SCIENTIFIC DISCUSSION

1. Introduction

The adult form of Paget's disease of the bone (PDB) is a common condition with a strong genetic component, characterised by focal increases in bone turnover, involving one or more bones throughout the skeleton. In affected areas, excessive osteoclastic bone resorption is followed by disorganised bone formation resulting in low-quality (woven) bone of reduced mechanical integrity. The cited prevalence of PDB varies considerably by geographic area and criteria for diagnosis. A positive family history increases the risk markedly, but the exact mode of inheritance remains to be established.

While the majority of patients remain asymptomatic, active PDB is associated with bone pain and risk of bone deformity, pathological fracture, osteoarthritis, and deafness. There is also a small but defined risk of the development of osteosarcoma. The activity of PDB is reflected in serum and urine levels of biochemical markers of bone turnover. Currently available literature does not provide any clear evidence that any marker is superior to serum total alkaline phosphatase (SAP) for sensitivity or specificity.

Pharmacological therapy of PDB aims to reduce bone turnover and is currently based on the use of second- or third-generation bisphosphonates. It should be noted that none of the treatments used in PDB have been shown to prevent complications such as deafness, fracture or deformity, or alter the natural history of the disease.

The Applicant Novartis Europharm Ltd submitted a complete stand-alone application for Marketing Authorisation for Aclasta for the proposed indication of "Treatment of Paget's disease of the bone". The active substance of Aclasta, zoledronic acid (zoledronate)is a nitrogen-containing bisphosphonate with a mode of action involving inhibition of the enzymatic activity of farnesyl diphosphate synthase (FPP synthase). Inhibition of FPP synthase is considered a main mechanism by which osteoclast activity is inhibited and apoptosis is promoted. Zoledronic acid, has been previously approved within the EU as Zometa (EMEA/H/C/336) for the treatment of malignancy-induced hypercalcaemia and prevention of skeletal-related events in patients with advanced malignancies involving bone. In the oncology indications, zoledronic acid is given repeatedly as an intravenous infusion of 4 mg over at least 15 minutes every 3-4 weeks. For Paget's disease, on the other hand, zoledronic acid is proposed to be given as a single intravenous infusion of 5 mg to induce a long-lasting biochemical remission. The Applicant uses a separate invented name and label for the benign indication to avoid any potential confusion between the different doses and dosing interval, compared with the oncology indications.

2. Quality aspects

Introduction
Aclasta contains zoledronic acid as the active substance. It is presented as a clear, colourless aqueous solution for infusion containing 5.33 mg /100 ml of zoledronic acid monohydrate, which is equivalent to 5 mg /100 ml of anhydrous zoledronic acid.

Other ingredients include mannitol, sodium citrate and water for injections. The container is a plastic vial with rubber stopper and aluminium with flip off component. An overfill is filled to the vials to permit withdrawal of the labelled amount of zoledronic acid.

Drug Substance
The active substance is identical to the one used for the centrally authorised product Zometa, powder and solvent for solution for infusion (EMEA/H/C/336). The details of the manufacturing process, purification, specifications and stability have already been assessed for the above-mentioned application and are briefly summarised below.

The chemical name of zoledronic acid is (1-hydroxy-2-imidazol-1-ylphosphonoethyl) phosphonic acid.

The active substance does not contain any chiral centers and thus it does not exhibit any optical isomers. The monohydrate form of zoledronic acid was selected, because of its good chemical and physical stability in the solid state at ambient temperature. The structure of the active substance has been confirmed using an array of suitable methods.

- Manufacture

The active substance is synthesised by multiple steps and purified. The levels of the impurities are supported by the results of toxicological studies and appropriate specifications have been set.

- Specification

The active substance specification is in accordance with the one accepted for the powder for solution for infusion formulation.

Drug Product

- Pharmaceutical Development

Due to the poor absorption of zoledronic acid after oral administration the pharmaceutical development was aimed at developing a parenteral formulation. In order to facilitate the administration to patients by health professionals a "ready to infuse-solution" was found more safe and easy to use. The excipients used are mannitol and water for injection. The amount of excipients has been optimised to develop an isotonic solution and a stable buffering system for zoledronic acid. All excipients used in the product are of non-animal origin and comply with their corresponding European Pharmacopoeia monographs.

The immediate packaging materials are commonly used for these types of formulations and are made from the same material as the one used for Zometa 4 mg/5ml concentrate for infusion (plastic colourless vials with bromobutyl rubber stoppers).

- Manufacture of the Product

The manufacturing process is a standard process for these kind of formulations and sterilisation is performed in line with the requirements of the Ph.Eur. All critical process parameters have been identified and controlled by appropriate in process controls. The validation report from production scale batches demonstrates that the process is reproducible and provides a drug product that complies with the in-process and finished product specifications.

- Product Specification

The specification for the finished product at release and shelf life includes tests for appearance, identification, assay, pH, impurities, particulate matter, degradation products, bacterial endotoxins and sterility. All tests included in the specification have been satisfactorily described and validated.
Batch analysis data from 6 batches have been presented. All batches met the test limits as defined in the release specification and test methodology valid at the time of batch release.

- Stability of the Product

Stability studies were carried out according to ICH requirements.

In all cases the stability results presented were satisfactory and support the proposed shelf life for the commercially packaged product under the conditions specified in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

The quality of Aclasta is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorization. There are no major deviations from EU and ICH requirements.

The active substance is the same as the one used in the already centrally authorised product Zometa, powder and solvent for solution for infusion (EMEA/H/C/336). It is well characterised and documented. The excipients are commonly used in these types of formulations and comply with Ph. Eur. requirements. The packaging material is commonly used and well documented. The

manufacturing process of the finished product is a standard process that has been adequately described. Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

3. Non-clinical aspects

Introduction
Pivotal non-clinical pharmacology and toxicology studies, conducted between 1987 and 2004, were in accordance with principles of GLP.

Pharmacology

- Primary pharmacodynamics (*in vitro/in vivo*)

In cultures of freshly isolated rabbit and human osteoclasts zoledronic acid (10-100 μM) induced morphological features similar to apoptosis and caspase-3-like activation. Osteoclastogenesis was inhibited in a dose-dependent manner with an IC_{50} of 15 nM *in vitro* in cultures of murine bone marrow cells stimulated to form osteoclasts by addition of macrophage-colony stimulating factor and ligand for the receptor activator NF-κB (RANKL).

Zoledronic acid also inhibited proliferation of human foetal osteoblastic cell line (hFOB) with an IC_{50} of 40 μM. In cultures of primary human trabecular osteoblasts, zoledronic acid increased osteoprotegerin, a decoy receptor that binds to RANKL and inhibits interaction with RANK, inhibiting osteoclastogenesis.

Inhibition of bone loss was investigated in ovariectomised (OVX) estrogen-deficient rats and monkeys. Efficacy and bone safety of zoledronic acid were evaluated in a 12-month study in the rat and in a 16-month study in the rhesus monkey. Treatment started immediately after ovariectomization in both studies and subcutaneous doses of up to 12.5 μg/kg/week were used. The cumulative doses were 390 μg/kg in rat and 862.5 μg/kg in monkey, as compared with an approximately 100 μg/kg human yearly dose. A higher skeletal turnover in rat and possibly in monkey could result in that drug exposure in bones in OVX animals might not have reached human exposure levels. These issues as well as potential indications of "frozen bone", were discussed during CHMP scientific advice procedures. It was concluded that the available studies plus an 8-month study in OVX rats (see below), together with clinical data could be accepted as sufficient for addressing bone safety in non-oncology indications.

Parameters assessed in the 12- and 16-month studies included bone mass, bone mechanics, bone histomorphometry and biochemical markers of bone metabolism. In the rat, a dose of 1.5 μg/kg/week often resulted in full efficacy as determined by the parameters studied. Bone mechanical parameters, femoral neck fracture, femur 3-point bending and vertebra compression were dose-dependently increased by zoledronic acid towards levels in intact controls.

Comparable effects were noted in monkey, but mechanical parameters did not attain statistical significance. Histomorphometry of vertebral cancellous bone showed that zoledronic acid increased trabecular area, trabecular number, node number in comparison with OVX control, while trabecular separation was decreased. Bone formation rate and mineral apposition rate were decreased dose-dependently by zoledronic acid. In monkey, ovariectomization had no remarkable effect on histomorphometric parameters of cancellous bone in the vertebra, radius and femur at week 69. Cancellous bone structure was not affected by zoledronic acid, but the activation frequency and bone formation rate were decreased at all doses, while mineral apposition rate was decreased at the high dose (12.5 μg/kg/week), only. In cortical bone, zoledronic acid had no effect on mineral apposition rate or on total Haversian bone. Porosity and bone formation rate were decreased by zoledronic acid in cortical bone of femoral shaft.

