Surgery to bone n (%)	5 (2%)	6 (3%)	7 (3%)
Change of antineoplastic therapy n (%)	10 (5%)	18 (8%)	14 (7%)
Hypercalcemia n (%)	0	0	2 (1%)

[1] Patients with vertebral and/or non-vertebral fractures are counted only once for total pathological fractures..

Among the secondary outcome measures, time to the first occurrence of any SRE was significantly longer with zoledronic acid 4 mg than placebo. The median time to the first occurrence of a SRE for the zoledronic acid 4 mg group (≥ 420 days) was 99 days longer than with placebo. However, the median time to progression of bone lesions was similar in the three treatment groups, and the median time to overall disease progression was also the same (84 days).
During the study or within 28 days of last dose of the study drug 114 patients died. Mortality was similar in the zoledronic acid 4 mg group (14.5%) and the placebo group (16.8%); the zoledronic acid 8/4 mg treatment group had higher mortality (22.0%). The most frequent cause of death was aggravated malignant neoplasm, but four patients from the 8/4 mg group died secondary to renal or urinary disorders.
The incidence of AE was similar in all groups, although some gastrointestinal AE such as nausea, vomiting, constipation, and anorexia were more frequent in the zoledronic acid 8/4 mg group. In this group renal AE were also more frequent than in the other groups, patients randomized before or after the 15-minute infusion amendment.
Renal function deterioration evaluated according to serum creatinine levels was more frequent in the zoledronic acid 4 and 8/4 mg groups than in the placebo group both before the 15-minute infusion amendment (19.8%, 33.3%, and 9.9%), and after (15.2%, 20.7%, and 11.5%).

Study 011

20 different primary tumour types were included in this study with non-small cell lung cancer being the predominant primary cancer (49%). The most frequent among others were renal cell carcinoma (10%), small cell lung cancer (8%), colorectal cancer (7%). The use of placebo in the control arm is

considered appropriate. The treatment groups were balanced with respect to demographic and disease characteristics at baseline. The proportion of patients experiencing at least one SRE, including and excluding TIH, is shown in the Table below. Although a 6% reduction in SRE was observed for Zometa 4 mg group, this was not a statistically significant difference from placebo (95% CI-15.2% to 1.9%).

Table 8 Proportion of patients having any SRE		95% C.I. for the difference	
	Proportion n/N	Zometa 4 mg	Zometa 8/4 mg
SRE excluding TIH			
Placebo	111/250 (44%)	(-15.2%, 1.9%)	(-18.2%,-1.4%)
Zometa 4 mg	97/257 (38%)	-	(-11.4%, 5.1%)
Zometa 8/4 mg	92/266 (35%)	-	-
SRE including TIH			
Placebo	117/250 (47%)	(-17.7%,-0.5%)	(-20.3%,-3.4%)
Zometa 4 mg	97/257 (38%)	-	(-11.0%,5.5%)
Zometa 8/4 mg	93/266 (35%)	-	-

Table 9: Proportion of patients having any SRE (-TIH) up to month 9 by stratum and treatment group in 011

		95% C.I. and P-value for the difference	
	Proportion	Zol 4 mg	Zol 8/4 mg
Lung cancer			
Placebo	59/130 (45%)	(-15.6%, 8.4%), p=0.557	(-23.3%, 0.1%), p=0.053
Zol 4 mg	56/134 (42%)	-	(-19.5%, 3.5%), p=0.175
Zol 8/4 mg	47/139 (34%)	-	-
Other solid tumors			
Placebo	52/120 (43%)	(-22.2%, 2.2%), p=0.110	(-20.1%, 4.3%), p=0.205
Zol 4 mg	41/123 (33%)	-	(-9.7%, 13.9%), p=0.727
Zol 8/4 mg	45/127 (35%)	-	-
Total			
Placebo	111/250 (44%)	(-15.2%, 1.9%), p=0.127	**(-18.2%,-1.4%), p=0.023**
Zol 4 mg	97/257 (38%)	-	(-11.4%, 5.1%), p=0.452
Zol 8/4 mg	92/266 (35%)	-	-

Proportion = (no. of patients with the event)/(total no. in the group) by month 9; Confidence interval for the difference (treatment labeled in the column minus row) of percent of patients with events.

The incidence of all SRE (with the exception of "surgery to bone") was consistently lower with zoledronic acid 4 mg than placebo, but only the difference between ZOMETA 8/4 mg and placebo was statistically significant. If TIH is included as an SRE, the proportion of patients having SREs in the ITT population as a whole became statistically significantly lower in both ZOMETA treatment groups than for placebo. However, statistical significance was not achieved for the lung cancer patients stratum. Subgroup analysis according to the pre- and post-15 minutes amendment shows that the effect of duration of infusion was negligible.

The skeletal morbidity rate (number of SREs per year) was 2.24 in Zometa 4 mg group and 2.73 in placebo group. With regard to secondary endpoints, zoledronic acid 4 mg delayed the time to first SRE by 67 days compared to placebo. Time to progression of bone lesions and progression of disease with zoledronic acid 4 mg were also longer: the median time to progression of bone lesions (145 days) and median time to progression of disease (89 days) were also longer than with placebo (109 days and 84 days, respectively), but these differences were not statistically significant.

