CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-858

MEDICAL REVIEW

MEDICAL TEAM LEADER MEMORANDUM

NDA: 21-858

DRUG: Ibandronate injection

COMPANY: Roche

INDICATION: Treatment of postmenopausal osteoporsis

PRIMARY REVIEWER: Theresa Kehoe, MD

PRIMARY REVIEWER'S RECOMMENDATION: Approve

BACKGROUND

Regulatory History of Ibandronate - Postmenopausal Osteoporosis

Roche's development of ibandronate for the prevention and treatment of postmenopausal osteoporosis (PMO) began with the 3-year fracture trial MF4380. This randomized, placebo-controlled, double-blind study compared the fracture efficacy of 0.5 mg or 1.0 mg intravenous ibandronate dosed every 3 months to placebo in 2860 osteoporotic women. After 3 years of treatment, despite statistically significant increases in lumbar spine and hip BMD in the ibandronate groups vs. the placebo group, the incidence of new vertebral fractures was 10.7%, 8.7%, and 9.2% for the placebo, 0.5 mg, and 1.0 mg groups, respectively(p=ns). A widely-accepted explanation for the failure of the intermittent, intravenous doses of ibandronate to significantly reduce the risk for vertebral fractures was the inability of these dosing regimens to adequately suppress markers of bone turnover throughout the entire 3-month intra-dosing intervals.

On May 16, 2003, the Agency approved the 2.5 mg daily oral dose of ibandronate for the prevention and treatment of postmenopausal osteoporosis (PMO). Approval was based on two pivotal studies. Study 4411 was a double-blind, placebo-controlled 3-year fracture trial of approximately 3000 osteoporotic women randomized 1:1:1 to ibandronate 2.5 mg daily, ibandronate 20 mg intermittently, or placebo. Study 4499 was a double-blind, placebo-controlled 2-year trial of more than 600 non-osteoporotic women randomized 1:1:1:1 to ibandronate 0.5 mg daily, 1.0 mg daily, 2.5 mg daily, or placebo.

Data from these two studies demonstrated that, relative to placebo, treatment with ibandronate 2.5 mg daily reduced the risk for vertebral fractures from 10% to 5% in women with osteoporosis and increased lumbar spine BMD by 3.0% in women with osteopenia.

On March 24, 2005, the Agency approved a 150 mg once-monthly dose of ibandronate for the treatment and prevention of PMO. Approval was based on the results of study BM16549, a 2-year, randomized, double-blind, active-control, non-inferiority study of 1600 osteoporotic women randomized 1:1:1:1 to ibandronate 2.5 mg oral daily, ibandronate 100 mg once-monthly (50 mg day 1 and 50 mg day 2), ibandronate 100 mg once-monthly (100 mg day 1), and ibandronate 150 mg (150 mg day 1).

The primary efficacy endpoint was the percent change in lumbar spine BMD from baseline to Month 12. Non-inferiority of the monthly doses vs. the daily dose was to be demonstrated if the lower bound of the 95% confidence interval for the differences between groups in the changes in lumbar spine BMD at one year was $\geq$ -1.0%. This figure was derived from data which indicated that the placebo-subtracted increase in lumbar spine BMD after one year of treatment with 2.5 mg daily ibandronate was approximately 3.0%. The non-inferiority margin of -1.0% retains approximately 2/3 of the treatment effect of the 2.5 mg dose.

The mean percent changes in lumbar spine BMD from baseline to Month 12 were 3.7% in the 2.5 mg daily group, 4.2% in the 50/50 mg monthly group, 3.9% in the 100 mg monthly group, and 4.8% in the 150 mg monthly group. The lower bound of the 95% confidence intervals for the differences between the three monthly doses vs. the daily dose were -0.06 (50/50mg), -0.40 (100mg), and 0.54 (150 mg). All three monthly dosing regimens were non-inferior to the 2.5 mg daily dose; the 150 mg monthly dose was also statistically significantly superior to the daily dose. The 150 mg dose was considered to have the most favorable risk-benefit profile.

Pivotal Trial for Intravenous Ibandronate

With the submission of NDA 21-858, Roche seeks to market intravenous ibandronate 3 mg q 3 months for the treatment of PMO. Data from study BM16550 provide the data upon which regulatory approval of the intravenous dosing regimen is based.

Synopsis of Study BM16550

Objectives: To determine if the ibandronate dose regimens of either 2 mg q 2 months or 3 mg q 3 months, given as an IV injection over 15 to 30 seconds, were noninferior to ibandronate 2.5 mg oral daily for the change from baseline to Year 1 in BMD .

Study Design: This is a randomized, double-blind, parallel-group, multi-center, multi-national, active-controlled study of 1194 patients with PMO. The study consists of a screening period of up to 30 days, a 24-month (or 104 week) treatment phase, and a 15-day follow-up phase following treatment completion. Patients were randomized in a 2:1:2:1 fashion to one of four groups:

- Group A: oral, placebo; IV, ibandronate 2 mg q 2 mo.
- Group B: oral, ibandronate 2.5 mg; IV placebo q 2 mo.
- Group C: oral, placebo; IV, ibandronate 3 mg q 3 mo.
- Group D: oral, ibandronate 2.5 mg; IV, placebo q3 mo.

All patients received vitamin D 400 IU/d and elemental calcium 500 mg/d, preferably as calcium carbonate. At one year, all patients were to have a serum 25-hydroxy vitamin D (25OHD) level of at least 40 nmol/L. Patients who had not achieved this threshold level for 25OHD were either to be withdrawn or provided with 800 IU vitamin D daily.

Study Population: Postmenopausal women, aged 55 to 80 years, with BMD T-scores between -2.5 and -5.0 were eligible for study participation. Subjects were excluded if they had a serum 25OHD level below 10 ng/ml, a serum creatinine > 2.4 mg/dl, a total serum calcium < 8.0 mg/dl, or a history of major upper GI disease.

Efficacy Endpoints: The primary efficacy parameter was the relative change from baseline at one year in mean BMD of the lumbar spine (L2 – L4) where BMD was assessed using DXA scans read by a central reading center. Important secondary endpoints were the relative (%) and absolute (g/cm2) changes from baseline BMD of the proximal femur (consisting of total hip, trochanter, and femoral neck) at one year; and the change from baseline (both relative and absolute) of trough levels of the biochemical marker of bone resorption, serum CTX.

Safety Endpoints: Safety parameters included adverse events, serious adverse events, premature withdrawals due to adverse events, adverse events of special interest including vertebral and non-vertebral fractures and Acute Phase Reactions (APR), renal events, and clinical laboratory tests. Additional safety parameters included ECGs for patients participating in the ECG substudy and histomorphometry of transiliac bone biopsies, serum intact PTH, and 25OHD for patients participating in the bone biopsy substudy.

