European Medicines Agency

London, 1 September 2005
Doc.Ref.: EMEA/278873/2005

**Bonviva**

International Nonproprietary Name:

**Ibandronic acid**

Following the procedure

**EMEA/H/C/501/X/01**

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.eu.int http://www.emea.eu.int
©EMEA 2005 Reproduction and/or distribution of this document is authorised for non commercial purposes only provided the EMEA is acknowledged

# 1 SCIENTIFIC DISCUSSION

## 1.1 Introduction and rationale

The MAH submitted an extension application under Annex II, point 2 iii to Commission Regulation (EC) No 1085/2003 to request the approval of a 150 mg tablet as a monthly dosing regimen of ibandronate only for the indication of "treatment of osteoporosis in postmenopausal women, in order to reduce the risk of vertebral fractures". This claim is based on the results of a phase III study MOBILE (BM16549) comparing 100 and 150 mg once monthly to 2.5 mg once daily.

Due to the inconveniences associated with intake of oral bisphosphonates (i.e. fasting conditions, frequent upper gastrointestinal intolerance) that may result in poor compliance, it was considered desirable to develop a more convenient drug formulation. Hence a 150 mg once monthly oral regimen is expected to offer greater convenience to postmenopausal women when compared to the currently approved 2.5mg once daily tablet.

**The development programme**

No new pre-clinical pharmacodynamic and pharmacokinetic studies have been performed in addition to those included in the previous submission for ibandronate 2.5 mg daily oral tablets. The previously performed studies in oestrogen-depleted animal models had demonstrated the intermittent treatment was equally effective when compared to daily treatment, provided the total cumulative dose was the same.

Three new single dose toxicity studies and two repeat-dose toxicity studies (of 2 weeks and 6 months duration respectively), with i.v.-administered ibandronate, were performed in rats. In the 6-month study zoledronate was used as a reference compound. The goal of the toxicity studies was to further characterise the renal effects and in particular to assess the renal safety when using ibandronate iv.

Four clinical studies have been conducted in total for the development of the monthly ibandronate formulations: Two bioequivalence studies (SB 743830/002 and SB 743830/003), a clinical pharmacology monthly oral pilot study (BP16331), and a pivotal Phase III study (BM16549) for the treatment of postmenopausal osteoporosis. In addition, a recently completed bioavailability study (BP16469) was performed to collect further information with regard to the effect of food on oral doses of ibandronate.

## Quality aspects

**Introduction**

*Composition*
Bonviva is presented as film-coated tablets containing ibandronic acid as the active substance in a core formulation, which also contains lactose, microcrystalline cellulose, crospovidone, povidone, stearic acid and colloidal silica. The film coating consists of a conventional Opadry/macrogol 6000 mixture. The product is packaged in alu-blisters.

**Active Substance**

Ibandronic acid is present in the tablets as the sodium salt monohydrate. Two polymorphs of the drug substance have been identified. Both polymorphic forms have similar solubility and intrinsic dissolution properties, therefore no effect of the crystal modification on the in vivo drug release is expected. This is confirmed by dissolution profiles of two 20 mg ibandronate batches prepared with different crystalline modifications in the drug substance. The modification present in the finished product is the same as in the respective active substance lot used for the manufacture.

The active substance quality and the batch control test procedures are identical to the ones that have already been approved for the 2.5 mg strength. The stability of the active substance has already been demonstrated with studies performed in accordance with the ICH requirements.

**Medicinal Product**

*Pharmaceutical Development*

The formulation is based on the development of the 2.5 mg strength. The pharmaceutical development resulted in tablets that dissolve rapidly in aqueous media.

The film-coated tablets are formulated with well-known excipients, which are identical to those used for the 2.5 mg strength. All excipients comply with Eur. Ph. Lactose monohydrate derives from cow's milk. The milk is sourced from healthy animals in the same conditions as milk collected for human consumption. The preparation of lactose monohydrate is in accordance with the Public Statement (EMEA/CPMP/571/02).

**Manufacture of the Product**

The manufacturing process involves conventional operations such as granulations, drying, sieving, blending, tablet compressing and film-coating.

All critical process parameters have been identified and are controlled by appropriate in process controls. The validation report demonstrates that the process is robust and produces tablets of consistent quality.

*Product Specification*

The finished product specification at release includes tests for assay, and uniformity of content, disintegration, and microbiological aspects. The specifications are in line with ICH Q6A and identical to the specifications approved for the 2.5 mg, except for the limits on degradation products, which have been decreased. The control tests comply with Ph. Eur. where relevant.

*Stability of the Product*

Stability studies were carried out according to the ICH requirements. The parameters tested were assay, degradation products, colour and disintegration.

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.**

This is a conventional standard formulation of a soluble substance resulting in a rapidly dissolving tablet. The active substance is very stable well characterised and documented. The excipients are commonly used 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.

## Non-clinical aspects

**Introduction**

The '*Note for Guidance on Postmenopausal Osteoporosis in Women'* (CPMP/EWP/522/95 rev 1; London, January 2001) recommends for medicinal products aimed for use in prevention and/or treatment of

postmenopausal osteoporosis in women an evaluation of bone quality in two species; the adult ovariectomised rat and an other animal with oestrogen deficiency. The studies should cover a period of 6 remodelling cycles and should include bone mass and bone density measurements, bone architecture, histology and histomorphometry as well as biomechanical testing of bone strength. These studies have been submitted with the original Marketing Authorisation application. The new studies presented to support the current application for 150 mg once a month are toxicological studies discussed in the relevant section.

**Pharmacology**

There have been no new pharmacological studies performed. The non-clinical primary pharmacology data previously submitted as part of the initial MAA for the 2.5 mg film-coated tablets included daily and intermittent administration of ibandronate in ovariectomised (OVX) rats, OVX dogs and ovariohysterectomised (OHX) monkeys and provide a good basis for the intended intermittent ibandronate administration in humans. The results of these studies have been assessed previously and are now summarised in a published study (Bauss and Russel, 2004[1]).

The duration of action of intermittently applied ibandronate most likely depends on a combination of dose, dosing frequency, and underlying bone turnover rate. Taking into account the age-dependent and OVX-dependent bone turnover changes in rats, it can be concluded that the bone remodelling time in OVX rats is about 5-6 times less than in humans. Since the bone remodelling time in pre-menopausal humans is about 90-120 days, the bone remodelling time in OVX rats can be calculated to be about 15-24 days. Thus, the therapy-free interval of 2, 4 and 6 weeks tested in OVX rats roughly represents 1, 2 and 3 remodelling cycles in rats. Conversely, a monthly dosing interval in humans, which was tested in the clinical study (BM16549/MOBILE), would correspond to a dosing interval of about 10 days in monkeys and of about 5-8 days in rats. Therefore, the studies performed in rats, dogs and monkeys roughly reflect a dosing duration of up to 5 years in humans. Since bone re-modelling times in postmenopausal women are increased, the numbers calculated can be regarded as a conservative estimate. Overall, these data indicate that the intermittent treatment regimens with ibandronate have been appropriately compared between species.

The safety pharmacology programme for the 2.5mg/day treatment regimen also supports intermittent dosing.

Overall, the previously submitted non-clinical pharmacology data support the present application (line extension) for the oral intermittent dosing with 150 mg ibandronate once monthly.

*Pharmacokinetics*

ADME studies were performed in the rat, dog and monkey and submitted with the initial MAA for the 2.5 mg film-coated tablet. No new Pharmacokinetic data were submitted as part of this application.

The non-clinical pharmacokinetic studies with ibandronate showed the known characteristics of aminobisphosphonates: A very low absorption rate from the GI tract, a high affinity to bone (about 40-50% of the administered ibandronate is located in bone with a very long half-life of 300-500 days), no biotransformation of the drug and a predominantly renal excretion of the unmetabolised drug.

It was shown in OVX rats that the concentration of ibandronate in vertebrae ($L_1$) and tibia was dose-dependent and linear. Importantly, subcutaneous ibandronate dosing once daily or cyclical intermittent every 25 days resulted in similar concentrations of ibandronate in vertebrae and tibia, if the applied total (cumulative) dose was about the same. These findings provide the basis for the similar pharmacodynamic effects observed with daily or intermittently applied ibandronate in rats.

*Toxicology*

[1] Bauss F, Russell RGG, 2004. *Ibandronate in osteoporosis: preclinical data and rationale for intermittent dosing*. Osteoporos Int.;15:423-433 (manuscript available on request for FDA)

The previously submitted toxicology programme characterised extensively the toxicity of ibandronate and supported the daily administration of 2.5 mg ibandronate for the treatment of postmenopausal women.