An 8-month study in OVX rats given a single iv injection of 0.8, 4, 20, 100 or 500 μg/kg of zoledronic acid or 200 μg/kg of alendronate 4 days prior to ovariectomy was conducted to evaluate the duration of a bone protective effect. Zoledronic acid dose-dependently reduced plasma osteocalcin. At week

32, levels were suppressed in the 100 and 500 µg/kg groups, only. Bone mineral density analysis of the proximal tibial metaphysis indicated that zoledronic acid from 20 µg/kg protected completely against bone loss up to 24 weeks. Alendronate had a similar but weaker effect. Analysis of cortical and cancellous bone separately showed that 4 µg/kg partially protected against cortical thinning up to 12 weeks and against cancellous bone loss for at least 32 weeks. Histomorphometric parameters in cancellous bone of the proximal tibia were not affected by zoledronic acid up to doses of 20 µg/kg, while the two higher doses decreased bone formation to 45 and 21%, respectively, of the sham control level. Zoledronic acid dose-dependently prevented loss of cancellous bone of proximal tibia as indicated by 3D-µCT images at week 32. Zoledronic acid prevented loss of strength of femoral metaphysis and diaphysis with effects at 20 µg/kg generally comparable with 200 µg/kg of alendronate. High doses of zoledronic acid 100-500 µg/kg tended to increase bone strength above sham control levels.

In a study in male 7-week old rats with bone histomorphometry assessed using static and dynamic parameters, mineralised bone tissue was increased dose-dependently by zoledronic acid. There was a dose-dependent decrease in the osteoid perimeter in the cancellous bone. The significance of the osteoid changes is unclear but could result from a decrease in the activation frequency of new remodelling bone units. Retardation of longitudinal bone growth was reported but apparently not related to a mineralisation disturbance of the growth plate.

Mineralisation parameters in monkey indicated that a continued loss of bone density (humerus and vertebra) occurred in both intact control and OVX control and was counteracted in OVX animals by doses ≥2.5 µg/kg. Reduction of the central and distal radius bone mineral density was prevented by zoledronic acid in OVX at 12.5 µg/kg/week. Zoledronic acid dose-dependently increased carbonate content, reduced serum calcium at week 26 at the high dose and increased parathyroid hormone (PTH) at week 52. Femoral neck stiffness was dose-dependently increased and activation frequency of new remodelling sites decreased. No evidence of a mineralising defect, no osteoid accumulation, and no woven bone was reported. The decline of bone mineral density (BMD) of the distal and central radius in both OVX and control groups was unexpected and could not be explained, however, it was prevented by doses of 12.5 µg/kg/week. Additionally, zoledronic acid dose-dependently decreased levels of biochemical markers of osteoblastic bone formation (alkaline phosphatase, osteocalcin) and of osteoclastic bone resorption (N-telopeptide, pyridinoline), compared with OVX control. In general, similar effects were seen in both rat and monkey.

- Safety pharmacology

Safety pharmacology studies of zoledronic acid covered major organ systems such as the cardiovascular and autonomic, respiratory, gastrointestinal and renal systems, and no remarkable effects were reported.

- Pharmacodynamic drug interactions

No studies were submitted.

Pharmacokinetics

The pharmacokinetics of zoledronic acid has been studied in rat and dog. No data are available for rabbit and mouse, species used in reproduction toxicity and safety pharmacology studies. The compound does not seem to be metabolised and, in view of the low tolerability in rabbits, the lack of data in the rabbit is not considered a significant problem for the interpretation of data.

- Absorption- Bioavailability

The primary parameters characterised indicate that the pharmacokinetics of zoledronic acid are overall similar to other bisphosphonates. In rats exposure was comparable after intravenous and subcutaneous doses with negligible gender differences.

- Distribution

Distribution studies in rat showed, as expected, that most of the dose was taken up by bone with tibia having the highest levels followed by vertebra and cranium. Initially about 60% of the dose is taken up

in the bones and 40% still remains in bone after 1 year. The apparent half-life of zoledronic acid in bone appears to be over 360 days. Quantitative analysis showed that, with the exception of long-term retention in bone, transient high levels were also observed in kidney and spleen.

After repeated intravenous doses of 0.15 mg/kg in rat, accumulation was evident both in bone and soft tissue. Steady-state levels were not attained after 16 days of daily dosing. Accumulation in soft tissues was, however, more than 2 orders of magnitude lower than in bone and declined with an apparent half-life of 150 to 200 days after treatment had stopped. In a 3-month study in rats given subcutaneous doses of 0.1 mg/kg/day, no accumulation in plasma was recorded.

- Metabolism (in vitro/in vivo)

Zoledronic acid is not metabolised. There is no evidence of metabolites circulating in plasma or being excreted in urine.

- Excretion

Zoledronic acid is primarily excreted unchanged through the kidneys after intravenous administration with less than 3% in the feces in rat and dog. Most of the radioactivity was excreted during the first 24 hours (renal plus fecal 33% of dose in rats and 23% in dogs) after which excretion proceeded at low rates so that approximately 60% of the dose was excreted after 12 months. No true elimination of radioactivity could be determined from selected bones such as tibia.

Toxicology

- Single dose toxicity

In single dose toxicity studies in rats, a minimum lethal dose of 8 mg/kg was identified after intravenous bolus injection. The cause of death at high single doses quite likely involved cardiac and/or renal effects.

- Repeat dose toxicity (with toxicokinetics)

The toxicity of zoledronic acid after repeated doses was investigated in rat and dog in studies up to 1 year using subcutaneous and intravenous (bolus or infusion) administration routes and various dosing schedules. The toxicological profile of zoledronic acid showed similarities with that of other bisphosphonates. The most common effects in toxicity studies were increased primary spongiosa in the metaphyses of long bones (non-proliferative hyperostosis) in growing animals, a finding reflecting pharmacological antiresorptive activity. At high doses, effects possibly irritant, in organs such as GI-tract (haemorrhage, erosions, also after iv administration), liver (hepatocellular necrosis, haemorrhage, inflammation), spleen (inflammation, haemorrhage), lungs (inflammatory lesions) were reported, as well as irritation at injection sites. Effects, possibly secondary to poor physical condition, were noted in lymphoid organs and reproductive tract. Renal effects were seen in rat and dog studies and were characterised by renal tubular necrosis/regeneration and inflammation with increased blood urea nitrogen (BUN) and creatinine values. Effects on renal function and integrity seemed to occur at decreasing doses with increasing study duration. In rat studies, males appeared more sensitive than females. Recently bisphosphonates have been associated with a potential to cause eye disorders in clinical use. Ophthalmological examinations in preclinical studies did not however indicate any untoward ocular effects.

Renal effects in rats (tubular necrosis, regeneration, hyaline casts, focal tubular basophilia) were reported in 10-day iv bolus (6 mg/kg/d), 2-week iv (3.2 mg/kg/d), 10-day sc (0.6 mg/kg/d) and 12-month sc (0.003 mg/kg/d) studies. No kidney effects were reported in the 13-week sc rat study at the high dose of 0.1 mg/kg/d. Renal effects in dogs (e.g. tubular degeneration/necrosis, inflammation, increase in connective tissue, cellular casts, tubular basophilia and urothelial hyperplasia) were noted in 3-month iv (0.2 mg/kg/d), 13-week iv infusion (0.25 mg/kg/3x week), 26-week iv infusion (0.25 mg/kg/3x week) and 26/52-week iv bolus (0.1 mg/kg/every 2^{nd} or 3^{rd} day) studies. In dog, kidney effects seemed to develop after cumulative doses of 2.2 g/kg both after injection and infusion. Renal effects appeared reversible after a 26 weeks recovery period. In a 26-week intravenous infusion study in dogs with administration every third week, kidney effects were recorded in all groups after 9 doses of 0.25 mg/kg. A renal NOEL of 0.25 mg/kg after 3 doses was proposed.

The dog studies indicate that infusion time is one factor that is involved in the expression of kidney toxicity, such that a shortening of the infusion time appeared to be coupled to less adverse renal effects. Furthermore, local kinetics of zoledronic acid in the kidney may influence potential for renal toxicity. The reason for the differences in the potential of zoledronic acid to cause kidney toxicity in various rat studies is not clear. Zoledronic acid used in malignancy indications that involve daily dosing may have significant renal toxicity. Although the current indication entails a single dose therapeutic regimen, a slow release of zoledronic acid from bone after a single dose and elimination via kidneys may represent a situation comparable to local repeated low exposure. However it is likely, that the exposure will be low enough for kidney toxicity not to be manifested in the time periods in question.