Approximately one third of the patients in each of the treatment groups died during the study or within 28 days of the last dose of study drug. The time to death was similar for all treatment groups. The most frequent cause of death was progression of the underlying cancer. SAE were reported for similar percentages of patients in the zoledronic acid and placebo treatment groups. Renal-related AE were more common in the zoledronic acid 4 mg group than in the placebo group before the 15-minute infusion amendment, but the frequency was similar after the amendment. However, some specific AE were more frequent in the zoledronic acid groups, particularly increased serum creatinine (4.0% in the 8/4 mg group, 2.7% in the 4 mg group and 0.5% in the placebo group), and acute renal failure (3.5%, 2.2% and 0.5%, respectively). Most SAE appeared to be related to the underlying disease, and most

were judged not to be study drug-related by the investigators. Renal SAE such as acute renal failure, irrespective of causality, occurred at a higher rate in the zoledronic acid patients: 7.2% in the 8/4 mg group, 5.1% in the 4 mg group and 3.6% in the placebo group.

Discussion of clinical efficacy

The composite primary endpoint reduction in the proportion of patients with any skeletal related events (SRE) as well as each type of event included in the composite endpoint are acceptable clinical measures for the impact of bone metastases for the patient. Although statistical significance has been demonstrated in some of the clinical trials the absolute differences between proportions are small and it is difficult to assess the true clinical benefit of such reductions. The important issue is, therefore, whether an *absolute* reduction in the proportion of patients with SRE from 44% (placebo group study 011) to 38% (Zometa 4 mg group study 011) or an *absolute* reduction in the proportion of patients with SRE from 44% (placebo group study 039) to 33% (Zometa 4 mg group study 039) represents a relevant clinical benefit regardless of the level of statistical significance. The effects on SRE are not easily translated into beneficial effects such as less palliative radiotherapy, less surgery because of pathological bone fracture or medullary compression. The data provided suggest that, overall, symptomatic SRE can be better controlled with Zometa 4mg, but none of the individual outcomes considered (less radiotherapy, less surgery, less cord compression) have been shown to improve compared with placebo, although any numerical difference may not be statistically significant. It is acknowledged that a prolongation of the time to first SRE by approximately 2 months and 3 months with Zometa (Study 011 and Study 039) is very supportive of clinical benefit. Likewise, the pre-planned Anderson-Gill analysis taking into account the time to each SRE further supports the consistency of the results. Improvement in quality of Life and pain control are postulated and probable but not directly supported by the data.

In study 010 (breast cancer and multiple myeloma) the MAH has compared ZOMETA with an approved active substance, AREDIA, and non-inferiority as regards efficacy has been documented. Even with a non-inferiority margin of 8%, this phase III trial has provided sufficient robust evidence for comparable activity for ZOMETA versus AREDIA.

In study 039 (prostate cancer) ZOMETA demonstrated statistically significant efficacy in reducing skeletal morbidity due to bone metastases in prostate cancer. However, this study is not without problems. It is not clear why the study failed to show efficacy for the 8/4 mg group. In contrast, ZOMETA 4 mg was statistically superior to placebo with proportions of patients with SRE of 33% and 44%, respectively.

Clinical study 011 supporting the indication “mixed bone metastases of solid tumours” failed to show statistical significance for the primary endpoint at the recommended dose of 4 mg. Moreover, a subgroup analysis, the same clinical study was not powered to detect statistical significance for, failed to show efficacy for both ZOMETA doses (4 mg and 8/4 mg) in patients with non-small cell lung cancer (approximately 50% of the patients included in the study). Results of the preplanned Anderson-Gill analysis, which takes into account the clinically meaningful endpoints total number of SREs and the time to each SRE showed that Zometa 4 mg reduced the overall rate of occurrence of SREs by approximately 27% compared to placebo. In the lung cancer stratum, the risk reduction of 27% with Zometa 4 mg versus placebo nearly reached statistical significance (p=0.06).

During an oral explanation by the MAH with the CPMP the efficacy in patients with bone metastases in solid tumours other than breast or prostate cancer (study 011) was not achieved for the primary endpoint of the proportion of patients with SREs. Secondary endpoints such as time to first skeletal event should also be considered important for such patients with short life expectancy. Skeletal morbidity rate was reduced by 11% if TIH is not included as an event and by 18 % if TIH is included. The decision to treat a patient should also take into consideration that the time needed for a treatment effect can be 2-3 months. The MAH discussed the possible impact of the large limits allowed for non-inferiority on documentation of efficacy of Zometa compared to pamindronate. Although study 010 could have supported claims of non-inferiority with as little as 40 % retention of the pamindronate effect, study results demonstrate an effect of 116% (95% CI: 72% to 159%) relative to pamindronate

in earlier placebo-controlled trials. The MAH provided additional analysis results of study 010 similar to those provided for studies 011 and 039; breakdown of individual events in each treatment group and an Andersen - Gill multiple event analysis was performed. Findings from these analyses support the objective of non-inferiority.