In support of the monthly oral regimen for the treatment of postmenopausal osteoporosis three new single dose toxicity studies and two new repeat-dose toxicity studies (with ibandronate administered by the intravenous route) were submitted. These new GLP-studies were conducted to support the renal safety of intermittent dosing.

Single dose toxicity studies

The three new single-dose studies were conducted in order to characterise the minimum nephrotoxic dose and the impact of $C_{max}$ on the incidence and severity of renal lesions.

In the first study, groups of 5-6 female Wistar rats were administered a single i.v.dose of 1-20 mg/kg ibandronic acid as a bolus dose and/or an i.v. infusion over 2.5-60 minutes. A Non Toxic Effect Level (NTEL) was not established since most animals had minimal microscopical degeneration or necrosis of PCT cells at 1 mg/kg. This is consistent with the NTEL of 0.3 mg/kg established in earlier studies of intermittent i.v. dosing in the rat.

In the second study, 3 groups of 11 male Wistar rats were administered 1 mg/kg ibandronic acid by bolus i.v. or a 15-minute i.v. infusion. Two of the groups had undergone unilateral nephroectomy whereas a sham operation was performed on the controls. As expected, serum creatinine and urea increased in the unilaterally nephrectomised animals. However, there was no difference in the histopathological lesions in the PCT between treatment groups and controls.

In the last single-dose study, groups of 6 female Wistar rats were given an i.v. bolus injection of 1, 3, 6 or 10 mg/kg of zolendronate or 1 or 3 mg/kg of ibandronic acid. Half the animals were examined one day after treatment and the remainder after 4 days. With both drugs, subclinical histopathological changes in the PCT were observed after 4 days at doses equal to or higher than 3 mg/kg.

Repeat-dose toxicity Studies

Two new repeat-dose studies were conducted in order to characterise the impact of $C_{max}$ and repeated dosing on the incidence and severity of renal lesions and to assess the risk for cumulative kidney toxicity in an intermittent i.v. dose regimen.

In the first study, groups of 5 male and female Wistar rats were treated for 2 weeks with 0, 1 or 3 mg/kg/day of ibandronic acid by i.v. bolus injection, i.v. infusion over 15 minutes or i.v. infusion over 60 minutes. One 3 mg/kg/day female died on day 10, presumably from acute renal failure. There was a dose- and infusion-time-related increase in serum ALT, AST, creatinine and urea, incidence of kidney discoloration, absolute and relative kidney weight and microscopic kidney lesions (tubular basophilia, dilatation, casts and necrosis), with secondary effects on body weight, food consumption and serum electrolytes.

In the second repeat-dose toxicity study, ibandronic acid was administered as an i.v. bolus injection or 15-30 minute-infusion to groups of 6 female Wistar rats at dose levels of 0 or 1 mg/kg every 3 weeks for a total of 6 months. One group remained untreated until the last study week and then received a single i.v. bolus injection (singe-dose group). This study design was also applied to zolendronate which was administered at 1 and 3 mg/kg/3 weeks as a positive control. At 1 mg/kg both bisphosphonates caused degeneration and/or necrosis of PCT cells which was somewhat more frequent after repeat than after single dosing. Repeat dosing of either drug also caused mild epithelial cell hypertrophy and hyperplasia of the collecting ducts and distal tubules, whereas these structures were not affected by single dosing. The incidence and severity of these changes were unrelated to the $C_{max}$ of ibandronic acid.

Ibandronate – Drug interaction

Specific toxicology studies with combined treatment of ibandronate with other potentially nephrotoxic drugs were not conducted. However, a number of dedicated nephrotoxicity studies were performed in animals to examine the renal effects in more detail, especially minimal nephrotoxic doses, to better understand the underlying pathomechanism, and to further evaluate the risk of renal safety under specific treatment regimes. The results from these studies and the published information on other classes of potentially nephrotoxic compounds, allows a risk assessment for the combination of ibandronate with other drugs based on theoretical considerations, i.e. comparison of findings and pathomechanisms. The main outcome of this risk assessment is summarised in the table 1. below:

***Table 1. Presentation of the risk assessment of renal damage under specific treatment regimes***

| Hypothetical mechanism | Relevant concomitant medicines | Estimated risk of toxic interactions | Comments |
|---|---|---|---|
| Effects on renal haemodynamics | Cyclosporine, amphotericin B, NSAIDs, ACE inhibitors, methotrexate | Negligible | Ibandronate has no direct effect on GFR or renal blood flow |
| Competition for intracellular transport mechanisms | - | Negligible | Ibandronate does not undergo active renal excretion |
| Intracellular accumulation of concomitant nephrotoxic medicines | Aminoglycosides, cephalosporins | Negligible | Different pathomechanisms |
| Distal tubular and/or collecting duct injury | Amphotericin B | Low | Amphotericin B causes distal tubular injury by inducing cell membrane pores and regional ischaemia |
| Intratubular obstruction | Acyclovir, sulfonamides, chemotherapeutic agents and methotrexate | Negligible | Ibandronate does not cause intratubular obstruction |
| Induction of renal papillary necrosis | NSAIDs | Low | Ibandronate has no toxic effect on renal papillae |

Based on the above, there is no overt evidence that co-administration of ibandronate with other commonly used potentially nephrotoxic, drugs is likely to increase the risk of nephropathy.

Ecotoxicity/environmental risk assessment

The Environmental Risk Assessment (ERA) was revised to account for the increase in use, which may result from the line extension. Including all brands, dosage forms and strengths, the revised risk quotient is 0.011. Since this is lower than 1, it is agreed that the proposed line extension is unlikely to result in any perceivable risk to the environment.

Reproductive and developmental studies

Reproduction and developmental toxicity studies were not performed, but are not required, as ibandronate will only be used in postmenopausal women.

Local tolerance / Skin irritation studies

Ibandronic acid proved corrosive in a skin irritation test in rabbits. Although this route is irrelevant to the proposed line extension, it nevertheless indicates that there may be a potential for irritation or burns to the oesophagus and/or gastric mucosa, particularly as the proposed tablet is 60 times stronger than the currently marketed product. However, the potential for the 150-mg tablet to cause GI tract intolerance was not evaluated non-clinically, but monitored closely in clinical trials. Since it would be impractical to administer the 150-mg tablet to experimental animals, this approach is considered acceptable.

Other toxicity studies

Other safety aspects (including potential of genotoxicity, carcinogenicity, local tolerance, skin irritation and sensitization, the risk of QT/QTc interval prolongation and all pharmacodynamic related effects) are considered to remain unaffected by the change of the treatment regimen from daily to monthly intervals.

*Discussion*

The new non-clinical studies to support the 150 mg dose once a month have focused on the toxicology of the dose and more specifically on the renal safety.

Three single-dose toxicity studies (as presented above) were conducted to characterise the minimum nephrotoxic dose and the impact of $C_{max}$ on the incidence and severity of renal lesions. In all studies, ibandronic acid was administered by i.v. bolus injection or by short-term i.v. infusion. The LTEL (Lowest Toxic Effect Level) was 1 mg/kg. At this dose level, unilateral nephrectomy did not increase the incidence and severity of PCT lesions in the remaining kidney. In a study (ies) comparing ibandronic acid with zolendronate (which has been reported to cause isolated cases of acute renal insufficiency in patients), both drugs caused similar pathology and the LTEL was 3 mg/kg in both cases.

When ibandronic acid was administered by i.v. injection or infusion at different speeds for 2 weeks at 0, 1 or 3 mg/kg/day, all changes in kidney pathology and kidney-related clinical chemistry parameters were found to depend on the $C_{max}$ values whereas pharmacodynamic effects such as changes in serum calcium and red blood cells (RBC) parameters were independent of injection speed.

In a 6-month study in which ibandronic acid was administered by i.v. injection or infusion at 0 or 1 mg/kg every 3 weeks or once at the end of the study, the only abnormal finding was subclinical degeneration and/or necrosis of PCT cells and mild epithelial cell hypertrophy and hyperplasia of the collecting ducts and distal tubules. There was no relationship between $C_{max}$ values and the incidence or severity of these findings. The severity of the PCT lesions was similar after single and repeat dosing, but the frequency was somewhat higher after repeat dosing (2/6 animals) than after single dosing (1/6 animals). Lesions of the distal tubules and collecting ducts were only seen after repeat dosing.