Statistical Considerations: The primary hypothesis was that the difference in the effects of daily oral ibandronate and IV ibandronate (the two dose regimens) on the relative change in lumbar spine BMD after 12 months of treatment was small, no more than 1%, the margin of clinical equivalence. This difference is 30% of the minimum treatment effect relative to placebo at 12 months in three prior studies (MF4411, MF4348, and MF4433) using a 2.5 mg oral daily dose of ibandronate (with a post-dose fasting period of at least 60 minutes) in women with PMO. Using a margin of clinical equivalence of 1%, the assumption that standard deviation equals 4.5% and a one-sided 2.5% significance level non-inferiority test, with a power of 80%, a sample size of 318 evaluable patients per treatment arm would be required in a parametric t-test situation.

Efficacy data were analyzed for two analysis populations: an intent-to-treat (ITT) population and a Per Protocol (PP) population. The company proposed that the primary efficacy analysis be based on results from the PP population. The PP population was defined as all patients in the ITT population who had no major protocol violations.

Subject Demographics: All groups were well-matched for baseline demographic characteristics. The mean age was 66 years; approximately 92% of the subjects were Caucasian; the average BMI was 25 kg/m^2; and the mean baseline lumbar spine BMD T-score was -3.2. Roughly 43% of the women had a history of an osteoporotic fracture. A

majority of women in each group had been on bone-active doses of estrogen or estrogen + progestin at some time in the past.

Subjects Disposition: A total of 1395 subjects were randomized into the study: 470 patients to 2.5 mg oral daily; 454 to 2 mg q 2 months; and 471 to 3 mg q 3 months. Approximately 85% of the subjects in each group completed one year of study. The most common reason for not completing Year 1 was adverse events.

Efficacy Results

Primary Efficacy Outcome: In the PP population, the mean percent changes in lumbar spine BMD from baseline to Year 1 were 3.8%, 5.1%, and 4.8% in the 2.5 mg oral, 2 mg q 2 month, and 3 mg q 3 month groups, respectively. In the ITT population, the mean percent changes in lumbar spine BMD from baseline to Year 1 were 3.6%, 4.8%, and 4.6% in the 2.5 mg oral, 2 mg q 2 month, and 3 mg q 3 month groups, respectively.

The increase in lumbar spine BMD at one year in both IV treatment groups was shown to be non-inferior to that in the daily treatment group for both the PP and ITT analysis populations. The lower bound of the 2-sided 95% CI (which is equivalent to a 1-sided 97.5% CI) of the difference in means between the two IV regimens and the daily regimen were greater than -1% for both IV groups.

Since non-inferiority was demonstrated for both IV groups compared to the daily treatment group, a preplanned analysis using the ANOVA model was used to test for superiority of both IV treatment groups over the daily treatment group. Using this analysis, the increase in lumbar spine (L2 – L4) BMD seen with both IV ibandronate regimens was shown to be superior to that seen with the daily dose of 2.5 mg ibandronate in both the PP ($p<0.001$) and ITT ($p< 0.001$) analysis populations.

Secondary Efficacy Outcomes: The mean percent changes in femoral neck BMD from baseline to Year 1 in the PP population were 1.6%, 2.0%, and 2.3% for the 2.5 mg oral, 2 mg q 2 month, and 3 mg q 3 month groups, respectively. The results in the ITT population were very similar. The change in femoral neck BMD in the 3 mg q 3 month group, but not the 2 mg q 2 month group, was statistically significantly superior to the 2.5 mg oral group. The median serum levels of serum CTx decreased by -63%, -65%, and -59% in the 2.5 mg oral, 2 mg q 2 month, and 3 mg q 3 month groups, respectively.

Safety Results

There were no unexpected or clinical significant findings from the analyses of bone biopsy or ECG data.

Bisphosphonates, in particular when administered intravenously, have been associated with uveitis, scleritis, bone pain, an acute phase reaction like syndrome, hypocalcemia, osteonecrosis of the jaw, and renal toxicity.

Uveitis, scleritis, and bone pain appear to be idiosyncratic reactions without identifiable risk factors.

As Dr. Kehoe notes in her review, one of the more common treatment-emergent adverse event known to be ibandronate-related is APR – a constellation of symptoms including myalgia, arthralgia, bone pain, influenza-like illness, and fatigue that often occur following high-dose oral and intravenous bisphosphonate use. The incidence rates of APR-like events in Study BM16550 were 4% in the oral dosing group, 14% in the 2 mg q 2 month group, and 10% in the 3 mg q 3 month group. The APR typically occurs within 3 days of drug administration and generally resolves spontaneously within 7 to 10 days. The risk for this reaction appears to decrease with repeat drug administration.

Transient hypocalcemia is an expected pharmacodynamic response to intravenous bisphosphonates. The risk for clinically significant hypocalcemia can be mitigated by adequate calcium and vitamin D supplementation prior to and following drug administration. The labeling should include a comment about the importance of ensuring that all patients receive adequate supplemental calcium and vitamin D.

Osteonecrosis of the jaw is a recently identified adverse event that is most likely causally related to bisphosphonates, at least intravenously administered bisphosphonates. The index cases were patients undergoing chemotherapy for a variety of cancers. It is unclear if non-cancer patients receiving multiple doses of intravenous or oral bisphosphonate are at increased risk for osteonecrosis of the jaw – although some cases in patients taking oral bisphosphonates for osteoporosis have been reported to AERS. The following language was recently added to the Precautions section of the intravenous bisphosphonate labels (similar language has been added to the labels of oral bisphosphonates approved for osteoporosis):

This language will be included in the intravenous ibandronte labeling.

Renal injury following use of intravenous bisphosphonates may take the form of focal segmental glomerulosclerosis, renal insufficiency, acute tubular necrosis, and in some cases, frank renal failure. Relatively small, transient increases in serum creatinine have been used as a surrogate for serious outcomes such as acute renal failure.

The precise pathophysiology of bisphosphonate-induced renal damage is unknown.

Based on data from clinical trials of zoledronic acid – a very potent intravenous bisphosphonate approved for treatment of bone metastases and hypercalcemia of malignancy, and under investigation for the treatment of Paget's disease and osteoporosis – indicate that the risk for renal injury is increased when the drug is administered over 5 minutes vs. 15 minutes and when patients have baseline renal insufficiency.

No subject in Study BM16550 developed renal failure following receipt of oral or intravenous ibandronate. The incidence of renal adverse events was low and similar among the three treatment groups.