Furthermore, the MAH presented a table indicating the proportion of prostate cancer patients having each component of SRE by lesion type (lytic, blastic, other) in study 039. The treatment effects were less pronounced in patients with blastic lesions.

Discussion of clinical safety

The primary safety population consisted of 3,337 patients (2,251 treated with ZOMETA) from 1 phase II and three randomized, controlled bone metastases studies. The supportive safety population consists of additional 493 patients from other completed secondary (phase I or open-label) bone metastases trials.

With regards to renal safety, it seems that the increase in infusion time to 15 minutes and decrease in dose from 8 mg to 4 mg ZOMETA has provided evidence that the renal profile of ZOMETA is now similar to pamidronate 90 mg and placebo. The individual changes in serum creatinine seen in these ongoing trials suggest that the changes are reversible and for the 4 mg ZOMETA group have become uncommon with the 15 minutes infusion time. It can be concluded that 8 mg dose is clearly associated with a higher risk of renal function, but for the recommended dose of 4 mg the risk of renal toxicity associated with Zometa as compared with either placebo or pamindronate appears to be justified and manageable.
Other adverse events suspected to be drug- related are presented in table .Nausea, fatigue, pyrexia, diarrhea, myalgia, arthralgia, cough, and headache occurred more frequently in the ZOMETA 4 mg, 8/4 mg, and AREDIA groups than in the placebo group. A dose relationship for ZOMETA was observed for hypophosphatemia and hypokalemia notable values.

Table 9: No. of patients with AEs (≥ 3%) most frequently suspected to be study drug-related, primary safety population

	Zol 4 mg (n = 145)	Zol 4 mg (n = 1099)	Zol 8/4 mg (n = 1007)	AREDIA (n = 631)	Placebo (n = 455)
Total no. of patients with an AE suspected to be drug-related	67 (46.2)	387 (35.2)	389 (38.6)	221 (35.0)	92 (20.2)
Adverse events (preferred term)					
Bone pain	24 (16.6)	100 (9.1)	82 (8.1)	54 (8.6)	18 (4.0)
Pyrexia	9 (6.2)	79 (7.2)	89 (8.8)	34 (5.4)	8 (1.8)
Nausea	8 (5.5)	64 (5.8)	71 (7.1)	44 (7.0)	20 (4.4)
Fatigue	8 (5.5)	45 (4.1)	43 (4.3)	31 (4.9)	7 (1.5)
Influenza-like illness	7 (4.8)	40 (3.6)	38 (3.8)	28 (4.4)	3 (0.7)
Headache NOS	5 (3.4)	37 (3.4)	20 (2.0)	18 (2.9)	3 (0.7)
Myalgia	7 (4.8)	35 (3.2)	31 (3.1)	17 (2.7)	5 (1.1)
Arthralgia	15 (10.3)	33 (3.0)	32 (3.2)	19 (3.0)	3 (0.7)
Rigors	3 (2.1)	31 (2.8)	42 (4.2)	21 (3.3)	3 (0.7)
Vomiting NOS	1 (0.7)	29 (2.6)	27 (2.7)	22 (3.5)	10 (2.2)
Pain NOS	5 (3.4)	18 (1.6)	16 (1.6)	20 (3.2)	1 (0.2)
Back pain	6 (4.1)	9 (0.8)	12 (1.2)	8 (1.3)	0 (0.0)

6.5. Benefit/ risk ratio and overall conclusion

In clinical trials 011 (mixed bone metastases from solid tumours) and 039 (prostate cancer), statistical significance with regard to the primary endpoint: reduction in the proportion of patients with any skeletal related events (SRE) has been demonstrated, however the absolute differences between proportions are small and the true clinical benefit of such reductions is difficult to assess.

Symptomatic SREs can be better controlled with Zometa, but there was no evidence of improvement in individual outcomes. Nevertheless, it is acknowledged that a prolongation of the time to first SRE by approximately 2 months and 3 months with Zometa in studies 011 and 039 respectively is very supportive of clinical benefit. Improvement in quality of Life and pain control are postulated and probable but not directly supported by the data. In study 010 (breast cancer and multiple myeloma patients) there is robust evidence of comparable activity for Zometa versus Aredia.

In overall, ZOMETA appears to have the expected safety profile for a bisphosphonate that is used in patients with advanced cancer. Renal safety is the most important safety aspect and this issue was discussed extensively during the assessment and approval of the TIH indication. The requested reassurance data on renal safety have been provided and it has been documented that ZOMETA 4 mg can be safely administered with 3-4 weeks interval as an 15 minutes IV infusion..

The MAH committed to provide PK data (even using limited sampling) after more than 3 cycles since patients may be treated for more than one year.

Based on the CPMP review of data on safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Zometa in the following indication:

> Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in patients with advanced malignancies involving bone,

Was favourable and therefore recommended the Type II variation to the terms of the marketing authorisation.