Renal safety margins were calculated based on human AUC and $C_{max}$ values determined in a bioequivalence study in postmenopausal women and from a supplementary Phase I study, using maximum values as well as the upper bound of the 90% confidence interval. Since there are no repeat-dose toxicity studies using intermittent oral administration, animal AUC and $C_{max}$ values were based on rat and dog studies using either intermittent (twice monthly) i.v. or daily oral administration of ibandronic acid. Based on maximum human values of 1000 ng.h/ml and 250 ng/ml, respectively, the AUC-based safety margins ranged from 1-3 and $C_{max}$-based safety margins were about 5-17. Based on the upper bound of the 90% confidence intervals, safety margins were approximately twice as high. These safety margins are comparable to those observed with other bisphosphonates and/or dosing regimens and suggest that the proposed dosing regimen of 150 mg ibandronic acid p.o. once a month is unlikely to be associated with any significant risk of kidney toxicity.

Specific toxicology studies with combined treatment of ibandronate with other potentially nephrotoxic drug were not conducted. Based on the available knowledge about the underlying pathomechanisms of the nephrotoxicity of ibandronate and published information from other classes of potentially nephrotoxic compounds, there is no overt evidence that co-administration of ibandronate with other commonly used, potentially nephrotoxic, drugs is likely to increase the risk of nephropathy.

## 3.6 Clinical aspects

### Introduction

An extensive clinical pharmacokinetic evaluation of ibandronate has been performed and submitted in the original MAA for Bonviva 2.5 mg daily. To support this line extension application (150 mg), clinical studies have been performed in order to investigate the tolerability, relative bioavailability and effect on bone turnover of three monthly oral doses of ibandronate (BP16331), the bioequivalence of single-unit tablets to multiples of the 50 mg tablets (SB743830/003 and SB743830/002), and bioavailability of various time intervals between food and tablet intake (BP16469). Additionally, in support of the newly proposed indication *"treatment of postmenopausal osteoporosis"* 2-year efficacy and safety data from the pivotal non-inferiority phase III study, BM16549 (MOBILE) was submitted.

### Pharmacokinetics

The pharmacokinetic data submitted during the original MAA for Bonviva 2.5 mg daily were derived from over 700 subjects (including studies performed in healthy male volunteers, healthy postmenopausal women, postmenopausal women with osteoporosis, patients with varying degrees of renal impairment and in patients with metastatic bone disease) within 24 clinical pharmacology studies, one phase II study (MF 4427) and from clinical pharmacology assessments within 2 therapeutic trials (MF 4386, MF 4348). In support of the once monthly oral regimen four additional PK studies have been performed:

A pilot Phase I study in postmenopausal women to investigate the tolerability, relative bioavailability and effect on bone turnover of three monthly oral doses of ibandronate (50 mg, 100 mg or 150 mg) given as multiples of 50 mg tablets (BP16331). Two studies investigating the bioequivalence of single-unit tablets (100 mg and 150 mg) to multiples of the 50 mg tablets (SB743830/003 and SB743830/002). Finally, a study, which investigated the effect on bioavailability of various time intervals between food and tablet intake, performed since the original MAA, is also included (BP16469).

These studies were submitted as part of the current application and provided additional information regarding dose dependency of ibandronate PK as well as new information regarding the importance of time intervals between administration of ibandronate and intake of food.

Apart from this information no new data regarding the ADME for ibandronate has been included. Moreover, two single-dose studies have been undertaken to demonstrate bioequivalence between the 100 mg or 150 mg tablets intended for marketing and multiples of 50 mg tablets used in the clinical studies.

The methods used are appropriate for the studies undertaken. For studies on bioavailability or bioequivalence the methods used are in accordance with the CPMP "*Note for Guidance on Postmenopausal Osteoporosis in Women"*. Analytical methods are the same as used in the original MAA for ibandronate 2.5 mg once daily raising no concerns regarding comparability of results.

### Bioavailability

No new data is presented. The original MAA investigated the dose proportionality in the range 2.5-50 mg orally and found no signs of dose-dependent PK. Oral bioavailability and dose proportionality for oral doses above 50 mg were investigated in the pilot study BP 16331.

The oral bioavailability of ibandronate is low (~0.6%), highly variable and is markedly reduced in the presence of food (see also below). After oral administration, ibandronate is rapidly absorbed with median peak plasma concentrations reached by one hour.

*Dose dependency*

Ibandronate 50, 100 and 150 mg (all as multiples of 50 mg tablets) were administered as oral doses every 30 days for 3 months. Serum samples for ibandronate measurement were collected following the first dose only; urine samples were collected following the first and third dose of ibandronate to characterize the pharmacokinetics of ibandronate. The relative bioavailabilities of the 100 mg and 150 mg dose relative to the 50 mg dose are shown in Table 2 below.

***Table 2: Parameter Estimates for $AUC_{0-\infty}$ Adjusted to a Dose of 50 mg (BP 16331)***

| | | | Mean Effect Ratio (Test / Reference) | |
|---|---|---|---|---|
| **Variable** | **Dose (mg)** | **Estimate** | **Estimate (%)** | **95% Confidence Region (%)** |
| Dose adjusted $AUC_{0-\infty}$ | 50 (pooled) | 27.5 | 100 | Reference |
| | 100 | 35.8 | 130 | [94, 180] |
| | 150 | 52.7 | 191 | [138, 265] |

The exposure following administration of 50, 100 or 150 mg as multiples of 50 mg tablets was not dose proportional, with both AUC and $C_{max}$ showing greater increase in exposure with increasing dose.

From a pure mathematical point of view 70 mg once monthly corresponds to 2.5 mg daily in cumulative dose and modelling of data from the pivotal study supporting the daily dosage regime (MF4411) suggests that 100 mg once monthly is likely to provide comparable BMD increase as daily treatment. However, by choosing 150 mg as target for once monthly therapy it is aimed at demonstrating superiority compared to once daily dosing and further compensate for the long interval between dosing (also discussed below).

The study BM 16549 (MOBILE) was designed to demonstrate that the 1- and 2- year increases in lumbar spine BMD with a monthly regimen were non-inferior to the daily-approved regimen, with clinical fractures being recorded as adverse events. It allows also the comparison between the 150 mg and 100 mg regimens regarding the BMD as it is discussed below. The results of the study are discussed in detail in the Clinical Efficacy section.

*Drug-food interaction*

It is currently recommended that ibandronate is taken 60 minutes before food based on studies included in the original MAA. In order to further characterise the effect of various time intervals between food and tablet intake on the bioavailability of ibandronate a new study (BP 16469) has been provided.
Twenty-four healthy male volunteers received, according to a randomized crossover design, a 20 mg tablet at the following times relative to a standard meal: 3 hours after a meal with a second standardized meal 1 hour post dose (Treatment A); 4 hours after a meal, with a second meal 1 hour post dose (Treatment B); 4 hours after a standardized meal in the evening with the subjects becoming supine 1 hour post dose (Treatment C); and 1 hour before the first meal of the day (Treatment D). Blood and urine samples were collected for 24 hours after drug administration to determine the pharmacokinetics of ibandronate.

Mean serum concentration-time profiles for the four treatments are shown in Figure 1 and the values for relative bioavailability are presented in Table 3.

**Figure 1. Mean Serum Ibandronate Concentration -Time Profiles After Administration of 20 mg Ibandronate at Various Time Intervals between Food Intake and Drug Administration (BP16469)**

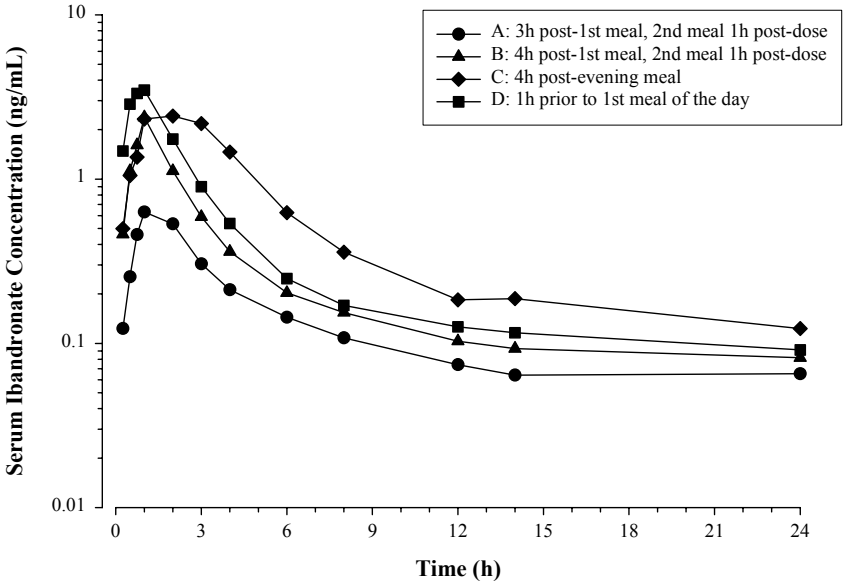



**Table 3 Parameter Estimates for $AUC_{last}$ (BP 16469)**

| Variable | Treatment | Estimate | Mean Effect Ratio (Test / Reference) | |
|---|---|---|---|---|
| | | | Estimate (%) | 95% Confidence Region (%) |
| $AUC_{last}$ | D | 8.33 | 100 | Reference |
| | A | 1.86 | 22 | [16, 31] |
| | B | 4.59 | 55 | [40, 77] |
| | C | 9.87 | 118 | [85, 165] |