In rat studies, common clinical chemistry changes included elevated alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), cholinesterase, $\alpha 2$, β globulin levels, increased alkaline phosphatase (AP), creatinine, BUN and Mg. After subcutaneous administration of doses over 0.6 mg/kg reduced erythrocytic parameters, increased granculocytic and coagulation parameters were noted. In a rat 1-month subcutaneous toxicity study, doses of 0.2 mg/kg increased white blood cells (WBC), decreased Ca, P, AP and AP liver isozymes. All changes were reversible except for AP. Increased levels of creatinine kinase were noted from 0.02 mg/kg/d. Histopathological target organs included GI-tract (gastric mucosal degeneration, multifocal necrosis of glandular epithelium), liver (degeneration, increased hepatocyte and Kupffer cell mitosis, periportal hepatocellular hypertrophy, phagocytic activity), adrenal (hypertrophy), spleen (clear macrophages, lymphocytolysis), lymph nodes (lymphocytolysis), thymus (lymphocytolysis, clear macrophages) and lung (increased cellular infiltration). Vasculitis and cellulitis fasciitis at the injection site were described. Skeletal muscle lesions in the thigh muscle were reported at doses over 0.06 mg/kg.

In view of the thymus lymphocytosis, increases of macrophages in spleen, lymph nodes, thymus atrophy, duodenum inflammation reported in a number of toxicity studies, the Applicant presented an evaluation and discussion on possible immunotoxic effects of zoledronic acid. The review of data, also considering dosing regimens in relation to the once yearly intended in clinical therapy, did not indicate any unexpected immunotoxicity. Bisphosphonates in the clinic are however known to have the potential to cause an acute-phase reaction.

In a 3-month subcutaneous toxicity study at doses $\geq$0.03 mg/kg/day, broken/shortened incisors were noted in males during the recovery period. Bisphosphonates have been reported to produce mineralisation defects specifically in rat incisor dentine. There was a non dose-dependent lengthening of metaphyseal primary spongiosa, increased metaphyseal bone diameters in femur and tibia (non-reversible) and a compensatory bone marrow hypercellularity. In a 6/12-month subcutaneous study, testicular atrophy was reported in the 0.01 mg/kg group at 12 months with changes showing reversibility. Examination of tibia from selected rats showed that mineralised tissue at the distal border changed to primary spongiosa. The changes were paralleled by a strong reduction in bone formation at the cellular and tissue levels. The effects were consistent with inhibition of bone resorption and consequent reduction of bone turnover, related to the pharmacological effect of zoledronic acid.

In dog studies, common clinical chemistry changes included elevated activated partial thromboplastin time (APTT), creatinine kinase, increased ASAT, ALAT, lactate and glutamate dehydrogenase, Mg and decreased erythrocytic parameters, AP bone isozyme activity and albumin levels. At doses over 0.02 mg/kg P, Ca and K were decreased. Increases in urea, bilirubin, total lipids, cholesterol, triglycerides and total protein were findings in several studies. Injection site lesions (cellulitis, phlebitis) were present in most studies. Stomach changes (gastric inflammation, mineralisation, ulceration, atrophy, oedema), bone changes (increased mesenchymatous tissue and/or bone deposition in medullary cavities of femur, sternum, rib) and slight mineralisation in the bone marrow were noted. The bone findings were not reversible and the effects were in part ascribed to the pharmacological activity of zoledronic acid. In a 26/52-week study, testicular changes, focal atrophy, degeneration and mineralisation of the seminiferous tubules were noted in some dogs at doses of 0.03 mg/kg at the end of 26 weeks, only.

Bone physical chemistry, morphometry and mechanical properties were studied in dogs after 6, 12 months treatment and following a 6-month recovery period. Physical chemistry parameters indicated a shift towards greater mineralisation between 6 and 12 months. At 12 months, the mineralisation profile in vertebrae had shifted towards higher densities. This was not noted in the femur, probably due to lower turnover in cortical bone. Tetracycline labelling was inadequate to assess dynamic parameters. At 6 and 12 months no difference in the structural parameters such as bone volume, trabecular thickness, cortical areas, cortical thickness were reported with regard to the proximal tibial side. Osteoid surface and volumes were decreased consistent with decreased bone turnover. Osteoid thickness and osteoid volume were not increased, indicative of the absence of mineralisation defect. Bone formation resumed after the 6-month recovery period, suggesting reversibility. Biomechanics indicated a significant increase in density and mechanical properties of trabecular bone with zoledronic acid treatment, prominent at 0.03 mg/kg. Cortical bone density and mechanical properties of cortical or trabecular bone structures were not affected. After 12 months, there was a trend towards an increase in density and mechanical properties of trabecular core. A significant increase in density and mechanical properties of whole vertebrae was also evident. The NOEL for bone safety was considered to be 0.1 mg/kg when given on alternating days for 16 weeks and then every 3rd day through week 52.

Interspecies comparisons were based on renal NOAEL in various studies, and for comparison a human systemic exposure of 1001 ngxhour/ml after 5 mg was used. Based on AUC after a single dose margins of exposure in dog studies was <1 to 3-fold higher than human exposure, while based on cumulative AUC values, exposure multiples of 4 to12 were obtained. In rat studies corresponding values ranged from 1 to 9 based on cumulative AUC, and <1 to 4 based on AUC values after a single dose. Exposure multiples based on Cmax values were generally higher for rat, but lower for dog.

- Genotoxicity in vitro and in vivo

Zoledronic acid was assessed for genotoxic potential in a standard battery of tests. There was no indication of the compound having genotoxic activity either in vitro or in vivo.

- Carcinogenicity

Long-term carcinogenicity studies in mouse and rat by oral gavage at doses up to 2.0 mg/kg/day showed an increased incidence of Harderian gland tumours in male mice, but the increase was within historical control limits since the Harderian gland tumours have no human correlate, such that the clinical relevance of this observation is limited.

- Reproductive and developmental studies

The reproductive toxicity of zoledronic acid was studied in rat and rabbit. The fertility and early embryonic developmental study was terminated early due to deaths/sacrifices linked to difficulties at parturition (dystocia) observed at doses as low as 0.01 mg/kg; effects partly ascribed to the calcium depleting effects of the compound. Toxicity was also evident in embryo/foetal development studies in rat. A marked increase in pre and post implantation loss, increased resorptions and a decreased number of viable foetuses was recorded at 0.6 mg/kg. In the second rat study foetal weights were decreased at doses over 0.2 mg/kg and post implantation increased at 0.4 mg/kg. Zoledronic acid was teratogenic in rat at doses ≥0.2 mg/kg with malformations such as cleft palate, displaced ventricle and dilatation of major vessels, dilated lateral brain ventricles, thickening or curving of the clavicle, humerus and ulna. The teratogenicity was considered a direct effect and not a consequence of maternal toxicity although evident.

Zoledronic acid was not well tolerated in rabbits and in a dose range finding study in pregnant rabbits doses over 0.2 mg/kg resulted in severe clinical signs, body weight loss and animals had to be sacrificed. In a second study doses over 0.01 mg/kg caused maternal toxicity. Signs of hypocalcaemia were recorded. Overall, the compound did not appear to be teratogenic in rabbits since the incidence of malformations was comparable in all groups.
No prenatal and postnatal development study was conducted as the findings in the fertility and early embryonic development study indicated this would not be meaningful. In general, effects noted in the studies were not unexpected. These observations have been adequately reflected in the SPC.

- Local tolerance

Similar to other bisphosphonates, zoledronic acid had local irritating effects upon subcutaneous or intravenous administration.

Ecotoxicity/environmental risk assessment

The potential for ecotoxicity, risk to the environment has been addressed in separate reports. Calculated predicted environmental concentrations do not indicate any cause for immediate concern.

Discussion on the non-clinical aspects

There are no validated animal models of Paget's disease. The etiology of the disease is unknown although it appears to be generally accepted that abnormal osteoclasts are central to the pathophysiology. As well as inhibiting bone resorption, zoledronic acid had less marked inhibitory effects on osteoblasts and decreased bone formation *in vivo*. Thus, inhibition of bone resorption and bone formation may occur concomitantly, but effects were dose-dependent with some maintenance of function and bone formation, although at levels lower than in controls.

Studies in estrogen-deficient animals indicated that bone mass was maintained and reduction of bone mechanic parameters of femur, tibia and vertebra in rat were dose-dependently prevented by zoledronic acid, and the effects were evident only when starting treatment prior to induction of bone loss. A study in which zoledronic acid treatment of OVX rats was initiated 8 weeks after ovariectomy demonstrated that the compound does not exert a "curative" effect. Animal bone studies generally showed expected effects with no significant undesirable changes occurring at relevant doses. Taken together the studies available for zoledronic acid are considered sufficient from the preclinical point of view.