Serum creatinine was measured pre-drug administration every 2 months for the 2 mg group and every 3 months for the 3 mg group. In one analysis of serum creatinine, the proportion of patients in each treatment group who had at least one post-baseline serum creatinine value which met one or more of the following three criteria was recorded:

(a) An increase of >0.5 mg/dL (>44 Mmol/L) in patients with a baseline creatinine of <1.4 mg/dL (<124 Mmol/L), **or**
(b) An increase of >1 mg/dL (>88 Mmol/L) in patients with a baseline value >1.4 mg/dL (>124 Mmol/L), **or**
(c) Any serum creatinine value which was 2-fold higher than the baseline value.

No patient in the oral ibandronate group had serum creatinine changes that met any of the above criteria. Four patients in the 2 mg q 2 month group and 2 in the 3 mg q 3 month group had baseline creatinine values below 1.4 mg/dl and had an increase from baseline of at least 0.5 mg/dl. One of the 4 subjects in the 2 mg q 2 month group had an on-treatment creatinine value that was 2X baseline.

The narratives for the two subjects from the 3 mg q 3 month group suggest that events other than ibandronate administration precipitated the transient increases in serum creatinine.

The narratives for the 4 subjects from the 2 mg q 2 month group suggest that ibandronate may have been a causative factor in the increase in creatinine in one case. It is difficult to assess the role ibandronate may have played in the other 3 cases due to concurrent illness and concomitant medication use.

Given the number of women who received study drug, one can reasonably conclude that intravenous ibandronate 3 mg q 3 months is not associated with a large increase in the risk for renal injury when used in a population of postmenopausal women with osteoporosis. However, small-to-modest increases in the risk for renal toxicity, particularly acute renal failure, with intravenous ibandronate treatment cannot be ruled out with the currently available exposure data.

In a paper co-authored by Roche pharmacologists, it was concluded that in comparison to zoledronic acid, "administering ibandronate intermittently [to rats] provides sufficient time for regeneration of potential subclinical renal damage.[1]" In a letter to the editor written in response to this paper, Raimund Hirschbert, a nephrologists from UCLA, pointed out what he considered to be serious flaws in the study's design. Two of these included the unblinded reading of renal histology scores and the use of doses of zoledronic that were as much as 105-times the clinically proven effective dose, and on the other hand, the use of a single dose of ibandronate that was below doses proven to be clinically effective.[2]

Dr. Hirschberg concluded that "most third-generation intravenous bisphosphonates have been found to cause acute or subacute renal injury with incidences that are clinically well managable. The mechanism(s) are not well understood but the experimental study by Pfister et al does not change this knowledge deficit in meaningful ways. Clinicians make therapeutic decisions based on risk-benefit assessments, are advised to strictly adhere to approved dosing schedules and should be vigilant about potential renal complications following intravenous bisphosphonate administration."

While there may be sufficient evidence of renal safety to approve ibandronate, 3 mg administered as a 15-30 second intravenous bolus q 3 months, for the treatment of PMO, I believe Roche should obtain additional controlled data to more fully characterize the renal safety profile of the proposed dosing regimen in the target population. This could be done as a phase 4 commitment.

Labeling

Following a t-con on January 4, 2006, the Division and Roche have come to final agreement on the labeling for intravenous ibandronate.

Conclusion and Regulatory Recommendation

Roche has provided adequate data to support the efficacy and safety of intravenous ibandronate, 3 mg administered as a 15-30 second bolus q 3 months, for the treatment of PMO.

Approve – contingent upon Roche's commitment to obtain phase 4 data to more fully characterize the renal safety profile of the proposed dosing regimen.

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[1] Pfister T, et al. The renal effects of minimally nephritic doses of ibandronate and zoledronate following single and intermittent intravenous administration in rats. Toxicology 191 (2003) 159-167.
[2] Hirschberg R. Nephrotoxicity of third-generation intravenous bisphosphonates. Letter. Toxicology 196 (2004) 165-167.

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/s/

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CLINICAL REVIEW

Application Type	NDA
Submission Number	21-858
Submission Code	S3
Letter Date	12/6/2004
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Reviewer Name	Theresa Kehoe
Review Completion Date	12/10/2005
Established Name	Ibandronate
(Proposed) Trade Name	Boniva
Therapeutic Class	Bisphosphonate
Applicant	Roche
Priority Designation	S
Formulation	i.v.
Dosing Regimen	3mg every 3 months
Indication	treatment of osteoporosis
Intended Population	postmenopausal women

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends approval of ibandronate 3mg i.v. delivered as a 15 – 30 second bolus every 3 months for treatment of postmenopausal osteoporosis with a postmarketing commitment for further evaluation of renal safety.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The sponsor proposes a risk management plan that predominantly focuses on product labeling, regular review of cumulative data and periodic safety updates. Roche has proposed specific labeling to address APRs, injection site reactions and hypocalcemia. However, the concern regarding renal toxicity with intravenous bisphosphonate use has not been adequately addressed by the proposed product label or risk management plan. Further monitoring will be required to assure the renal safety of i.v. ibandronate. The Office of Drug Safety was consulted to assist in the development of an adequate risk management plan.

1.2.2 Required Phase 4 Commitments

The sponsor has agreed to conduct further study of the renal safety of i.v. ibandronate, particularly in patients at higher risk of renal failure. The agreed upon study will be one year in duration, comparing the renal effects of placebo, i.v. ibandronate delivered by 15 – 30 second bolus and i.v. ibandronate delivered as a 15 minute infusion. Renal laboratories (including but not limited to serum creatinine, creatinine clearance as estimated by the 4v-MDRD formula, albumin creatinine ratio, and alpha 1 microglobulin levels) will be assessed 10 – 14 days post dose. Sample size and other study details remain to be worked out.

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The sponsor is submitting this New Drug Application (NDA) for the treatment of postmenopausal osteoporosis with an intravenous ibandronate regimen of 3mg every 3months. The single pivotal trial to support registration is BM16550, a Phase 3, randomized, double-blind,

parallel group, multicenter, two-year study comparing the efficacy and safety of intravenous ibandronate 2mg every 2 months and 3mg every 3 months to 2.5mg daily oral ibandronate in women with postmenopausal osteoporosis. Efficacy is based on the non-inferiority of the changes in lumbar spine bone mineral density (BMD) after one year of treatment. Because of concern regarding of the high annualized ibandronate dose (12mg) compared to the previously approved daily regimen (5.5mg), the Year 2 bone histomorphometry data were requested and submitted as a major amendment to the application in November, 2005. To further address the concerns regarding renal toxicity, the company submitted renal laboratories for the second year of the study in December, 2005.