Following administration of ibandronate after an overnight fast (reference), serum levels rose rapidly, reaching an average maximum concentration of 3.9 ng/mL with a mean $t_{max}$ of 0.75 hours, and then declined in a multiphasic manner. Lower exposures were observed for the two treatments which simulated a mid-day administration, with the average maximum concentrations reduced by about one third following a 4 hour pre-dose fast and to only about one fifth of the reference level following a 3 hour pre-dose fast. For an evening administration, where dosing followed a 4 hour fast but subjects then retired at 1 hour post-dose, the average maximum concentration was similar to that for the reference fasted treatment (reference). However, an evening dose is not recommended due to practicalities such as staying fasted for four hours after the evening meal and timing the bedtime to be at least five hours after the evening meal.

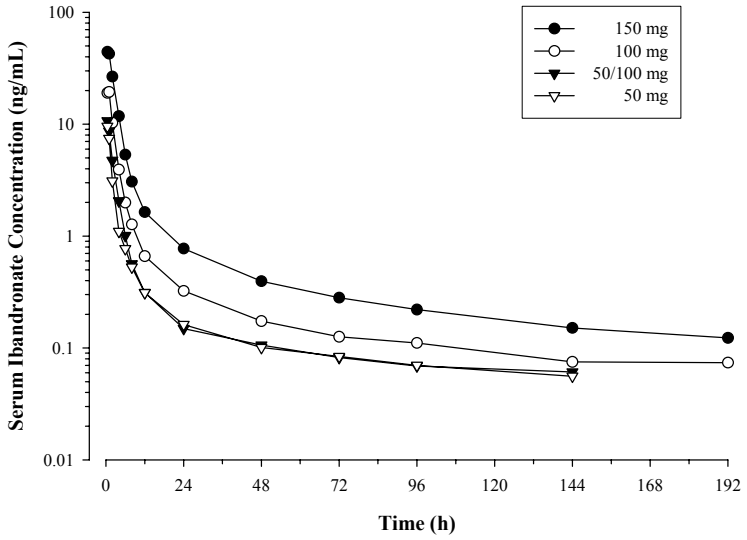
This study has substantially contributed to the knowledge of the sensitivity of ibandronate to food administration.

*Dose proportionality*

The original MAA investigated the dose proportionality in the range 2.5-50 mg orally and found no signs of dose-dependent PK. In the BP16331 study, 36 postmenopausal women each received 50 mg (1 × 50 mg tablet), 100 mg (2 × 50 mg tablets), or 150 mg (3 × 50 mg tablets) oral doses every 30 days for 3 months. The 50 mg group was subdivided into two groups of 18; one group received 50 mg on all 3 occasions and a second group that received 50 mg for the first dose and 100 mg (2 × 50 mg) for the second and third doses (50/100 mg group). Serum samples for ibandronate measurement were collected following the first dose only; urine samples were collected following the first and third dose of ibandronate to characterize the pharmacokinetics of ibandronate.

Mean serum concentration-time profiles for the four treatments are shown in Figure 2. Variability in serum concentrations at individual time points within treatments was high and this was reflected in estimates of peak concentration ($C_{max}$) and AUC with coefficients of variation across the three doses in the ranges 66 - 206% and 57 - 158% respectively. Average estimated half-lives were 27, 33, 59 and 72 hours for subjects receiving 50 mg, 50/100 mg, 100 mg and 150 mg respectively. This apparent trend towards increased half-life with increasing dose is a direct consequence of the incomplete description of the very slow rate of decline of the terminal portion of individual curves. This is caused by the generally lower serum concentrations with low doses that frequently were below the quantification limit before reaching the scheduled last time point.

**Figure 2. Mean Serum Ibandronate Concentration-Time Profiles After First Oral Administration of 50, 100 and 150 mg Ibandronate to Postmenopausal Women (BP 16331)**




The relative bioavailabilities of the 100 mg and 150 mg dose relative to the 50 mg dose are shown in Table 4. The exposure following administration of 50, 100 or 150 mg as multiples of 50 mg tablets was not dose proportional, with both AUC and $C_{max}$ showing greater increase in exposure with increasing dose. The reason for this dose-dependent PK with doses above 50 mg has not been fully elucidated, but was not associated with any adverse events or other safety issues.

**Table 4. Parameter Estimates for $AUC_{0-\infty}$ Adjusted to a Dose of 50 mg (BP 16331)**

| Variable | Dose (mg) | Estimate | Mean Effect Ratio (Test / Reference) | |
|---|---|---|---|---|
| | | | Estimate (%) | 95% Confidence Region (%) |
| Dose adjusted $AUC_{0-\infty}$ | 50 (pooled) | 27.5 | 100 | Reference |
| | 100 | 35.8 | 130 | [94, 180] |
| | 150 | 52.7 | 191 | [138, 265] |

Knowing that bisphosphonates are nephrotoxic in animals and may be associated with rare skeletal adverse events such as aseptic osteonecrosis, the long-term safety (> 12 month) of the 150 mg once monthly dose in comparison to the current 2.5 mg daily administration has been carefully considered (see clinical safety).

***Bioequivalence***

Bioequivalence of a single 100 mg or 150 mg tablet of ibandronate relative to 2 × 50 mg or 3 × 50 mg tablets of ibandronate was evaluated in study SB 743830/003 (100 mg) and study SB 743830/002 (150 mg) respectively.

The single unit dose tablet formulation of 100 mg was bioequivalent to 2x50 mg tablets. The single unit dose tablet formulation of 150 mg was bioequivalent to 3x50 mg tablets. In both studies the 90% confidence intervals for the ratio of the adjusted geometric means for ibandronate AUC(0-∞) and Cmax were contained within the acceptance range of 0.80 to 1.25 according to the CPMP "*Note for guidance on the investigation of bioavailability and bioequivalence*", (CPMP/EWP/QWP/1401/98, rev. 2001). This range was prespecified in the study protocol for AUC, but not for Cmax (the prespecified equivalence range for Cmax was 0.75 to 1.33).

Bioequivalence between the 100 mg or 150 mg tablets intended for marketing and the corresponding doses given as multiples of 50 mg tablets has been demonstrated.

*Distribution*

No new data has been provided which is acceptable. From the original MAA it is known that the volume of distribution is high (~90L), most likely related to substantial distribution within skeletal tissue, i.e. preclinical studies indicating that ibandronate binds primarily to bone, with some uptake in the spleen, liver and kidney. The amount of dose removed from the circulation via the bone is estimated to be 40% to 50%. Ibandronate is moderately bound to human plasma proteins (84% - 86% at therapeutic drug concentrations) and is not taken up by erythrocytes or platelets. The protein binding for ibandronate is relatively constant over clinically relevant concentrations (0.5 - 2000 ng/mL).

*Elimination*

No new data has been provided, but only the following information is available. Plasma elimination of ibandronate is multiphasic. Renal clearance and distribution into bone accounts for the rapid and early decline in plasma concentrations, which reach 10% of the $C_{max}$ within 3 to 8 hours. This is followed by a slower clearance as ibandronate redistributes back into the blood from the bone. The observed apparent terminal half-life for ibandronate is generally in the range of 10 to 72 hours, but this is likely to be a gross underestimate as the values calculated are largely a function of the duration of study, the

dose used and assay sensitivity. The 'true' terminal half-life is likely to be substantially longer than 72 hours as is common with other bisphosphonates.

*Pharmacokinetic interaction studies*

No new *in vitro* data has been submitted. Due to the lack of biotransformation of ibandronate the potential for drug-drug interactions through inhibition or induction of CYP-isozymes are unlikely to occur.