In a case with a compound such as zoledronic acid subject to rapid sequestration and retention in bone, the clinical relevance of animal models used in toxicology studies would not seem appropriately assessed using conventional methods based on e.g. metabolite comparisons and exposure levels. Considering excretion routes and distribution pattern, the species used seem generally relevant.

Data from the toxicology programme indicated that the most frequent effect induced by zoledronic acid was an increase in primary spongiosa in the metaphyses related to the pharmacological activity in addition to adverse effects that were primarily directed at the kidney, liver and gastrointestinal tract.

4. Clinical aspects

Introduction

The clinical study programme is summarised in the Table below.

Table Summary of all studies in Paget's disease

Study No.	Study objective, population	Treated Patients	Study Duration	Medication, Dosing scheme	Type of control
Large efficacy trial (completed)					
2305	Ph III, double-blind, randomized safety/efficacy trial in Paget's disease	178	6 months	1 x 5 mg Zol (single 15 min iv infusion) 30 mg risedronate/day (2 months)	active control
2304	Ph III, double-blind, randomized safety/efficacy trial in Paget's disease	171	6 months	1 x 5 mg Zol (single 15 min iv infusion) 30 mg risedronate/day (2 months)	active control
Large dose-ranging trial					
002	Ph II, double-blind, randomized dose-ranging trial in Paget's disease	176	3 months	1 x 50, 100, 200, 400 µg Zol 1 x placebo (60 min iv infusion)	placebo control
Small dose-ranging trial					
001	Ph I, open, rising dose	16	2 weeks	1 x 24, 72, 216, 400 µg Zol	no

All clinical trials were GCP-compliant as claimed by the company.

- Pharmacokinetics

Pharmacokinetic data are mainly from previous studies in cancer patients. There are no specific pharmacokinetic data for patients with Paget's disease, but the disease state is not expected to affect the pharmacokinetics and conclusions from previous studies can be extrapolated to the present application.

- Absorption

Not applicable

- Distribution

At the end of infusion, plasma concentrations showed a rapid, multiphasic decline reaching < 1% of peak levels after 24 hours. Thereafter, low plasma levels persisted over a long period (≤ 0.1% of peak levels at day 29 after a 16 mg dose). The initial rapid decline is suggested to reflect the combined processes of binding and uptake in bone and renal elimination. The persisting, low levels thereafter reflect the slow re-distribution from bone. The long-term binding of zoledronic acid to bone is the rationale for the single-dose administration proposed for Paget's disease of the bone.

In vitro, ^{14}C-zoledronic acid in blood showed no major affinity for red blood cells. Plasma protein binding was moderate (approximately 56%) and did not vary with concentration. Animal data and the low recovery of ^{14}C-zoledronic acid in humans indicate that most of the drug is bound to bone tissue.

- Elimination

Study 506, with ^{14}C-zoledronic acid, indicated no metabolism in humans. The compound was primarily eliminated unchanged via renal excretion, but recovery of radioactivity was low. Most of the recovered radioactivity was excreted within 24 hours after end of infusion (29%). After 72 hours, 32% was recovered and at later timepoints the concentrations in urine were generally below the detection limit. In a pooled data set of 64 patients from studies J001, 503 and 506, the CL_R of zoledronic acid represented 75±33% of the estimated creatinine clearance (CLcr), which averaged 84 ml/min. The renal and total plasma clearances of zoledronic acid were strongly correlated to CLcr.
In preclinical studies, less than 5% of a dose was excreted in faeces.

Due to the slow re-distribution of zoledronic acid from bone, which may be dependent on bone re-modelling, the terminal t1/2 could not be adequately determined. A t1/2 γ of 146 hours was estimated from the population pharmacokinetic analysis, but was thought likely to be an underestimation. The AUC area under the curve 0-24 hours ($AUC_{0\text{-}24\ hours}$) was therefore used for estimation of key pharmacokinetic parameters.

In a new study no. 1101 in 10 cancer patients, the half-life after a single 4 mg dose was estimated to be 198 hours. Cumulative excretion of drug in urine after 24 hours was 32.6% of the dose. Plasma clearance was 4.85 L/hr and CL_R 2.44 L/hr. Thus, CL_R was about 50% of the total clearance and the remainder is likely to be binding to bone.

- Dose proportionality and time dependencies

The $AUC_{0\text{-}24\ hour}$ was dose proportional between doses of 2 and 16 mg. According to the population pharmacokinetic analysis, the predicted plasma clearance at doses 2, 8 and 16 mg was 108%, 92% and 79%, respectively, of the clearance at a 4 mg dose. Thus, clearance appeared to decrease slightly with increasing doses.

There was no significant accumulation in plasma at multiple doses given every 28 days. The $AUC_{0\text{-}24\ hours}$ at later doses was 1.13-fold higher than after the first dose. Assessment of time-dependency was not considered to be important for the present application, since only a single dose is recommended.

- Special populations

Impaired renal function

The exposure was about 30-40% higher in patients with mild to moderate impairment. In a population pharmacokinetic analysis, CL_R in patients with CLcr of 20, 50 and 140 ml/min was estimated to be 37%, 72% and 149%, respectively, of that for a patient with CLcr of 80 ml/min. No dose adjustment is considered necessary at mild to moderate impairment while due to paucity of data, zoledronic acid is not recommended to patients with severe renal impairment.

Impaired liver function

No study was performed in patients with hepatic impairment, as zoledronic acid is not metabolised in the liver nor excreted via bile, and hepatic impairment is therefore not expected to affect the pharmacokinetics of the compound.

Gender, Race, Weight and Age

In the population pharmacokinetic analysis on the pooled data set of 64 patients from three studies, there were no effects of gender, race, body weight or age that would warrant specific dose adjustments.

Children

No data are available, and Aclasta is not recommended in children and adolescents.

- Pharmacokinetic interaction studies

Previously submitted studies indicated no inhibition of hepatic enzymes *in vitro* by zoledronic acid (CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 or CYP4A9/11).

No *in vivo* interaction studies have been performed, since zoledronic acid is not metabolised, and shows no potential for inhibition of cytochrome P450 enzymes.

Induction was not discussed, but has not been identified as a problem for other bisphosphonates and, moreover, would not be expected to occur at a single dose administration.

The risk for pharmacokinetic drug-drug interactions is expected to be low.

Pharmacodynamics

- Mechanism of action

Like other bisphosphonates, zoledronic acid inhibits bone resorption by osteoclasts and, secondarily, bone turnover by binding to bone surfaces, especially in areas of high bone turnover. As demonstrated in the Zometa dossier, zoledronic acid reduces the osteoclastic hyperactivity of lytic or blastic bone lesions.

- Primary and secondary pharmacology

Preclinical and clinical data showed that zoledronic acid has potent bisphosphonate effects on bone turnover, which should make it potentially useful for the indication treatment of PDB. The clinical studies submitted in Paget's disease provided additional information concerning pharmacodynamics in this population and separate PK/PD studies were not considered necessary. Relevant biomarkers for studying the efficacy of zoledronic acid were chosen.

Combined data from PDB studies 2304 and 2305 showed that the median levels of serum and urine resorption markers C-telopeptide (CTx) were decreased to within normative ranges by 10 days of dosing.

Bone histomorphometry data from a limited number of M6 bone biopsies obtained within trial 2304 demonstrated the expected reduction in bone turnover with an anti-resorptive agent. Osteoblast function as evaluated by fractional mineralising surfaces indicated continued bone turnover with zoledronic acid. No mineralisation defects were evident and the mineral apposition rate was also unchanged relative to placebo. Qualitative assessment indicated no evidence of abnormal bone quality.

Additional histomorphometric data will be made available from the post menopausal osteoporosis programme (POP) studies with zoledronic acid 5 mg annually.

Clinical efficacy

- Dose response studies

The two early dose-ranging trials 001, 002 contributed little data of interest. The studies showed no clinically relevant efficacy to reduce bone markers at doses under 200 µg. Although signs of efficacy were noted with the highest dose of 400 µg (47% reduction of serum alkaline phosphatase at 3 months), this extrapolates to changes that are considerably less than the ≥75% reduction of SAP excess or SAP normalisation, which is required to meet the definition of a clinical responder.

The dose selected for the pivotal PDB trials is the same as that being evaluated for once yearly administration within the ongoing POP for zoledronic acid. It could be noted that the CHMP, during scientific advice, expressed reservations whether this would be the optimal dose for POP and that it might carry an unnecessary risk of over-suppression of bone turnover in POP. Whether this argument is of relevance for (extralesional) bone safety in PDB remains speculative. It may be relevant to note that the 5 mg dose recommended for PDB is substantially less than the annual cumulative dose administered in the majority of oncology patients.