1.3.2 Efficacy

Both ibandronate intravenous dosing regimens were non-inferior to the daily 2.5mg oral regimen, based on relative change in lumbar spine BMD at one year. Increases in lumbar spine BMD ranged from 3.6% in the 2.5mg daily group, 4.6% in the 3mg i.v. q3month group, to 4.8% in the 2mg i.v. q2month group. Serum CTX values decreased in all treatment groups, with a slightly higher decrease seen in the 2.5mg daily group (-53%), compared to -49% in the 3mg i.v. q3month group, and -48% in the 2mg i.v. q2month group.

The major difficulty in assessing the efficacy of intermittent intravenous ibandronate dosing is the validity of the surrogate endpoint, lumbar spine BMD, in predicting fracture efficacy. The focus of this issue is study MF4380, the original pivotal trial for i.v. ibandronate, evaluating doses of 0.5mg and 1mg every 3months. This trial revealed a lack of significant fracture reduction efficacy despite significant increases in lumbar spine BMD. The lack of fracture efficacy was attributed to insufficient dose or insufficient dose frequency, or both. Because of this underlying uncertainty, this reviewer believes that superiority to the approved 2.5mg daily oral dose is a more prudent requirement for approval. The increase in lumbar spine (L2 – L4) BMD seen with both the 2mg i.v. q2month and the 3mg i.v. q3month ibandronate regimens was statistically superior to the 2.5mg daily dose with respect to increases in lumbar spine BMD ($p < 0.0001$). When compared to the highest dose in the original i.v. ibandronate fracture study MF4380, 1.0mg i.v. ibandronate showed mean lumbar spine BMD increases of 3.3% at one year, whereas in study BM16550 the 2mg i.v. q2month dose had a mean increase of 4.8% and the 3mg i.v. q3month dose had a mean increase of 4.6%. When compared to Year 1 data from study MF4411, the successful, pivotal 2.5mg fracture efficacy trial, lumbar spine BMD increases were comparable (4.8% with 2mg i.v. q2month dose, 4.6% with the 3mg i.v. q3month dose and 4.9% with 2.5mg daily from study MF4411). Therefore, these data suggest that both the 2mg i.v. q2month dose and the 3mg i.v. q3month dose of ibandronate are clinically comparable and may be clinically superior to ibandronate 2.5mg daily. This provides more reassurance that treatment with intravenous ibandronate every 3 months would confer fracture reduction efficacy.

1.3.3 Safety

Overall, the tolerability of i.v. ibandronate was similar to that of daily oral ibandronate. The nature and frequency of adverse events were similar for all treatment groups. Four deaths occurred during the first year of the study and four additional deaths occurred during the safety

update period of trial BM16550. The causes of death are consistent with the postmenopausal population's baseline age and related comorbid conditions and are similar to causes of death in the general population of patients. The overall incidence of serious adverse events was similar between the treatment groups. Fracture was the most commonly reported serious adverse event. Serious events in the gastrointestinal and cardiac systems occurred in slightly more patients receiving ibandronate 2mg i.v. q2 months. Withdrawal due to adverse events occurred more frequently in the 3mg i.v. q3month group (10%, compared to 8% in the 2.5mg daily oral group and 7% in the 2mg i.v. q2month group). Gastrointestinal and musculoskeletal adverse events accounted for the majority of events leading to early withdrawal from the study. These events were evenly distributed between the treatment groups. Adverse events that were more frequently reported in the intravenous dose groups were influenza-like illness, fatigue and myalgia.

Symptoms of acute phase reaction (APR) have been reported with intravenous bisphosphonate use. APR-like symptoms were reported in all treatment groups. The overall incidence of subjects with APR-like events was higher in the intravenous treatment groups (4% in the 2.5mg daily group, 14% in the 2mg i.v. q2month group, and 10% in the 3mg i.v. q3month group). A total of 18 subjects, 2 in the daily oral group and 16 in the intermittent i.v. groups, withdrew from the study due to APR-like symptoms. An additional four subjects, all in intermittent i.v. dose groups, had dose modifications made due to APR-like symptoms and 32 subjects (5 in the daily oral group and 27 in the intermittent i.v. groups) required concomitant medical therapies for symptom relief.

Clinical osteoporotic fractures were recorded as adverse events. The proportion of subjects sustaining a clinical osteoporotic fracture was similar between the treatment groups, occurring in 3% in the 2.5mg daily group, 2% in the 2mg i.v. q2month group, and 3% in the 3mg i.v. q3month group. Osteomyelitis and/or osteonecrosis of the jaw has been reported in two subjects receiving ibandronate. There were no adverse event reports or laboratory evidence of hypocalcemia in study BM16550. However, the timing of the mineral laboratories did not allow for assessment of the expected calcium nadir. In an open-label, non-controlled multicenter study in normocalcemic subjects with breast cancer, there was a dose related decrease in serum calcium levels with a higher than anticipated calcium nadir in the 3mg i.v. ibandronate group. In this group, the age of the subjects closely approximated the expected age of the postmenopausal population. Calcium levels fell below 8.0mg/dL in 67% of subjects and below 7.5mg/dL in 27% of subjects receiving 3mg i.v. ibandronate.

Renal toxicity with intravenous bisphosphonate use is of great concern. Findings in animals suggest that renal toxicity is proportional to dose and rate of administration. Lessons learned from the intravenous zoledronate trials for the treatment of bone metastases supports the findings in animals that the rate of infusion is inversely related to the potential for renal toxicity (i.e., increases in serum creatinine). When i.v. zoledronate infusion times were lengthened from 5 minutes to 15 minutes, the absolute and relative risks of renal deterioration were lowered, though not completely ameliorated. In the ibandronate clinical development program, i.v. bolus administration of ibandronate was used and is the administration regimen being pursued for approval by the sponsor.

In study BM16550, six subjects, all receiving i.v. ibandronate, were reported to have either chronic renal failure, renal impairment or blood creatinine increased as an adverse event. Mean creatinine levels did increase minimally in all treatment groups at the end of the two year study. However, fourteen subjects (3 in the 2.5mg daily oral group, 7 in the 2mg i.v. q2month group and 4 in the 3mg i.v. q3month group) with baseline creatinine less than 1.4mg/dL did have elevations in creatinine of more than 0.5mg/dL. Most concerning is that there were an insufficient number of subjects with baseline creatinine greater than 1.4mg/dL to adequately assess the impact of ibandronate in this higher risk population – many of whom will be found in the target postmenopausal osteoporosis population.