No new *in vitro* data has been submitted. The active renal secretory pathway that appears to be involved is specialized, involving neither acidic nor basic tubular transport processes and thus, ibandronate is not anticipated to interfere with the excretion of other drugs by those systems in humans**.** Potential pharmacokinetic interactions between ibandronate and drugs likely to be concurrently administered and whose pharmacology suggested a potential interaction have been examined. Interaction studies in postmenopausal women and in patients with multiple myeloma demonstrated the absence of any interaction potential with tamoxifen, hormone replacement therapy (estrogen), or melphalan/prednisone. Although ranitidine caused an increase in ibandronate bioavailability of about 20%, this is considered to be of no clinical significance and no dose adjustment is required when ibandronate is administered with $H_2$-antagonists or other drugs that increase gastric pH. In addition to the low and variable absorption of ibandronate in the presence of food, products containing calcium and other multivalent cations, such as aluminium, magnesium and iron, are likely to interfere with absorption.

**Pharmacodynamics**

The antiresorptive effects of bisphosphonates are well established and have not been further investigated in the present application. However, dose finding for the once monthly treatment has been performed in a pilot Phase I study investigating the tolerability, relative bioavailability and effect on bone turnover of three monthly oral doses of ibandronate (50 mg, 100 mg or 150 mg) given as multiples of 50 mg tablets. Urinary markers of bone turnover were used as primary endpoint. In addition to these studies results from computer PK/PD-simulations have been provided investigating the behaviour of a monthly oral ibandronate regimen in terms of effect on the urinary excretion of the C-telopeptide of the alpha chain of type I collagen (uCTX). Studies of hormone replacement therapy and alendronate therapy suggest that a 'threshold' level of suppression of biochemical markers of bone turnover is predictive for a positive and clinically meaningful response in BMD. Attainment of steady state in uCTX under regular dosing as well as non-compliant patient behaviour was explored using this PK/PD model.

Results from this simulation clearly shows that both once monthly doses are expected to result in relative suppression of uCTX equivalent to that which has been seen with the current 2.5 mg daily dosing recommendation. Moreover, the PK/PD model was also used to evaluate the effect of non-compliance (e.g. missed doses or 'late' doses) on the time course and AUC for uCTX (percent change from baseline). This simulation show that if one monthly dose is missed after 1, 2, 3, 6 and 8 regular doses, a small increase in AUC of uCTX is incurred (between 2.5% and 16.7% increase in AUC as compared to compliant drug intake over 15 months), with the uCTX time course profiles reconciling within 3 months. If the dose is taken 'late' e.g. within 7 days of the next scheduled dose, then a smaller transient increase in the AUC of uCTX of ~ 0.7% is predicted, with the uCTX time course profiles reconciling within 6 months. Thus, based on mathematical modelling on marker of bone turnover, there is no concern that a 3-week delayed or even a missed dose may compromise efficacy. 'Real life' compliance with their once monthly therapy as compared to e.g. daily or weekly dosage regimens is to be submitted post-authorisation.

**Clinical efficacy**

**Introduction**

The approval of a 2.5 mg daily oral tablet formulation of ibandronate for the prevention and treatment of postmenopausal osteoporosis (February 2004) was based on the results of the pivotal Phase 3 study MF4411, in which a reduction in the risk of new morphometric vertebral fractures and progressive increases in bone mineral density (BMD) in lumbar spine and hip of patients with postmenopausal osteoporosis was demonstrated.

**Clinical Studies**

In support of the newly proposed indication *"treatment of postmenopausal osteoporosis"* 2-year efficacy and safety data from the pivotal non-inferiority phase III study, BM16549 (MOBILE) is submitted.

The evaluation of the efficacy of the once monthly treatment of osteoporotic postmenopausal women with ibandronate is based on a single pivotal multicenter, randomised, double-blind, parallel group Phase III study (BM16549) which was designed to demonstrate non-inferiority, in terms of lumbar BMD changes from baseline, between daily and monthly ibandronate applications.

The study enrolled 1609 postmenopausal women between the age of 54 and 80 years who had osteoporosis as indicated by a lumbar spine (L2 – L4) BMD T-score of <-2.5. Patients were randomly allocated in a double-blind manner to one of four treatment groups; 100 mg monthly (on a single day, n=402), 100 mg monthly (split over two consecutive days, n=404), 150 mg monthly (n=401) and 2.5 mg daily (n=402). Stratification according to baseline lumbar spine BMD was performed in order to ensure that across all treatment groups, the distribution of baseline BMD was comparable. Due to the large number of centres in this study, patients were also stratified by center.

The study BM 16549 included women with a mean lumbar spine (L2 - L4) BMD T-score below -2.5 but not lower than -5.0

A significant risk reduction for new vertebral fractures with 2.5 mg ibandronate daily was demonstrated in patients with a BMD T-score ≤ -2.0 SD and in the subgroup of patients with a BMD T-score ≤ -2.5 SD in the pivotal fracture study MF4411 (in original application). Thus regarding the study population there is no relevant difference between the studies MF4411 and BM16549.

The doses of ibandronate were 2.5 mg/daily and 50/50 mg, 100 mg or 150 mg once monthly (to be taken in the morning with plain water after an overnight fast of at least 6 hours, and patients were to remain fasting and upright for one hour post dose). As generally recommended, all patients received calcium (500 mg/day) and vitamin D (400 IU/day) supplements (to be taken in the evening).

Bone mineral density measurements by dual-energy X-ray absorptiometry (DXA) were analysed at a central reading site. CTX measurements were performed at a central laboratory. Both the investigators and the sponsor were blinded to the results of the BMD and CTX analyses during the study.

Results after 2 years

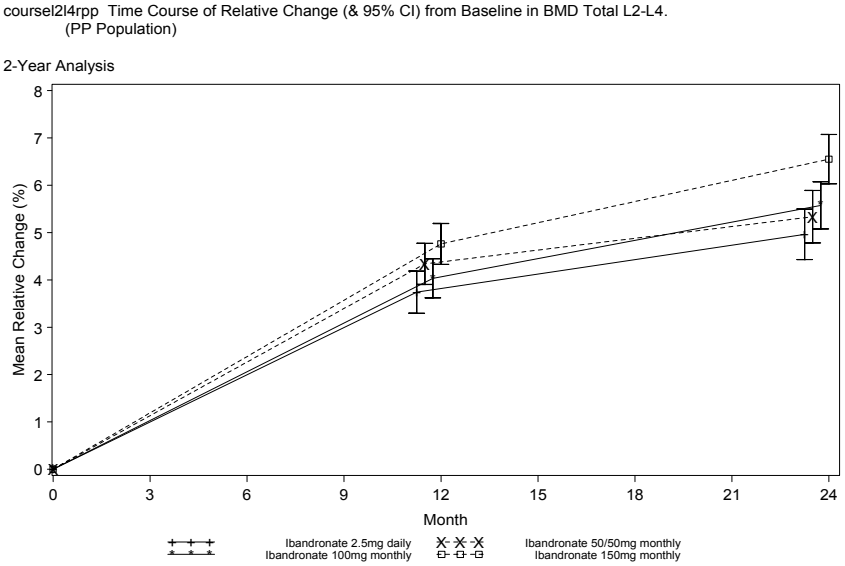
Ibandronate 150 mg once monthly was associated with a significant and robust increase in BMD at the lumbar spine (LS) and proximal femur (Table 5). This increase was significantly and consistently greater than that seen with the 2.5 mg daily regimen after two years. Furthermore, the mean additional increase in BMD during the second year of treatment was greatest in the 150 mg monthly group (1.6%), as shown in Figure 3.

**Table 5: Mean Relative Change from Baseline in BMD at the Lumbar Spine and Proximal Femur After One and Two Years of Treatment (Per-protocol Population)**

| | BM 16549 Ibandronate Year 1 | | | BM 16549 Ibandronate Year 2 | | |
|---|---|---|---|---|---|---|
| | **2.5 mg daily n = 314 -315** | **100 mg monthly n = 306** | **150 mg monthly n = 314 - 316** | **2.5 mg daily n = 292 - 294** | **100 mg monthly n = 277 - 278** | **150 mg monthly n = 289 - 291** |
| LS BMD % increase from baseline | 3.74% | 4.03% | 4.76%*γ | 4.96% | 5.58% | 6.55%*γ |
| TH BMD % increase from baseline | 1.96% | 2.69%* | 3.01%* | 2.50% | 3.52%* | 4.16%*γ |
| FN BMD % increase from baseline | 1.72% | 1.88% | 2.19% | 1.91% | 2.62%* | 3.12%* |
| Troch. BMD % increase from baseline | 3.19% | 3.82%* | 4.59%*γ | 4.02% | 5.31%* | 6.18%*γ |

* $p < 0.05$ vs. 2.5 mg daily; $^{\gamma}$ $p < 0.05$: 150 mg vs. 100 mg monthly

**Figure 3: Time Course of Relative Change (95% CI) from Baseline of Lumbar Spine BMD over 2 Years**




In addition, the increase in LS BMD after one and two years of treatment was consistently greater in the 150 mg monthly Ibandronate group, when compared with 100 mg monthly and 2.5 mg daily, in patients at highest risk for osteoporotic fractures (Table 6).