In summary, the choice of dose of zoledronic acid in Paget's disease has not been properly justified by dose-response or other preparatory studies. Nevertheless, the benefit/risk of the proposed regimen has been assessed from the two available controlled studies in the target population, and in addition some safety data from the ongoing POP trials.

- Main studies

Two largely identical Phase III studies (2305, 2304) have been performed in support of the indication for the treatment of PDB, focusing on effects on alkaline phosphatases over six months of a single dose of 5 mg zoledronic acid and aiming to demonstrate non-inferiority of this regimen *vs.* an approved regimen of risedronate 30 mg *q.d.*, dosed during 60 days.

Studies 2305 and 2304

METHODS

Study Participants

Trials 2305, 2304 enrolled male and female patients >30 years with a confirmed diagnosis of PDB and serum alkaline phosphatases (SAP) at baseline ≥2xULN. The minimum washout periods for prior calcitonin and bisphosphonate therapy were set at 90 and 180 days, respectively. Patients with calculated GFR <30 ml/min or urine protein ≥2+ were excluded from participation.

Demographic and baseline disease characteristics are summarised in the tables below. The trials enrolled similar populations

Table Baseline demographic characteristics trials 2305, 2304 (ITT population)

	Study 2304		Study 2305	
	Zoledronic acid (N=90)	**Risedronate (N=82)**	**Zoledronic acid (N=92)**	**Risedronate (N=93)**
Sex – n (%)				
Male	62 (68.9)	61 (74.4)	62 (67.4)	57 (61.3)
Female	28 (31.1)	21 (25.6)	30 (32.6)	36 (38.7)
Race – n (%)				
Caucasian	84 (93.3)	80 (97.6)	84 (91.3)	84 (90.3)
Black	6 (6.7)	2 (2.4)	3 (3.3)	3 (3.2)
Other	0 (0.0)	0 (0.0)	5 (5.4)	6 (6.5)
Age (years)				
Mean (SD)	70.4 (10.25)	72.1 (9.91)	71.3 (9.42)	68.2 (11.15)
Median	72.0	74.0	72.5	70.0
Range	42.0 – 94.0	44.0 – 87.0	45.0 – 92.0	34.0 – 88.0
Age – n (%)				
<65 years	25 (27.8)	17 (20.7)	21 (22.8)	29 (31.2)
≥65 years	65 (72.2)	65 (79.3)	71 (77.2)	64 (68.8)

Table Baseline disease characteristics trials 2305, 2304 (ITT population)

	Study 2304		Study 2305	
	Zoledronic acid (N=90)	Risedronate (N=82)	Zoledronic acid (N=92)	Risedronate (N=93)
Baseline SAP (U/L)				
Mean (SD)	424.5 (335.35)	423.0 (267.35)	431.0 (308.11)	427.4 (348.56)
Median	329.0	321.0	342.5	301.0
Range	229.0 - 2822.0	214.0 - 1971.0	230.0 - 2338.0	222.0 - 2377.0
Baseline SAP – n (%)				
< 3xULN	47 (52.2)	45 (54.9)	46 (50.0)	56 (60.2)
≥ 3xULN	43 (47.8)	37 (45.1)	46 (50.0)	36 (38.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
Creatinine clearance at baseline (mL/min)				
Mean (SD)	86.8 (36.51)	84.5 (36.34)	84.2 (28.75)	89.2 (30.26)
Median	77.7	79.2	81.6	88.2
Range	30.6 - 217.8	29.4 - 228.0	(36.0 - 180.0)	(34.2 - 192.6)
Creatinine clearance at baseline – n (%)				
< 30 mL/min	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
30 to < 40 mL/min	3 (3.3)	2 (2.4)	2 (2.2)	1 (1.1)
40 to 50 mL/min	10 (11.1)	7 (8.5)	8 (8.7)	9 (9.7)
> 50 mL/min	77 (85.6)	72 (87.8)	82 (89.1)	83 (89.2)
Last Paget's disease therapy before randomisation - n (%)				
Bisphosphonates	39 (43.3)	39 (47.6)	50 (54.3)	52 (55.9)
Oral	23 (25.6)	28 (34.1)	33 (35.9)	35 (37.6)
IV	13 (14.4)	10 (12.2)	14 (15.2)	16 (17.2)
Clodronate	3 (3.3)	1 (1.2)	3 (3.3)	1 (1.1)
Other	2 (2.2)	2 (2.4)	6 (6.5)	5 (5.4)
None	49 (54.4)	41 (50.0)	36 (39.1)	36 (38.7)
Washout for bisphosphonates - n (%)				
<180 days	1 (1.1)	0 (0.0)	2 (2.2)	2 (2.2)
180 to < 365 days	4 (4.4)	1 (1.2)	5 (5.4)	3 (3.2)
≥365 days	34 (37.8)	38 (46.3)	43 (46.7)	47 (50.5)

Additional baseline disease characteristics of interest were presented by the Applicant. The distribution with respect to the proportion of patients with polyostotic/monostotic disease is consistent with the characteristics of the general population with Paget's disease.

Treatments

A single dose of zoledronic acid 5 mg given as an infusion over 15 min (followed by risedronate placebo) *vs.* risedronate 30 mg *q.d.* for 60 days. The regimen for risedronate is that approved throughout Europe.

All patients were supplemented with calcium and multivitamins, including vitamin D.

Objectives

The primary objective was to show non-inferiority of zoledronic acid relative to risedronate with respect to the primary efficacy variable, proportion of responders at six months. See also below

(statistical methods). The objective was considered to be acceptable by the CHMP during scientific advice.

Outcomes/endpoints
The primary efficacy variable was the proportion of patients who achieved therapeutic response, defined as normalisation of SAP or at least 75% reduction from baseline of *excess* SAP at the end of six months.

Secondary efficacy variables included (log transformed values for bone markers)
- Relative change in SAP at D28
- Relative change in serum and urine CTx at D10
- Time to first therapeutic response
- Proportion of patients achieving SAP normalisation at D28
- Change in pain scores (BPI-SF) over time

Exploratory analyses included
- Proportions of patients who achieved SAP normalisation at D 10, 63, 91, 182

Sample size
Sample size calculations were based on the non-inferiority criterion of –0.16 for the primary efficacy variable. This margin is argued to maintain at least 75% of the effect of risedronate *vs.* etidronate. See also below (statistical methods).

Randomisation and blinding (masking)
The two main efficacy trials 2304 and 2305 were carried out double-blinded and randomized. Standard tools (IVRS) and procedures were used.

Statistical methods
The following analysis sets were defined: ITT (all randomised), MITT (randomised patients with baseline and at least one post baseline SAP determination) Safety (all patients who received at least one dose of study drug) and PP (exclusion of all major protocol violations).

Missing data were handled as follows:
For the proportion of patients who achieved therapeutic response and the proportion who achieved SAP normalisation, LOCF was used. No imputation was used for other efficacy parameters.

According to the SAP, non-inferiority of zoledronic acid vs. risedronate could be concluded if a Δ of greater than –0.16 (two-sided 95% CI) was observed. In addition, and as a pre-planned strategy to test superiority of zoledronic acid, between-treatment difference in the proportion of patients who achieved therapeutic response at six months was evaluated by logistic regression with treatment and baseline SAP (<3xULN or ≥3xULN) as explanatory variables

A closed testing procedure was used for secondary efficacy claims (CTx at D10, SAP change at D28, SAP normalisation at D28, BPI-SF, time to first therapeutic response).

RESULTS
Patient disposition is given in the Table below.

Table Subject disposition trials 2305, 2304 (ITT population)

	Study 2304		Study 2305	
	Zoledronic acid n (%)	**Risedronate n (%)**	**Zoledronic acid n (%)**	**Risedronate n (%)**
Total no. of patients - n(%)				
Randomized	90 (100)	82 (100)	92 (100)	93 (100)
Completed	86 (95.6)	76 (92.7)	85 (92.4)	89 (95.7)
Discontinuations – n(%)				
Total	4 (4.4)	6 (7.3)	7 (7.6)	4 (4.3)
Primary reason				
Adverse event	2 (2.2)	2 (2.4)	1 (1.1)	0 (0.0)
Protocol violations	1 (1.1)	0 (0.0)	3 (3.3)	2 (2.2)
Patient withdrew consent	1 (1.1)	2 (2.4)	3 (3.3)	2 (2.2)
Lost to follow up	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)

Numbers analysed

The analysis populations are summarised in the Table below.