When looking at shift tables for creatinine clearance, a slightly higher percentage of subjects with mild renal impairment that received the 3mg dose shifted into moderate renal impairment (13% vs. 11% for the other 2 groups). Urinary protein was not evaluated in study BM16550. Review of smaller Phase 1, 2 and 3 studies in different treatment populations revealed a weak but concerning signal of increased proteinuria, which may represent the earliest signs of renal damage, with bolus bisphosphonate doses of 2mg or higher. Ibandronate doses of 4mg and higher were not given as i.v. bolus, but as i.v. infusion over 15 minutes to 2 hours. There are no trials in the postmenopausal osteoporotic population comparing the pharmacokinetic or clinical effects of i.v. bolus ibandronate administration and i.v. infusion ibandronate administration for the proposed doses .

Given the knowledge of renal toxicity seen with i.v. bisphosphonate administration and the benefit of lengthening infusion times for preserving renal function, coupled with lack of adequate data comparing rate of ibandronate administration in the postmenopsaul population at greater risk of renal toxicity (i.e. baseline creatinine > 1.4mg/dL), leads this reviewer to remain concerned with the safety of a 15 – 30 second i.v. bolus administration, especially in patients at high risk of renal insufficiency. A longer infusion time may be beneficial but further study would be required to assess this.

The company is pursuing approval of the ibandronate 3mg i.v. q 3months regimen for the treatment of postmenopausal osteoporosis. This dose has been shown to be non-inferior to the currently approved 2.5mg oral daily dose, as assessed by increases in lumbar spine bone density at one year. This reviewer believes the administration schedule should be an infusion of at least 15 minutes, not bolus administration. Some patients may experience acute phase reaction symptoms that will limit use of the medication. The risk of hypocalcemia following i.v. administration necessitates that all subjects receive adequate calcium and vitamin D, particularly within the first 2 to 3 weeks following drug administration.

1.3.4 Dosing Regimen and Administration

The intravenous ibandronate development program's initial pivotal fracture trial demonstrated suboptimal fracture efficacy at doses of 0.5mg i.v. q3month and 1mg i.v. q3month. The rationale for this unsuccessful trial was an insufficient dose of ibandronate and/or an inappropriately long dosing interval. This interpretation was supported by the results of biochemical markers which suggested that bone turnover suppression was decreasing toward the

end of the dosing interval. The company concluded that optimal fracture efficacy was likely to require more sustained suppression of bone resorption which could be achieved by more frequent injections, the administration of a higher dose, or both.

In a randomized double-blind, placebo-controlled, 2-year trial evaluating placebo, 1mg and 2mg ibandronate i.v. q3 month, lumbar spine BMD increases with 2mg ibandronate i.v. q3 month were superior to the increase seen with the 1mg month regimen and numerically greater than those seen in study MF4411 for 2.5mg ibandronate daily. However, because of the limitations of comparing results across trials, the company felt that this regimen may not be fully comparable to the daily oral regimen. After analyses and extrapolation of the dose-response curves, the company decided to study both the 3mg i.v. q3month dose and a 2mg i.v. q2month dose. In the postmenopausal osteoporosis population, all dosing was administered as an i.v. bolus injection. As discussed in the safety review section, this administration rate is of concern.

1.3.5 Drug-Drug Interactions

Specific drug interaction studies have shown no evidence of interaction between ibandronate and tamoxifen in healthy postmenopausal women or between ibandronate and melphalan/prednisone in patients with multiple myeloma.

1.3.6 Special Populations

Ibandronate is intended for the treatment and prevention of postmenopausal women with osteoporosis. Studies of i.v. ibandronate have predominantly enrolled women. Therefore, gender analyses are not possible. The average age of enrolled subjects, including subjects in the pharmacokinetic/pharmacodynamic study, was approximately 65 years. These and previously reviewed studies have disclosed no age group in which the drug was not effective or in which drug dose adjustments would be required. Since nearly all patients in the osteoporosis trials were Caucasian, the effects of race/ethnicity on the safety and efficacy of ibandronate are not known.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Hoffman-La Roche, Inc. has submitted this new drug application for ibandronate sodium [1-hydroxy-3-(methylpentyl-amino) propylidene] bis-phosphonic acid)], trade name Boniva seeking approval of a new injectable formulation of ibandronate. Ibandronate is a member of the bisphosphonate class of medications. Roche proposes to market this intravenous formulation of ibandronate at a dose of 3mg every 3 months for the treatment of postmenopausal osteoporosis (PMO).

2.2 Currently Available Treatment for Indications

Current medications approved for the treatment of postmenopausal osteoporosis include salmon calcitonin (Miacalcin nasal spray and Fortical nasal spray), daily and monthly oral ibandronate sodium (Boniva), daily and weekly oral alendronate sodium (Fosamax), daily and weekly oral risedronate sodium (Actonel), the oral selective estrogen receptor modulator raloxifene (Evista), and teriparatide (Forteo). Current medications available for the prevention of postmenopausal osteoporosis include estrogen +/- progestin (Menostar, Premarin, Premphase, Prempro), raloxifene (Evista), daily oral ibandronate, daily and weekly oral alendronate sodium (Fosamax), and daily and weekly oral risedronate sodium (Actonel).

2.3 Availability of Proposed Active Ingredient in the United States

The daily oral dose of 2.5mg ibandronate was approved for the prevention and treatment of postmenopausal osteoporosis (PMO) in May, 2003. The monthly oral dose of 150mg ibandronate was approved for the treatment of postmenopausal osteoporosis in March, 2005.

2.4 Important Issues With Pharmacologically Related Products

Bisphosphonates are used in the prevention and treatment of postmenopausal and corticosteroid-induced osteoporosis, Paget's disease of bone, hypercalcemia of malignancy, and bony metastases. Safety concerns that appear more prominent with intravenous bisphosphonates include acute phase reactions, hypocalcemia and worsening of renal function. Other concerns that have emerged with postmarketing data include the occurrence of eye inflammation, bone pain and osteonecrosis of the jaw. Class labeling for bisphosphonates regarding the use of these drugs in women of childbearing age and the potential for fetal toxicity after remote exposure to the drug has recently been implemented.