**Table 6: Mean (n) Relative Change from Baseline in BMD at the Lumbar Spine After One and Two Years of Treatment in High Risk Subgroups (Per-protocol Population)**

| | BM 16549 Ibandronate Year 1 | | | BM 16549 Ibandronate Year 2 | | |
|---|---|---|---|---|---|---|
| | **2.5 mg daily** | **100 mg monthly** | **150 mg monthly** | **2.5 mg daily** | **100 mg monthly** | **150 mg monthly** |
| -5.0 ≥ Baseline LS BMD T-score < -3.5 (n) | 4.61 (106) | 5.09 (100) | 5.21 (106) | 5.79 (101) | 6.15 (87) | 7.29* (99) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Age ≥70 years (n) | 4.07 (93) | 4.53 (92) | 4.87 (98) | 5.80 (86) | 6.23 (79) | 6.81 (92) |
| Previous fractures since age 45 (n) | 3.69 (154) | 4.12 (137) | 4.46 (145) | 4.81 (146) | 5.68 (122) | 6.69* (130) |

* $p < 0.05$ vs. 2.5 mg daily

*Responder Rate*

The "CPMP *Note for Guidance on Postmenopausal Osteoporosis in Women* (CPMP/EWP/552/95 rev 1)" defined responders to treatment as the incidence of patients who had an increase in BMD above baseline.

In study BM 16549, responders were defined by the incidence of patients who had an increase in BMD above or equal to baseline, and also as the incidence of patients whose lumbar spine or total hip BMD increased by ≥ 6% or ≥ 3% from baseline, respectively, after one and two years of treatment.

After one and two years of treatment with Ibandronate 150 mg once monthly, more than 90% of patients had an increase in lumbar spine or total hip BMD greater or equal to baseline, and this was significantly greater compared with the 2.5 mg daily treatment group (LS: Year 1, $p = 0.008$; Year 2, $p = 0.004$; TH: Year 1 and Year 2, $p < 0.001$). After two years, the incidence of responders in the 150 mg monthly treatment group after 2 years was also greater than that in the 100 mg monthly treatment group at lumbar spine (93.5% vs. 87.8%; $p = 0.019$) and total hip (93.4% vs. 88.8%; $p = 0.053$).

Considering both lumbar spine and total hip BMD increase, after one and two years of treatment with Ibandronate 150 mg once monthly, more than 80% of patients had an increase at both sites greater or equal to baseline. This BMD gain was significantly greater when compared with the 2.5 mg daily (Year 1 and Year 2, $p < 0.001$) treatment group, and after two years with the 100 mg monthly ($p = 0.014$) treatment group.

The greatest incidence of patients with a lumbar spine BMD increase of ≥ 6% when compared to baseline, was seen in the 150 mg monthly Ibandronate group after one and two years of treatment (34.4% and 54.3% respectively); the incidence of responders was significantly greater than in the 2.5 mg daily treatment group (Year 1, $p = 0.005$ and Year 2, $p < 0.001$), and significantly greater than in the 100 mg monthly Ibandronate group after two years ($p = 0.032$).
After one and two years of treatment, the greatest incidence of patients with a total hip BMD increase of ≥ 3% when compared to baseline was seen in the 150 mg monthly Ibandronate group; the incidence of responders was significantly greater than in the 2.5 mg daily treatment group (Year 1 and Year 2, $p < 0.001$). Table 7 summarises these results.

**Table 7. Mean Percentage of Patients with BMD Increases at the Lumbar Spine and Total Hip After One and Two Years of Treatment (Per-protocol Population)**

| | **BM 16549 Ibandronate Year 1** | | | **BM 16549 Ibandronate Year 2** | | |
|---|---|---|---|---|---|---|
| | **2.5 mg daily n = 314 - 315** | **100 mg monthly n = 304 - 306** | **150 mg monthly n = 310 - 316** | **2.5 mg daily n = 292 - 294** | **100 mg monthly n = 276 - 278** | **150 mg monthly n = 287 - 291** |
| % Patients with LS BMD ≥ baseline | 83.8% | 86.6% | 90.8%* | 86.4% | 87.8% | 93.5%*Y |
| Patients with LS BMD ≥ 6% | 24.2% | 31.7%* | 34.4%* | 35.4% | 45.3%* | 54.3%*Y |
| % Patients with TH BMD ≥ baseline | 76.8% | 86.9%* | 90.5%* | 78.4% | 88.8%* | 93.4%* |
| % Patients with TH BMD ≥ 3% | 34.0% | 44.1%* | 47.8%* | 40.4% | 59.2%* | 65.1%* |
| % Patients with LS and TH BMD ≥ baseline | 65.6% | 77.6%* | 83.5%* | 70.5% | 79.3%* | 87.1%*Y |

* $p < 0.05$ vs. 2.5 mg daily; Y $p < 0.05$: 150 mg vs. 100 mg monthly

**Reduction in Bone Turnover**

The effect of monthly Ibandronate dosing on biochemical markers of bone turnover, are consistent with the higher level of BMD improvement over time.
The 150 mg monthly dose produced significantly greater reductions in bone resorption activity (assessed using serum CTX) than the oral daily regimen (Table 9). Similarly, it also reduced bone formation (Table 8)

**Table 8: Median Relative Decrease Compared to Baseline in Serum CTX and BSAP after One and Two Years of Treatment (Per-protocol Population)**

| | BM 16549 Ibandronate Year 1 | | | BM 16549 Ibandronate Year 2 | | |
|---|---|---|---|---|---|---|
| | 2.5 mg daily n = 271 - 272 | 100 mg monthly n = 276 | 150 mg monthly n = 266 - 267 | 2.5 mg daily n = 220 - 221 | 100 mg monthly n = 211 | 150 mg monthly n = 233 - 235 |
| Serum CTX | 67% | 67% | 76%* | 62% | 60% | 68%* |
| BSAP | 28% | 35% | 39% | 23% | 32% | 37% |

* $p < 0.05$ vs. 2.5 mg daily

Responders were defined as those patients with a decrease in serum CTX from baseline of ≥ 50%, corresponding to the least significant change, or ≥ 70%.
The incidence of patients with a ≥ 50% decrease in serum CTX from baseline levels was greater in the 150 mg monthly group (Year 1, 83.1%; Year 2, 78.7%), than in the 100 mg monthly group (Year 1, 71.0%; Year 2, 63.5%) and the 2.5 mg daily group (Year 1, 73.5%; Year 2, 65.6%). The incidence of responders after one and two years of treatment was significantly greater in the 150 mg monthly treatment group compared with the 2.5 mg daily treatment group ($p < 0.05$) (Table 9).
Similarly, the incidence of patients with a ≥ 70% decrease in serum CTX from baseline levels was also greater in the 150 mg monthly group (Year 1, 62.5%; Year 2, 48.1%), than in the 100 mg monthly group (Year 1, 47.8%; Year 2, 35.1%) and the 2.5 mg daily group (Year 1, 44.1%; Year 2, 35.3%) (Table 9). After one and two years of treatment, the incidence of responders was significantly greater in the 150 mg monthly treatment group compared with the 2.5 mg daily treatment group ($p < 0.05$).

**Table 9: Mean Percentage of Patients with a Serum CTX Decrease After One and Two Years of Treatment (Per-protocol Analysis)**

| | BM 16549 Ibandronate Year 1 | | | BM 16549 Ibandronate Year 2 | | |
|---|---|---|---|---|---|---|
| | 2.5 mg daily n = 272 | 100 mg monthly n = 276 | 150 mg monthly n = 267 | 2.5 mg daily n = 221 | 100 mg monthly n = 211 | 150 mg monthly n = 235 |
| Patients with a decrease in Serum CTX ≥ 50% | 73.5% | 70.1% | 83.1%* | 65.6% | 63.5% | 78.7%* |
| Patients with a decrease in Serum CTX ≥ 70% | 44.1% | 47.8% | 62.5%* | 35.3% | 35.1% | 48.1%* |

* $p < 0.05$ vs. 2.5 mg daily

In conclusion, the new submitted 2-years data confirm that 12-month data further demonstrating significantly higher efficacy on BMD of the 150 mg dose compared to the daily dose and the lower 100 mg monthly dose.