Table Patients in analysis populations by treatment, trial 2305 and 2304

	Zoledronic acid 5 mg single IV infusion n (%)		**Risedronate 30 mg/day x 60 days n (%)**	
	2304	**2305**	**2304**	**2305**
ITT	90 (100)	92 (100)	82 (100)	93 (100)
MITT	88 (97.8)	88 (95.7)	82 (100)	89 (95.7)
PP	75 (83.3)	69 (75.0)	67 (81.7)	81 (87.1)
Safety	89 (98.9)	88 (95.7)	82 (100)	90 (96.8)

The lower fraction included in PP (zoledronic acid) was explained by lower compliance to oral placebo.

Outcomes and estimation

Primary efficacy data are given in the Table below. The primary efficacy variable was the proportion of patients who achieved therapeutic response at 6 months. A therapeutic response was defined as the normalization of SAP or a reduction of at least 75% from baseline (Visit 1) in SAP excess (difference between measured level and midpoint to the normal range).

Table Proportion of patients with therapeutic response at 6 months, trials 2305, 2304 (MITT population)

Treatment	N	Proportion	Difference [1] 95% CI	Odds ratio [2] 95% CI	p-value [3]
2305					
Zoledronic acid	88	0.95	0.20 (0.09, 0.31)	7.13 (2.56, 25.41)	< 0.0001
Risedronate	89	0.75	---	---	---
2304					
Zoledronic acid	88	0.97	0.23 (0.12, 0.35)	10.37 (3.40, 45.21)	< 0.0001
Risedronate	82	0.73	---	---	---

[1] Difference of zoledronic acid minus risedronate.
[2] Odds ratio of zoledronic acid over risedronate and its 95% CI is based on the logistic regression model.
[3] P-value given by the likelihood ratio test for the treatment comparison in the logistic regression model.

The lower limit of the one-sided 97.5% CI for the difference between the treatment groups was greater than –0.16 in both studies 2305 and 2304, meeting the non-inferiority criterion. When testing for superiority, the lower limit of the CI was greater than 0, indicating that zoledronic acid had a significantly higher proportion of patients who achieved therapeutic response compared to risedronate (20% higher). The results of the 95% CI were confirmed by the statistically significant treatment effect in the logistic regression model from both studies (all $p<0.001$), and odds ratio of 7.13 (95% CI: 2.56, 25.41) in Study 2305, and odds ratio of 10.37 (95% CI: 3.40, 45.21) in Study 2304. Consistent, statistically significant results were shown in the PP-population.

The relevant variable proportion of subjects with SAP normalisation was tested as a secondary variable at D28 (2305: zoledronic acid 0.09, risedronate 0.01, $p<0.01$; 2304: zoledronic acid0.06, risedronate 0, $p<0.01$).

Data for SAP normalisation at six months (tested as exploratory variable) are summarised below.

Table Proportion of subjects with SAP normalisation at 6 months (MITT population)

Treatment	N	Proportion (%)	Difference (95% CI)	Odds ratio (95% CI)	p-value
2305					
Zoledronic acid	88	0.89 (89%)	0.32 (0.19, 0.46)		< 0.0001
Risedronate	89	0.56 (56%)			
2304					
Zoledronic acid	88	0.89 (89%)	0.29 (0.15, 0.43)		< 0.0001
Risedronate	82	0.60 (60%)			

Findings for serum and urine CTx (secondary variables) and serum P1NP (exploratory) were consistent with those for SAP.

Time to first therapeutic response (secondary variable) was significantly shorter with zoledronic acid, compared with risedronate (62.7 *vs.* 108.2 days (ITT), risk ratio 3.31 [2.28;4.81]) in Study 2305 and (62.7 vs. 103.1 (ITT), risk ratio [2.54, 5.58]) in Study 2304.

BPI-SF scores declined over time on study in both treatment arms in both trials, without significant differences or trends to superiority of zoledronic acid. In the pooled results, a similar decrease in pain severity and pain interference scores relative to baseline were observed over 6 months for Aclasta and risedronate.

Experience with retreatment is non-existent.

Ancillary analyses

Subgroup analyses for key efficacy variables were performed for

- Baseline SAP <3xULN or ≥3xULN
- Race
- Sex
- Last PDB therapy (oral bisphosphonate, IV bisphosphonate, clodronate, others, none)
- Washout period for bisphosphonates (<180, 180 to <365, ≥365D)
- Age (<65, 65-74, ≥75 years)

The findings for the primary efficacy criterion in these subgroup analyses were very similar between trials 2305 and 2304.

The findings for the primary efficacy criterion for the combined trials are summarised in the tables below.

Table Proportion of patients who achieved therapeutic response at 6 months by demographic factor – combined active-controlled studies (MITT population)

Subgroup	Zoledronic acid n/N (Proportion)		Risedronate n/N (Proportion)	
Age				
< 65 years	45/45	(1.00)	37/45	(0.82)
65-74 years	62/64	(0.97)	46/59	(0.78)
≥75 years	62/67	(0.93)	44/67	(0.66)
Sex				
Female	117/121	(0.97)	86/116	(0.74)
Male	52/55	(0.95)	41/55	(0.75)
Race				
Caucasian	158/163	(0.97)	120/161	(0.75)
Black	7/8	(0.88)	1/4	(0.25)
Other	4/5	(0.80)	6/6	(1.00)

Table Proportion of patients who achieved therapeutic response at 6 months by disease factors – combined active-controlled studies (MITT population)

Subgroup	Zoledronic acid n/N (Proportion)		Risedronate n/N (Proportion)	
Baseline SAP				
< 3xULN	87/90	(0.97)	74/99	(0.75)
≥ 3xULN	82/86	(0.95)	53/72	(0.74)
Last Paget's therapy				
Oral bisphos.	53/55	(0.96)	33/60	(0.55)
IV bisphos.	22/25	(0.88)	21/26	(0.81)
Clodronate	6/6	(1.00)	2/2	(1.00)
Others	8/8	(1.00)	6/7	(0.86)
None	80/82	(0.98)	65/76	(0.86)
Washout for bisphosphonates				
< 180 days	3/3	(1.00)	1/2	(0.50)
180-<365 days	8/8	(1.00)	2/4	(0.50)
≥ 365 days	70/75	(0.93)	53/82	(0.65)

When the baseline SAP > 3xULN category is divided into two groups (3-6 xULN, >6xULN) the therapeutic response rate remains consistent across the zoledronic acid subgroups with 96% and 93%

of the patients in the two subgroups achieving therapeutic response compared to a 95% therapeutic response rate in the overall group.

- Clinical studies in special populations

There were no studies performed in special populations.

- Analysis performed across trials (pooled analyses and meta-analysis)

None

- Supportive studies

None

- Discussion on clinical efficacy

The pivotal clinical trials were performed essentially in accordance with CHMP scientific advice. The study samples are considered reasonably representative of the intended target population, although of mild to moderate average disease severity. Short-term efficacy on the accepted surrogate variable SAP is robust with 95% response rate for the primary responder criterion, consistent over subgroups and corroborated by findings for other bone turnover markers. The attainment of 89% response rate for SAP normalisation at six months is also reassuring, is significantly superior to what was achieved with the approved comparator risedronate, and appears to be considerably in excess of what has been published for other bisphonates.

In the primary efficacy analysis (MITT), zoledronic acid was clearly superior to risedronate in both trials (proportions of responders 2305: 0.95 *vs*.0.75; OR 7.13 [2.56; 25.41]; 2304: 0.97 *vs*. 0.73, OR 10.37 [3.40; 45.2]). This was consistent in PP analysis. Normalisation of SAP at six months (exploratory) was noted in the proportions 0.89 *vs*. 0.56 and 0.89 *vs*. 0.60 in the two studies. Changes in SAP corroborated those for serum and urine CTx. Findings in subgroups (demographics, baseline disease severity, prior bisphosphonate exposure yes/no) were consistent with the primary analysis.

Time to first therapeutic response was shorter with zoledronic acid, compared with risedronate in both trials.

There was no difference between treatments regarding response in BPI-SF pain scores in either study.

The lack of radiographic data is acknowledged as a deficiency, but such data has not been requested in other applications for this indication.

Follow-up data in responders are currently being collected in extensions to both trials for patients who were classified as therapeutic responders at the end of the 6-month core study. Data for a median follow-up of 18 months from time of dosing were made available in response to CHMP Day 120 List of Questions (D120 LOQ). In this analysis, 141/143 zoledronic acid-treated patients maintained their therapeutic response, compared with 71/107 of the risedronate-treated patients. Additional long-term data will be reported to the CHMP post-marketing.

There is currently no actual experience of retreatment with zoledronic acid in PDB.

Clinical safety

- Patient exposure

Taking into account data supplied in the response to CHMP D120 LOQ, the safety assessment considered data obtained in approximately 541 patients with PDB: 157 patients in early-phase trials who received doses less than 5 mg zoledronic acid (24-400 µg), 177 patients in trial 2305 and 2304 who received 5 mg of zoledronic acid, 172 patients who received the active comparator, risedronate, and 35 patients in early phase studies who received placebo.