2.5 Presubmission Regulatory Activity

In May 2000, the pivotal i.v. ibandronate study MF4380 revealed suboptimal fracture efficacy for the 0.5mg i.v. q3month and 1.0mg i.v. q3month dosing regimens. It was agreed at that time

that the ongoing oral ibandronate program may be sufficient for filing of an NDA for ibandronate in the treatment and prevention of PMO, if the data were sufficiently positive (i.e., small p-value for fracture efficacy and strong inverse correlation between change in BMD and fracture risk). Ibandronate (oral formulation), with the pivotal trial MF4411, was submitted and approved in the United States for the prevention and treatment of postmenopausal osteoporosis (PMO) in May, 2003. Subsequent product development focused on intermittent dosing. It was agreed that a bridging BMD non-inferiority study comparing monthly oral ibandronate doses to the approved 2.5mg daily oral dose would be sufficient for approval of an intermittent dose regimen. The increase in lumbar spine BMD with the 150mg monthly oral ibandronate dose was found to be superior to the lumbar spine BMD increase seen with 2.5mg daily oral ibandronate. Ibandronate 150mg monthly was approved for the treatment of postmenopausal osteoporosis in March, 2005. The company also decided to pursue development of the intravenous formulation of ibandronate for the treatment of postmenopausal osteoporosis. After discussions with the Agency, it was agreed that approval of the intravenous ibandronate formulation could be achieved with a bridging BMD non-inferiority study using the 2.5mg daily oral ibandronate dose as the active control.

2.6 Other Relevant Background Information

The intravenous formulation of ibandronate was first approved in June of 1996 in the European Union for the treatment of hypercalcemia of malignancy. Since that time it is has been approved in multiple other countries for the treatment of hypercalcemia of malignancy. The intravenous formulation of ibandronate was approved for the treatment of osteoporosis in Argentina (July 1997), Uruguay (March 1998), and Mexico (April 1998). Marketing approval has never been refused, suspended or restricted.

The oral formulation of ibandronate, 2.5mg daily, was approved for the treatment and prevention of postmenopausal osteoporosis in the European Union in March 2004.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

(Please see Dr. Chikhale's review for complete details)

3.2 Animal Pharmacology/Toxicology

(Please see Dr. Kuijper's review for complete details)

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sponsor is submitting this New Drug Application (NDA) for the treatment of postmenopausal osteoporosis with an intravenous ibandronate regimen of 3mg every 3months. The single pivotal trial to support registration is BM 16550, a Phase 3, randomized, double-blind, parallel group, multicenter, two-year study comparing the efficacy and safety of intravenous ibandronate 2mg every 2 months and 3mg every 3 months to 2.5mg daily oral ibandronate in women with postmenopausal osteoporosis. Efficacy is based on the non-inferiority of the changes in lumbar spine bone mineral density (BMD) after one year of treatment. Newly submitted supporting data includes study JM16651, a randomized, double blind, parallel-group, placebo-controlled, multicenter pilot study in postmenopausal osteoporotic women in Japan investigating the dosing regimen response of monthly and bimonthly intravenous ibandronate (0.5mg i.v. q1month, 1.0 mg i.v. q1month and 2mg i.v. q2month) compared to placebo. Data from multiple previously submitted clinical and clinical pharmacology trials were referenced, as noted in the table below.

4.2 Tables of Clinical Studies

Intravenous Ibandronate Studies						
		Subjects enrolled (% compl)	Age years	Population	Study Duration	Primary Endpoint
Clinical Studies						
BM16550 P2/3, R, DB	Total	1395 (85)*	66.0	osteoporotic women, >5 years post menopause	24 month *** data submitted based on 12 month	non-inferiority of LS BMD changes
	2.5mg qd	470 (87)	65.7			
	2mg iv q2m	454 (84)	66.6			
	3mg iv q3m	471 (84)	65.8			
JM16651 P2/3, R, DB	Total	228 (87)		osteoporotic women, >5 years post menopause, prevalent OP Fx	6 month	change in LS BMD
	placebo	57 (89)	66.2			
	.5mg iv q1m	57 (82)	65.4			
	1mg iv q1m	57 (95)	67.3			
	2mg iv q2m	57 (89)	67.1			
Previously Submitted and Reviewed Clinical Studies in Osteoporotic Subjects						
MF4411 P3, R, DB, PC	Total	2946 (81)*		postmenopausal osteoporotic women prevalent OP Fx	3 years	new morph vertebral fx rate
	placebo	982 (80)	68.8			
	2.5mg qd	982 (82)	68.7			
	20mg int	982 (82)	68.7			
MF4380 P3, R, DB, PC	Total	2862 (93)*		postmenopausal osteoporotic women prevalent OP Fx	3 years	new morph vertebral fx rate
	placebo	899 (95)	67.2			
	0.5mg iv 3m	884 (93)	66.8			
	1.0mg iv 3m	874 (91)	66.9			
MF4361 P2, R, PC	Total	126 (90)	64.0	osteoporotic women, >5 years post menopause	1 year	LS BMD
	placebo	26 (92)	64.2			
	0.25 iv q3m	24 (88)	63.0			
	0.5 iv q3m	27 (93)	64.3			

Intravenous Ibandronate Studies						
		Subjects enrolled (% compl)	Age years	Population	Study Duration	Primary Endpoint
	1.0 iv q3m	26 (88)	64.4			
	2.0 iv q3m	23 (96)	64.0			
MF4470	Total	520 (92)		osteoporotic women, >5 years post menopause	2 year (stopped at 1yr)	LS BMD
	placebo	128 (94)	65.5			
	1.0 iv q3m	131 (96)	66.5			
	2.0 iv q3m	261 (89)	65.5			
Submitted and Reviewed Studies in Other Populations						
MF4328 P2, OL	Total	148 (96)	56.0	normocalcemic breast cancer patients with bone mets	4 weeks	AEs urinary biomarkers of bone turnover
	0.5 iv bolus	15 (93)	61.5			
	1.0 iv bolus	23 (91)	58.5			
	2.0 iv bolus	54 (98)	56.0			
	3.0 iv bolus	15 (100)	66.0			
	4.0 iv infus	16 (88)	46.0			
	6.0 iv infus	25 (100)	49.0			
MF4265	Total	466 (53)		women with breast cancer and bone mets	treatment at least 60 weeks, maximum 96 weeks	new bone complications
	placebo qm	158 (45)	54.5			
	2.0 iv qm as bolus	154 (57)	55.3			
	6.0 iv qm as infusion	154 (58)	56.1			
MF7141 P1, XO	placebo	16 (100)	30.9	healthy young men	24 hours	renal safety parameters
	2.0 iv bolus					
* Year 1 completion data						

4.3 Review Strategy

This review focuses on the non-inferiority trial, study BM16550. Because of the prior i.v. ibandronate (study MF4380) which failed to demonstrate fracture efficacy despite increases in BMD, particular attention was paid to the magnitude of BMD and biomarker changes and the occurrence of fractures. Because the annualized ibandronate dose of 12mg for both the 2mg i.v. q2months and 3mg i.v. q3months doses evaluated in study BM16550 is much higher than the 2.5mg daily dose (5.5mg annualized dose), the sponsor was required to submit the 2 year histomorphometry data from study BM16550 for review prior to decisions regarding approval. In addition, the company submitted the 2 year laboratory data for creatinine to support the renal safety of the i.v. bolus administration regimen.