*Discussion*

The primary objective of the pivotal BM 16549 was to show non-inferiority of lumbar spine (L2 - L4) BMD changes after one year of treatment with oral ibandronate at monthly doses of 100 mg and 150 mg, versus daily treatment with 2.5 mg ibandronate. As the mean increase in lumbar spine BMD relative to baseline in all monthly treatment groups (4.1% - 4.9%) at one year was demonstrated to be non-inferior to the 2.5 mg daily regimen (3.9%) this objective was met.

Regarding the 150 mg monthly treatment regime, the increase in BMD relative to baseline was in subsequent analyses shown to be superior to that in seen in the 2.5 mg daily treatment group. Subsequent post-hoc analyses revealed that treatment with monthly doses of 150 mg ibandronate was superior to monthly doses of 100 mg ibandronate. In all treatment groups an absolute increase from baseline in mean lumbar spine was observed after one year of treatment. At the proximal femur, increases from baseline in total hip (2.0% - 3.1%), femoral neck (1.7% - 2.2%) and trochanter (3.2% - 4.6%) BMD after one year of treatment with ibandronate were seen with both the daily and monthly treatment regimens.

The mean increase in BMD was more pronounced for the 100 mg and 150 mg monthly treatment groups compared to the daily treatment group in the femoral neck and thereby the total hip, whereas this was not the case in the trochanter region.. More patients treated with monthly doses of 100 mg or 150 mg ibandronate versus daily treatment with 2.5 mg ibandronate, responded to treatment with an increase in BMD values equal to or above baseline at the lumbar spine, total hip and trochanter

For both the 100 mg and 150 mg monthly treatment groups, more patients responded to treatment with an increase in lumbar spine BMD of 6%, or an increase in total hip BMD of 3% at one year than in the 2.5 mg daily treatment group. All dosing regimens of ibandronate suppressed bone resorption as assessed by serum CTX. At all time points the decrease in serum CTX was greater in the 150 mg monthly treatment group compared to the other groups. More patients in the 150 mg monthly treatment group were classified as responders and had a decrease in serum CTX from baseline of ≥ 50% or ≥ 70% than in the daily treatment group.

The efficacy of ibandronate over 2 years in the study BM16549 confirms the results of the 1-year analysis. A significant greater effect ($p<0.05$) with 150 mg/monthly compared the 2.5 mg/daily application has been observed regarding the relative increase in spinal BMD from baseline (150 mg/mo: 4.76%, 1 y; 6.55%, 2 y), or responder rate (LS BMD) judged as equal or increase from baseline (150 mg/mo: 90.8%, 1 y; 93.5%, 2 y), or judged as increase from baseline > 6% (150 mg/month: 34.4%, 1 y; 54.3%, 2 y), or bone turnover judged as decrease in serum CTX trough values (150 mg/month: 76%, 1 y, 68%, 2 y), or judged as percent responder >50% decrease (83%, 1 y, 78%, 2 y), or >70% decrease (62%, 1 y, 48%, 2 y).

A significant greater effect ($p<0.05$) with 150 mg/monthly compared to the 100 mg/month application has been observed regarding the relative increase in spinal BMD from baseline at 2 y (100 mg/month: 5.58%, 150 mg/month: 6.55%[)]. The responders in LS BMD increase judged as equal or increase from baseline at 2 y (100 mg/month: 87.8%; 150 mg/month: 93.5%[r]), or judged as increase from baseline > 6% at 2 y (100 mg/month: 45.3%; 150 mg/month: 54.3%)

Since the increase in BMD obtained with bisphosphonates correlates with mechanical properties of bone, generally, an increase in BMD in shorter period of times could have a positive effect on the risk reduction of new vertebral fractures.

**Clinical safety**

Clinical safety data are available from the use of oral monthly ibandronate in the pivotal trial BM 16549 comparing dosages of 100 mg and 150 mg monthly ibandronate to 2.5 mg daily ibandronate (N=1602). In addition, safety data are included from a pilot dose finding study BP 16331, a randomised, double blind, parallel-group, placebo-controlled, multicenter pilot study in 144 healthy postmenopausal women investigating the tolerability and safety, pharmacokinetics and effect on bone turnover of three oral monthly doses (50 mg, 100 mg, 150 mg) of ibandronate. This was the first ibandronate study with monthly treatment regimens. Safety data are also included from two bioequivalence studies in 148 postmenopausal women (study SB 743830/002 conducted to demonstrate bioequivalence between a single 150 mg tablet and three 50 mg ibandronate tablets and study SB 743830/003 conducted to demonstrate bioequivalence between a single 100 mg tablet and two 50 mg ibandronate tablets) as well as a food effect study in 24 healthy male volunteers (BP 16469). Data from these studies have not been pooled since the studies differed in terms of patient population, study objectives, study design (including the nature of the control),

extent of exposure, and the nature and schedule of the various assessments for efficacy, safety, pharmacokinetics and pharmacodynamics.

Among the individual body systems, there was no major difference in the overall incidence of adverse events across the treatment groups after two years of treatment. The most commonly affected body systems were infections and infestations (36.5% in the 2.5 mg daily group compared with 36.9% in the 100 mg and 33.8% in the 150 mg monthly groups), musculoskeletal and connective tissue disorders (28.1% in the 2.5 mg daily group compared with 32.1% in the 100 mg and 34.8% in the 150 mg monthly groups), and gastrointestinal disorders (32.2% in the 2.5 mg daily group compared with 32.8% in the 100 mg and 32.3% in the 150 mg monthly groups).

The slightly higher incidence of musculoskeletal and connective tissue disorders in the monthly treatment groups was due to a variety of adverse events that each occurred in only one to two patients, but primarily to a higher incidence of pain in extremity (heterogeneous locations) in the 100 mg (3.3%) and in the 150 mg monthly groups (5.6%) compared to daily treatment group (2.0%).

**Relationship of Adverse Events to Treatment**

The overall incidence of adverse events assessed as remotely, possibly or probably related to trial treatment was comparable across the treatment groups, being reported by 36.1% in the 100 mg and 36.9% in the 150 mg monthly groups, compared with 32.4% in the 2.5 mg daily group.

The most frequently reported adverse events considered remotely, possibly or probably related to treatment were those of the gastrointestinal system (20.8% for 2.5 mg, 24.2% for 100 mg and 22.2% for 150 mg) and the musculoskeletal system (6.8% for 2.5 mg, 6.6% for 100 mg and 9.3% for 150 mg).

**Intensity of Adverse Events**

The majority of adverse events in each treatment group were mild or moderate in intensity. Severe or life-7threatening adverse events were reported with a similar incidence in the 2.5 mg daily [70 (23.2%) and 2 patients respectively, of the 302 patients who reported an adverse event], in the 100 mg [50 (16.0%) and 4 patients respectively, of the 313 patients who reported an adverse event] and in the 150 mg [54 (17.0%) and 3 patients respectively, of the 317 patients who reported an adverse event], monthly groups.
The body systems most commonly affected by severe adverse events, were infections and infestations, musculoskeletal and connective tissue disorders, and gastrointestinal disorders, and the overall rates were generally similar in all groups.

**Serious Adverse Events**

Regarding the Serious Adverse Events (SAEs) over the two years of the study it was shown that there is no significant imbalance in the SAE data for 150 mg monthly Ibandronate compared with the currently approved 2.5 mg daily Ibandronate, with a higher incidence of SAEs in the 100 mg monthly group, with no evidence of causal relationship.

**Adverse Events Leading to Withdrawal from Trial Treatment**

The incidence of adverse events leading to premature withdrawal from trial treatment over the two years of the study was similar across all treatment groups (10.4% in 2.5 mg daily group, 11.1%, and 9.3% in 100 mg and 150 mg monthly treatment groups, respectively). In each treatment group, this was only slightly higher than that reported during the first year of the study (8.9% in the daily group, 9.1% and 7.8% in the 100 mg and 150 mg monthly groups, respectively), and the incidence of adverse events leading to withdrawals during the second year of treatment was well-balanced among all groups (1.5 % in the 2.5 mg daily group, 2.0% and 1.5% in the 100 mg and 150 mg monthly treatment groups, respectively.

Compared to the data reported after one year of treatment, there was no evidence that the incidence of withdrawals during the second year of treatment increased appreciably in any of the body systems, or in one treatment group compared to another. From six months onwards, the rate of discontinuation due to an

adverse event was similar in all treatment groups, with only a different rate for all monthly groups occurring during the first three months. The withdrawal rate in the 150 mg monthly group remained lower than that in the 100 mg monthly group.

**Events of special interest**

Upper Gastrointestinal Adverse Events

The overall incidence of upper gastrointestinal adverse events over the two years of the study was similar in the 2.5 mg daily treatment group (22.8%), and 150 mg (22.5%) monthly groups, and slightly higher in the 100 mg monthly group (25.8%). The two-year data confirm the similar upper gastro-intestinal tolerability of the 150 mg monthly dose, compared to the 100 mg monthly and 2.5 mg daily, as reported in the one-year study report.