Pooled data from the four trials in the target population constituted the major safety population. Further, post-marketing data for Zometa in oncology indications were taken into account.

- Adverse events (AE)

Adverse events (≥5%) in the major safety population are summarised per System Organ Class (SOC) in the Table below.

Table Adverse events overall and by body system (≥ 5% patients in any group) (Paget's disease, safety population)

	Phase III studies		Phase I/II studies	
	Zoledronic acid 5 mg n (%)	Risedronate n (%)	Zoledronic acid <5 mg (24-400 µg) n (%)	Placebo n (%)
Patients studied				
Total no. studied	177 (100.0)	172 (100.0)	157 (100.0)	35 (100.0)
Total no. with an AE	146 (82.5)	133 (77.3)	120 (76.4)	29 (82.9)
System organ class				
General disorders & administrat. site conditions	69 (39.0)	35 (20.3)	43 (27.4)	9 (25.7)
Musculoskeletal & connective tissue disorders	66 (37.3)	55 (32.0)	71 (45.2)	17 (48.6)
Nervous system disorders	51 (28.8)	35 (20.3)	32 (20.4)	9 (25.7)
Gastrointestinal disorders	50 (28.2)	41 (23.8)	20 (12.7)	6 (17.1)
Infections & infestations	50 (28.2)	46 (26.7)	31 (19.7)	6 (17.1)
Respiratory, thoracic & mediastinal disorders	19 (10.7)	18 (10.5)	16 (10.2)	3 (8.6)
Injury, poisoning & procedural complications	17 (9.6)	21 (12.2)	9 (5.7)	1 (2.9)
Metabolism & nutrition disorders	17 (9.6)	10 (5.8)	5 (3.2)	0 (0.0)
Skin & subcutaneous tissue disorders	15 (8.5)	13 (7.6)	15 (9.6)	3 (8.6)
Investigations	11 (6.2)	9 (5.2)	14 (8.9)	1 (2.9)
Renal & urinary disorders	10 (5.6)	12 (7.0)	6 (3.8)	1 (2.9)
Eye disorders	8 (4.5)	3 (1.7)	9 (5.7)	0 (0.0)
Vascular disorders	8 (4.5)	5 (2.9)	5 (3.2)	4 (11.4)
Psychiatric disorders	5 (2.8)	8 (4.7)	5 (3.2)	2 (5.7)

Studies : 2304, 2305, 001, 002

A tabulation of the most frequent AEs suspected to be drug-related (investigator's assessment) in the PDB population is given below.

Table Most frequent AEs (≥ 2% patients in any group) suspected to be drug related (Paget's disease, safety population)

	Phase III studies		Phase I/II studies	
	Zoledronic acid 5 mg n (%)	Risedronate n (%)	Zoledronic acid <5 mg (24-400 µg) n (%)	Placebo n (%)
Patients studied				
Total no. studied	177 (100)	172 (100)	157 (100)	35 (100)
Total no. with an AE	92 (52.0)	43 (25.0)	65 (41.4)	16 (45.7)
Adverse events				
Flu-like symptoms	16 (9.0)	9 (5.2)	4 (2.5)	0 (0.0)
Pyrexia	13 (7.3)	1 (0.6)	3 (1.9)	0 (0.0)
Rigors	13 (7.3)	1 (0.6)	4 (2.5)	0 (0.0)
Headache	12 (6.8)	6 (3.5)	7 (4.5)	2 (5.7)
Myalgia	11 (6.2)	6 (3.5)	3 (1.9)	0 (0.0)
Nausea	10 (5.6)	3 (1.7)	6 (3.8)	1 (2.9)
Bone pain	9 (5.1)	2 (1.2)	8 (5.1)	2 (5.7)
Fatigue	9 (5.1)	3 (1.7)	12 (7.6)	0 (0.0)
Arthralgia	7 (4.0)	3 (1.7)	16 (10.2)	3 (8.6)
Lethargy	7 (4.0)	1 (0.6)	1 (0.6)	1 (2.9)
Influenza	6 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)
Pain	6 (3.4)	4 (2.3)	2 (1.3)	0 (0.0)
Hypocalcemia	5 (2.8)	1 (0.6)	0 (0.0)	0 (0.0)
Asthenia	4 (2.3)	1 (0.6)	2 (1.3)	0 (0.0)
Diarrhea	4 (2.3)	0 (0.0)	1 (0.6)	1 (2.9)
Dyspepsia	4 (2.3)	4 (2.3)	0 (0.0)	0 (0.0)
Dyspnea	4 (2.3)	0 (0.0)	1 (0.6)	0 (0.0)
Back pain	3 (1.7)	2 (1.2)	13 (8.3)	1 (2.9)
Paraesthesia	2 (1.1)	0 (0.0)	3 (1.9)	1 (2.9)
Body temperature increased	1 (0.6)	2 (1.2)	4 (2.5)	0 (0.0)
Hot flush	1 (0.6)	0 (0.0)	1 (0.6)	2 (5.7)
Night sweats	1 (0.6)	0 (0.0)	0 (0.0)	1 (2.9)
Chest wall pain	0 (0.0)	0 (0.0)	2 (1.3)	1 (2.9)
Flushing	0 (0.0)	0 (0.0)	2 (1.3)	1 (2.9)
Injection site reaction	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)
Muscle cramp	0 (0.0)	1 (0.6)	4 (2.5)	0 (0.0)
Edema peripheral	0 (0.0)	0 (0.0)	1 (0.6)	1 (2.9)
Pain in extremity	0 (0.0)	2 (1.2)	11 (7.0)	3 (8.6)

Studies : 2304, 2305, 001, 002

Generally, the AE profile appears to be that expected with an IV bisphosphonate and also consistent with findings in other trials of zoledronic acid in benign conditions (0041, 0041E1, 2201). Flu-like symptoms, headache and fatigue frequently occurred within the first 3 days of administering zoledronic acid. The majority of these symptoms resolved within 4 days of the event onset. A majority of the patients (95/177) in the zoledronic acid 5 mg group reported their adverse events in the first 3 days after initiating study drug. Thereafter, more adverse events were reported in the risedronate group.

Adverse events of special interest

Renal adverse events

Renal abnormality was defined as a serum creatinine rise of > 0.5 mg/dL from baseline, or a > 2+ protein value by dip-stick. In the original submission, there were no events of raised serum creatinine at D9-11 post infusion in the PDB population (protocol-defined analysis) and only one episode of transient, asymptomatic proteinuria. In study 2304 there were no renal adverse events associated with deterioration of renal function or renal abnormalities reported for zoledronic acid. For risedronate, there were three adverse events that met the definition of deterioration of renal function. An overview of clinical renal AEs in the major safety population is given in the Table below.

Table Renal adverse events (Paget's disease, safety population)

	Phase III studies		Phase I/II studies	
	Zoledronic acid 5 mg	**Risedronate**	**Zoledronic acid <5 mg (24-400µg)**	**Placebo**
Patients studied				
Total no. studied	177 (100.0)	172 (100.0)	157 (100.0)	35 (100.0)
No. with renal AEs	2 (1.1)	3 (1.7)	0	0
Adverse event				
Creatinine clearance decreased	1 (0.6)	0 (0.0)	-	-
Urinary retention	1 (0.6)	0 (0.0)	-	-
Hematuria	0 (0.0)	2 (1.2)	-	-
Renal impairment	0 (0.0)	1 (0.6)	-	-

Studies: 2304, 2305, 001, 002
A subject with multiple occurrences within an AE is counted only once in the AE category.

The two events reported with zoledronic acid 5 mg relate to one case of protocol-defined increase in serum creatinine occurring at six months post administration, and one case of urinary retention, respectively.

Available data in the PDB population create no specific concern regarding renal safety of IV zoledronic acid. Renal adverse events will be specifically monitored post-marketing.

Upper gastrointestinal adverse events

In the PDB safety database, there was no marked difference between zoledronic acid and risedronate regarding reporting rates for upper gastrointestinal AEs (18.6% and 16.3%, respectively).

Uveitis/iritis/scleritis

There were no reports of these events in the PDB population.

Osteonecrosis of the maxillofacial region

This has recently been highlighted in the literature as a complication of pamidronate and zoledronic acid when used in oncology indications. No events of this type are reported in the current dossier. Post-marketing surveillance is considered to be necessary.

Bone safety

Available data create no specific concerns (see section on Pharmacodynamics).