4.4 Data Quality and Integrity

The Division of Scientific Investigation (DSI) was not consulted for this NDA.

4.5 Compliance with Good Clinical Practices

All studies appear to have been conducted in accordance with FDA guidelines on "Good Clinical Practice" and the principles of the Declaration of Helsinki. However, in study BM16550, sponsor audits revealed that one investigator in Mexico was not originally added to the IND within the required timeframe, in violation of Agency regulations. This situation was rectified. In addition, at the same site, it could not be confirmed that the investigator was blinded to BMD results. This study site enrolled 29 (2%) subjects into study BM16550. As this study is a non inferiority study with an active comparator, the validity of the data from this site is most likely not compromised, even in the event of investigator unblinding.

4.6 Financial Disclosures

Financial disclosure information was provided by the sponsor and reviewed by this reviewer for study BM16550. Sixty-five investigators submitted financial disclosure information and had nothing to report. No financial disclosure information was available for nine investigators.

5 CLINICAL PHARMACOLOGY

Please see Dr. Lau's review for complete details.

5.1 Pharmacokinetics

The pharmacokinetic profile of i.v. ibandronate is dose-proportional between 2 and 6 mg in single dose studies. There are no pharmacokinetic data comparing intravenous bolus administration and i.v. infusion in the postmenopausal osteoporotic population. There is also a lack of pharmacokinetic information for i.v. ibandronate use in postmenopausal osteoporotic subjects with renal insufficiency.

5.2 Pharmacodynamics

Study BM16550 evaluated the pharmacodynamic properties of the intravenous ibandronate doses. The primary pharmacodynamic endpoint in the study was the relative changes from baseline (%) for serum C-telopeptide of the α chain of type I collagen (CTx). The percent change from baseline in CTx was slightly higher in the daily oral treatment group (-53%) compared to the two i.v. ibandronate treatment groups (-48% and -49%).

5.3 Exposure-Response Relationships

Roche has constructed a mathematical model to predict the time course in uCTx following oral and/or intravenous ibandronate dosing. Data from studies MF9853 (a phase 1 PK, PD trial of i.v. ibandronate), MF4361 (a phase 1 dose-finding trial of i.v. ibandronate) and MF4411 (the pivotal daily oral postmenopausal osteoporosis treatment trial) were used to develop the model. This is the most comprehensively validated model compared to other bisphosphonate PK/PD models. The validation was done in a retrospective manner and the model awaits prospective validation.

Simulations were performed using the model to demonstrate the behavior of intravenous ibandronate regimens in terms of uCTx. No modeling was performed to evaluate safety.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication: Treatment of Postmenopausal Osteoporosis

6.1.1 Methods

This review focuses on the pivotal efficacy trial BM16650, a randomized double-blind, parallel group study. Results will be evaluated in conjunction with the previously reviewed trials MF4411, the pivotal fracture efficacy trial for 2.5mg daily ibandronate and MF4380, the suboptimal fracture efficacy trial of intermittent i.v. ibandronate.

6.1.2 General Discussion of Endpoints

The primary endpoint in study BM16550 is non-inferiority in relative change of lumbar spine bone mineral density with the monthly oral ibandronate regimen when compared to daily oral ibandronate, an active control that has been approved for the treatment of postmenopausal osteoporosis. While fracture trials are required for registration of new osteoporosis treatments, non-inferiority trials have been acceptable and used to evaluate new weekly dosing regimens for other approved daily bisphosphonates. Ibandronate is the first intravenous bisphosphonate seeking approval for treatment of postmenopsaul osteoporosis. One difficulty with this non-inferiority approach is that a large trial of intermittent i.v. ibandronate dosing failed to show statistically significant fracture efficacy despite statistically significant increases in bone mineral density when compared to placebo. This failed efficacy trial illustrates that while it is currently the best surrogate marker to predict osteoporotic fracture risk, bone mineral density is not always an adequate or accurate indicator of risk reduction.

6.1.3 Study Design

Study BM16550 is a randomized, double-blind, parallel group, multi-center study to demonstrate non-inferiority at one year. The study is continuing blinded for a second year. A confirmatory analysis will be performed after 24 months of treatment. The study enrolled women with postmenopausal osteoporosis who were not required to have a prevalent vertebral fracture. All subjects received one daily oral study drug (either 2.5mg ibandronate or placebo) and an intravenous study drug on an every 2 or 3 month schedule, as outlined in the table below.

Study BM16549: Study Drug Dosing Schedule			
Group	Daily Dose	i.v. dose, q2month	i.v. dose, q2month
A	placebo	2mg	
B	2.5mg	placebo	
C	placebo		3mg
D	2.5mg		placebo

As well, all subjects received vitamin D 400 IU/day and elemental calcium 500mg/day and were instructed to take the supplements in the evening. Based on a request by the Canadian Therapeutics Products Directorate, patients in the Canadian centers were provided with 1000 mg daily of calcium as supplemental therapy. As well, the Directorate requested additional monitoring of 25-hydroxy vitamin D levels at Months 3 and 12. Subjects not showing an upward trend towards a level of 40 nmol/L (16.7 ng/mL) of 25-hydroxy vitamin D were to be either withdrawn or provided with 800 IU Vitamin D daily. None of the 66 Canadian subjects enrolled in the study required discontinuation due to vitamin D levels. Two subjects did required increases in supplemental vitamin D dose.

The primary efficacy endpoint was the relative change from baseline at one year in mean BMD of the lumbar spine (L2 – L4). Secondary endpoints included the absolute change (g/cm^2) from baseline in mean lumbar spine (L2 – L4) BMD at one year; the relative (%) and absolute (g/cm^2) change from baseline in total hip, trochanter, femoral neck BMD at one year; percentage of responders (subjects with BMD above or equal to baseline at Year 1); and the relative and absolute change from baseline of trough serum CTx at 3, 6, and 12 months.