Flu – Like Symptoms

Special attention was paid to adverse events occurring within three days of each monthly treatment that might be indicative of a Flu-like reaction. Similar to what had been reported after one year of treatment, the overall incidence of patients with Flu-like events (as pre-defined) remained higher over the two years of the study, in the monthly groups, than in the 2.5 mg daily group. This difference was due primarily to a higher rate of adverse events classified as general disorders (mainly 'influenza like illness' and 'acute phase reaction'), and musculoskeletal disorders (primarily myalgia).
Regardless of the dose, most of the Flu-like symptoms occurred following the first dose, and the majority of events (excluding nausea) which occurred during the first three months of treatment, did not reoccur after the second and third doses.

Clinical Fractures

Over the two years of the study, 112/1583 (7.1%) patients experienced a clinical fracture defined as a symptomatic radiologically confirmed fracture, including all vertebral and non-vertebral fractures. This incidence is similar to the one reported by Rizzoli and colleagues (2002)[2], with alendronate 70 mg once-weekly (7.3%).
Over the two years of the study, the overall incidence of all non vertebral fractures was similar in the 150 mg (5.3%) and 100 mg (5.1%) monthly groups, compared with the 2.5 mg daily group (5.1%), lower than reported with risedronate 35 mg once weekly (8.5%).

Renal Safety

There is no evidence that the higher total systemic dose delivered by the 150 mg monthly dose adversely affects renal function relative to the 2.5 mg daily dose. After two years of treatment with 150 mg once monthly, no differences have been seen in the incidence of defined increases in serum creatinine or in changes to estimated creatinine clearance between the 2.5 mg daily, 100 mg and 150 mg monthly groups. This is consistent with the high margin of safety derived by comparison to the no adverse effect dose level in chronic toxicity testing in two animal species.

Osteonecrosis of the Jaw

The mechanism underlying osteonecrosis of the jaw (ONJ) is currently not known. Likewise it is not known if it is due to intrinsic properties of the molecule, the absolute dose, the cumulative dose or whether the underlying condition (most cases have been associated with cancer) represents the largest risk.

Deaths

[2] Rizzoli R, et al. 2002. *Two-Year Results of Once-Weekly Administration of Alendronate 70 mg for the Treatment of Postmenopausal Osteoporosis*. J Bone Miner. Res; 17: 1988-1996.

Over the two years of the study there were six deaths. Four deaths occurred during the first year of treatment (myocardial infarction [one patient in the 2.5 mg daily group], cardiopulmonary failure, and cerebrovascular accident [one patient each in the 100 mg monthly group], and haemorrhagic cerebral infarction [one patient in the 150 mg monthly group]), and two deaths occurred during the second year of treatment (acute respiratory failure [one patient in the 2.5 mg daily group], and cerebrovascular accident (one patient in the 50/50 mg monthly group). All deaths are considered as unrelated to treatment, and a predisposing history or confounding factors were present in all patients. The two-year data confirm the safety profile observed after one year, with regards to relationship, intensity and deaths.

***Discussion***

The major part of safety data arises from the pivotal study BM 16549. In this study the nature and overall incidence of AEs was comparable between treatment groups. However, there was a higher incidence of musculoskeletal and connective tissue disorders in the 50/50 mg and 150 mg monthly treatment groups compared to the daily treatment group. In accordance with that the most frequent individual AEs were arthralgia, back pain, pain in extremity, localized osteoarthritis, myalgia, and bone pain and the rate of musculoskeletal AEs was considerably higher in the 50/50 mg and 150 mg groups compared to the daily group.

Furthermore, in terms of AEs considered 1) remotely, possibly or probably or 2) possibly or probably related to treatment there was a higher incidence of musculoskeletal events in the 150 mg group in the monthly treatment groups as compared to the daily treatment group. Although, these differences might be due to a higher frequency of pre-existing osteoarthritis and localized osteoarthritis in the 150 mg monthly group, further analyses addressing this topic are needed. Additionally, Flu-like symptoms, which were transient and mainly attributable to a higher rate of influenza-like illness were higher in the monthly treatment groups than in the 2.5 mg daily treatment group. These events were most frequent in the 150 mg monthly group and were not serious in nature or severe in intensity. This potential difference between a daily dosing and the monthly treatment regimes has been appropriately reflected in the SPC. The overall incidence of SAEs was higher in the monthly treatment groups (6.8%-7.8%) compared with the 2.5 mg daily treatment group (4.8%). There was no significant imbalance in the SAE data for 150 mg monthly ibandronate group compared with the currently approved 2.5 mg daily ibandronate. The two groups where a total of 100 mg ibandronate was administered monthly, show a higher incidence of SAEs. The increased incidence is due in part to significant imbalances in SAE reporting in three body systems, a review of which has found no evidence of a causal relationship. The remainder of the imbalance is due to small differences occurring in several body systems, which it is not considered to represent a safety trend. This explanation provided seems to justify that there actually is no causal relationship between these events and the treatment. For the most commonly represented body systems (GI and cardiac disorders, infections and infestations), the incidence of SAEs was similar across all treatment groups. There were no differences between daily and monthly dosing with regard to deaths, serious or severe/life-threatening AEs, premature withdrawals or laboratory abnormalities. There were no differences between treatment groups regarding GI AEs, renal function abnormalities or decreases in calcium levels. The frequency and nature of AEs were in general comparable to incidences reported in previous ibandronate trials. No safety advantage was seen with the 50/50 mg dose, which was administered over two days compared with 100 mg or 150 mg administered on a single day.

In conclusion the two years safety data provide evidence that the use of 150 mg once-monthly dose is associated with a generally acceptable safety profile. Especially no indications of nephrotoxicity or development of aseptic osteonecrosis appear after 2 years of treatment.

## 1.7 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**

Administration of ibandronate 150 mg as a once monthly dose is a promising new therapeutic approach for treatment of postmenopausal osteoporosis minimizing the patient inconvenience associated with daily administration of bisphosphonates. The new **non-clinical** studies undertaken to support the 150 mg dose once a month have focused on the toxicology of the dose and more specifically on the nephrotoxicity and the severity of the renal lesions. During these studies these safety margins are comparable to those observed with other bisphosphonates and/or dosing regimens and suggest that the proposed dosing regimen of 150 mg ibandronic acid p.o. once a month is unlikely to be associated with any significant risk of kidney toxicity.

**Clinical**

The CHMP concluded that the benefit/risk of Ibandronate 150 mg monthly dose is considered as positive in the claimed indication. Selection of the 150 mg dose as compared to lower doses for once monthly administration does not lead to any clinically important adverse effects although this dose results in a considerable increase in cumulative systemic exposure as compared to once daily dosing of 2.5 mg. The results from the submitted pivotal phase-III study demonstrate that oral ibandronate, at a dose of 150 mg once monthly, is **non-inferior** to the approved 2.5 mg daily regimen. Subsequent post-hoc analyses revealed that treatment with 150 mg monthly doses of ibandronate was superior to monthly doses of 100 mg ibandronate. In terms of **safety** no new major safety aspects occurred from the present dataset. It appears that the small difference between the 150 mg/month and 100 mg/month group in patients having possible/probably related AEs and the fact that the serious AEs and withdrawals due to AEs were similar, justifies the clinical use of the 150 mg/month tablet. However, long-term data are needed to fully assess the safety of the proposed dosing regimen. The once monthly administered dosing has not previously been investigated and clinical effects of non-compliance could be questioned. However, the MAH has provided a thorough simulation of the effects of non-compliance at different time-points on biochemical markers of bone turnover clearly demonstrating limited effects with possible minor clinical consequences. Furthermore, the Flu-like events also associated with the 150 mg dose appear to be transient, non-serious, mostly not treatment-limiting, and manageable,
Until assuring long-term safety data are available these safety issues need to be continuously reflected in the SPC.

In conclusion, the two years safety data provide evidence that the use of a 150 mg once-monthly dose is associated with a generally acceptable safety profile. Especially, there are no indications of nephrotoxicity or any development of aseptic osteonecrosis after 2 years of treatment.

**Benefit/risk assessment**
Based on these results the risk/benefit-ratio for use of ibandronate 150 mg once monthly in the treatment of postmenopausal osteoporosis is considered to be positive. The proposed indication:

*"Treatment of osteoporosis in postmenopausal women, in order to reduce the risk of vertebral fractures. Efficacy on femoral neck fractures has not been established."*

is in accordance with data provided and therefore acceptable.