- Serious adverse event/deaths/other significant events

The only SAEs assessed as potentially related involved one report of cerebrovascular accident, occurring 69 days post administration of 5 mg zoledronic acid in study 2305, and one report of ECG changes 9 days following 100 µg of zoledronic acid in trial 002.

SAEs suspected to be drug-related in other completed trials in benign indications included isolated cases of flu-like symptoms.

Table Serious adverse events (excluding death) (Paget's disease, trials 2305, 2304)

Patient Identity	Age/Sex	Preferred term	Day of onset	Relation to drug
zoledronic acid 5 mg (study 2304)				
0303/00125	71/M	Embolic stroke	114	Not suspected
0604/00095	75/M	Peripheral ischemia	125	Not suspected
		Sympathectomy	131	Not suspected
		Leg amputation	157	Not suspected
0401/00037	79/F	Arthritis	2	Suspected
0504/00117	53/M	Cellulitis orbital	132	Not suspected
0507/00046	76/M	Difficulty in walking	3	Not suspected
		Spinal column stenosis	3	Not suspected
		Asthenia	3	Suspected
Risedronate (study 2304)				
0303/00272	73/M	Lower limb fracture	19	Not suspected
0107/00252	76/M	Dysphagia	60	Not suspected
0605/00190	79/F	Abdominal pain upper	101	Suspected
0605/00199	81/F	Renal impairment	173	Not suspected
		Lower resp. tract infection	173	Not suspected
		Confusional state	173	Not suspected
		Urinary tract infection	173	Not suspected
		Staphylococcal infection	224	Not suspected
0401/00118	77/M	Acute coronary syndrome	73	Not suspected
0401/00157	72/M	Hepatic cyst	154	Not suspected
		Pyrexia	154	Not suspected
		Rigors	154	Not suspected
0504/0065	52/F	Hypocalcemia	12	Suspected
0507/0136	87/F	Abdominal pain	80	Not suspected
		Constipation	80	Not suspected
		Abdominal Pain	88	Not suspected
		Back pain	88	Not suspected
zoledronic acid 5 mg (study 2305)				
0104/00250	77/M	Femur fracture	98	Not suspected
0305/00058	83/M	Back pain	93	Not suspected
		Cerebrovascular accident	93	Suspected
		Spinal fracture	93	Not suspected
0308/00369	77/F	Asthma	101	Not suspected
		Dyspnea	101	Not suspected
		Enterobacter sepsis	157	Not suspected
0501/00137	76/F	Escherichia infection	104	Not suspected
Risedronate (study 2305)				
0254/00054	73/M	Chest pain	54	Not suspected
0455/00295	52/F	Endometrial hyperplasia	95	Not suspected
0601/00187	83/F	Humerus fracture	84	Not suspected

No unexpected signal has been created by these data.

In the major safety population (all patients with PDB given ≥ 1 dose of study drug) there was a total of four deaths, all occurring in trial 002 using sub-therapeutic doses of zoledronic acid, and none assessed to be related to study drug.

- Laboratory findings

Clinically notable hypocalcaemia (serum calcium <1.87 mmol/l) or AE of hypocalcaemia was reported in 8/177 patients in studies 2305 and 2304 following zoledronic acid 5 mg and with serum calcium nadir usually occurring before or by D10 post injection. Truly symptomatic hypocalcaemia was reported in two patients, both of which showed non-compliance with calcium and vitamin D supplementation.

- Safety in special populations

No specificities regarding the AE profile were noted in predefined subgroups or in relation to specific concomitant drug intake.

- Safety related to drug-drug interactions and other interactions

As noted in the section on pharmacokinetics, the potential for pharmacokinetic drug – drug interactions is low. No specific dynamic interactions of concern are foreseen apart from those related to known class effects.

- Discontinuation due to adverse events

There was only one discontinuation due to AE in the major safety population. Corresponding data from the finalised trials in benign indications are unremarkable.

- Post marketing experience

The data available refers to zoledronic acid as Zometa, indicated in oncology patients. As already discussed, dosage regimens for zoledronic acid and co-morbidity spectrum are quite different in the oncology setting compared with for the currently sought indication. Apart from the recently identified issue of maxillofacial osteonecrosis, the safety experience with Zometa is not considered to have raised unexpected concerns.

- Discussion on clinical safety

The main adverse effects of zoledronic acid by intravenous infusion are flu-like symptoms in the first 3 days following administration. These symptoms occur very commonly, are usually transient and resolve spontaneously within 2-4 days. Bone pain, arthralgia, myalgia, fever, and hypocalcaemia have also been observed commonly. All of these symptoms have been reported previously with other bisphosphonates.

The occurrence of symptomatic hypocalcaemia with zoledronic acid despite vitamin D and calcium supplementation created concern in the primary assessment. In response to CHMP D120 LOQ, the applicant provided additional data and discussion on this issue. In the pivotal trials, transient hypocalcaemia, usually with the nadir at or before D10 post injection was noted in eight patients treated with zoledronic acid. The two cases with the lowest serum calcium values were truly symptomatic and were associated with non-compliance with calcium and vitamin D supplementation. The wording in the SPC of sections 4.2 and 4.4 has been strengthened, in order to emphasise the importance of adequate calcium supplementation post infusion; this approach should ensure manageable safety in clinical practice. Hypocalcaemia is targeted for focused surveillance within PSURs.

Based on preclinical and clinical data, there is a concern for renal toxicity of IV bisphosphonates. Monitoring of renal function was performed 9-11 days following the initial dose in pivotal trials, and such monitoring is also specified per protocol in ongoing trials in non-malignant indications. No renal abnormalities (increase in serum creatinine or proteinuria $\geq$2+) occurred due to zoledronic acid infusion in the PDB population. Due to the concern for potential renal events, individuals with creatinine clearance below 30 ml/min were excluded from the trials. The exclusion of patients with severe renal impairment has been reflected in the SPC. Renal toxicity is targeted for focused surveillance within PSURs.

Events of iritis/uveitis/scleritis were not seen in the PDB population so far, but are, appropriately, listed in the SPC as occurring with bisphosphonate therapy. This area will also be focused on in PSURs.

The limited amount of (extralesional) bone safety data available was discussed in the pharmacodynamic section. Additional biopsy data from POP trials will be reported to the CHMP. The specific bone safety issue of maxillofacial osteonecrosis, highlighted for pamidronate and zoledronic acid in oncology indications has so far not been reported in non-malignant indications. Targeted surveillance within PSURs is considered necessary.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality
The quality of the 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. There are no unresolved quality issues, which have a negative impact on the Benefit/Risk balance of the product.

Non-clinical pharmacology and toxicology
Overall, the primary pharmacodynamic studies provided adequate evidence that zoledronic acid had inhibitory effects on osteoclasts inhibiting bone resorption and as well as reducing bone turnover. The general safety pharmacology studies showed no remarkable effects. The pharmacokinetics of zoledronic acid has been studied in rat and dog. The findings revealed in the toxicology programme have been adequately reflected in the SPC.

Efficacy
The pivotal clinical trials were performed in accordance with CHMP scientific advice and in an acceptable sample of the patient population. Short-term efficacy on the accepted surrogate variable SAP is robust. The attainment of replicated 89% response rate for SAP normalisation at six months is reassuring, is significantly superior to what was achieved with the approved comparator risedronate, and also appears to be considerably in excess of what has been published for other bisphosphonates. Follow-up data are still preliminary, as regards to maintenance of long-term response.

Safety
The updated safety database has been adequately presented. Hypocalcaemia appears to occur more frequently in patients receiving i.v. zoledronic acid compared with oral risedronate, even if usually mild and without clinically significant consequences. Hypocalcaemia is included in the SPC as a common side effect for Aclasta. Renal adverse events and osteonecrosis of the maxillofacial region will be specifically monitored post-marketing.

Benefit/risk assessment
Aclasta (zoledronic acid) is the first i.v. bisphosphonate proposed for the treatment of Paget's disease in the EU. Zoledronic acid is a potent bisphosphonate. The dose claimed is poorly substantiated. However, efficacy on usually accepted intermediary endpoints was demonstrated to be superior to that of an approved regimen of oral risedronate in two adequate clinical trials, and the safety profile is considered to be manageable within the restrictions imposed by the agreed SPC.

Data on maintenance of effect after a single dose are preliminary. The available data on long-term efficacy/safety and their limitations have been pointed out in the SPC. The Applicant intends to collect further data from the ongoing extension program in order to define these parameters. These data will be reported to CHMP when the 2-year follow up data is available.

Overall, and taking into account the commitments to provision of additional efficacy and safety data post-marketing, the benefit/risk balance is acceptable.

Recommendation
Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by a unanimous decision that the benefit/risk ratio of Aclasta in the treatment of Paget's disease of bone was favourable and therefore recommended the granting of the marketing authorisation.