6.1.4 Efficacy Findings

6.1.4.1 Relative Change from Baseline at One Year in Lumbar Spine (L2 – L4) BMD: As outlined in the table below, increases in lumbar spine BMD from baseline to Month 12 were greater in both i.v. treatment groups (4.8% for the 2mg q2month group and 4.6% for the 3mg q3month group) compared to the daily oral treatment group (3.6%). The ITT analysis is shown. Analyses with the per protocol population produced similar results. The increase in lumbar spine BMD at one year in both i.v. treatment groups was shown to be non-inferior to that in the daily treatment group, as the lower bound of the 2-sided 95% CI of the difference in means between the i.v. regimens and the daily regimen was greater than -1%. Since non-inferiority was demonstrated for the i.v. treatment groups, a preplanned ANOVA analysis was used to test for superiority over the daily treatment group. The increase in lumbar spine BMD seen with both i.v. treatment groups was superior to that seen with 2.5mg daily ($p < 0.001$). An exploratory analysis of change from baseline in lumbar spine BMD excluding all fractured vertebra showed similar results with non-inferior and superiority with both i.v. dosing groups, when compared to the daily ibandronate dose.

BM16550: Lumbar Spine BMD: Relative Change from Baseline (ITT)			
	2.5 po qd	**2mg iv q2mo**	**3mg iv q3mo**
N	458	442	458
Baseline BMD (n)	458	442	458
(g/cm^2)	0.748 ± 0.071	0.747 ± 0.074	0.746 ± 0.075
Month 12 BMD (n)	434	412	429
(g/cm^2)	0.774 ± 0.077	0.784 ± 0.077	0.780 ± 0.080
Absolute Change (g/cm^2)	0.027 ± 0.030	0.036 ± 0.028	0.034 ± 0.028
95% CI*		0.006 , 0.013	0.004 , 0.011
% Change from Baseline	3.6 ± 4.0	4.8 ± 3.9	4.6 ± 3.9
95% CI**		0.693 , 1.746	0.526 , 1.568

BM16550: Lumbar Spine BMD: Relative Change from Baseline (ITT)			
	2.5 po qd	2mg iv q2mo	3mg iv q3mo
N	458	442	458
Treatment Effect***		1.22	1.05
p value		0.000	0.000
* parametric analysis of difference in means of absolute change from baseline, compared to active control ** parametric analysis of difference in means of relative change from baseline, compared to active control ***Difference in the mean value compared to active control			

Multiple subgroup analyses were performed, including geographic location (USA/Canada, Western Europe, Eastern Europe, rest of the world); baseline BMD T-score (Group 2: < -2.5 and ≥ -3.0, Group 3: < -3.0 and ≥ -3.5, and Group 4: < -3.5 and ≥ -5.0); continent; age (< 70 and ≥ 70 years); race; calcium compliance; cumulative calcium dose group based on tertiles (Group 1: ≤ 182 g, Group 2: > 182 g to ≤ 183.7 g, Group 3: > 183.7 g); presence of previous fractures since age 45 years (yes and no); measurement device (hologic and lunar); use of bone effective treatment with the potential to decrease BMD (yes and no) and use of bone effective treatment with the potential to increase BMD (yes and no). In all subgroups, the difference in the relative change from baseline at one year in lumbar spine (L2 – L4) BMD was consistent with the results seen in the total group.

6.1.4.2 Hip BMD, Relative and Absolute Change: Increases in BMD from baseline to Month 12 were greater in both i.v. treatment groups for the total hip, femoral neck and trochanter compared to the daily treatment group. For the total hip, the lower bound of the 2-sided 95% CI of the difference in means (relative change from baseline) was greater than zero for both 2mg q2month and 3mg q3month treatment groups compared to the 2.5mg daily treatment group, suggesting statistical superiority over the BMD increases seen with 2.5mg ibandronate daily in the per-protocol population. In the ITT population, only the 2mg q2month treatment group showed superiority. For the femoral neck, only the 3mg q3month treatment group was superior to the daily oral treatment group in both the per-protocol and intent-to-treat populations. For the trochanter, both i.v. treatment regimens appeared to be superior to the 2.5mg daily treatment group in both the per-protocol and intent-to-treat populations.

BM16550: Hip BMD: Relative Change from Baseline (ITT)			
	2.5 po qd	2mg iv q2mo	3mg iv q3mo
N	458	442	458
Total Hip			
Baseline BMD (g/cm^2)	0.734 ± 0.102	0.744 ± 0.099	0.740 ± 0.100
Month 12 BMD (g/cm^2)	0.748 ± 0.101	0.763 ± 0.098	0.754 ± 0.098
Absolute Change (g/cm^2)	0.012 ± 0.021	0.018 ± 0.020	0.016 ± 0.022
% Change from Baseline	1.6 ± 2.9	2.4 ± 2.7	2.2 ± 3.4
95% CI*		0.365 , 1.194	0.179 , 0.998
Femoral Neck			
Baseline BMD (g/cm^2)	0.639 ± 0.102	0.651 ± 0.100	0.647 ± 0.098
Month 12 BMD (g/cm^2)	0.651 ± 0.100	0.665 ± 0.098	0.660 ± 0.099
Absolute Change (g/cm^2)	0.009 ± 0.024	0.012 ± 0.023	0.014 ± 0.025
% Change from Baseline	1.6 ± 4.0	2.0 ± 3.6	2.2 ± 4.0
95% CI*		-0.183 , 0.880	0.097 , 1.147
Trochanter			

BM16550: Hip BMD: Relative Change from Baseline (ITT)			
	2.5 po qd	**2mg iv q2mo**	**3mg iv q3mo**
Baseline BMD (g/cm^2)	0.568 ± 0.089	0.575 ± 0.089	0.574 ± 0.089
Month 12 BMD (g/cm^2)	0.586 ± 0.090	0.598 ± 0.089	0.592 ± 0.087
Absolute Change (g/cm^2)	0.015 ± 0.024	0.022 ± 0.022	0.019 ± 0.025
% Change from Baseline	2.8 ± 4.3	3.9 ± 4.0	3.6 ± 5.8
95% CI*		0.473 , 1.771	0.204 , 1.486
* parametric analysis of difference in means of relative change from baseline, compared to active control			

6.1.4.3 Percentage of Responders: Responders were defined as those patients who had an increase in BMD above or equal to baseline after one year of treatment. In addition, responders were also defined as: patients whose lumbar spine (L2 – L4) or total hip BMD increased by ≥ 6% or ≥ 3% from baseline, respectively, at one year.

As outlined in the table below, the percentage of patients classified as responders was greater in both i.v. treatment groups than in the 2.5mg daily treatment group. At the lumbar spine, 83% of subjects were responders in the 2.5mg po daily group, while 91% in the 2mg i.v. q2 month group, and 90% in the 3mg i.v. q3month group were considered responders. The percentage of subjects with ≥ 6% increase in BMD at the lumbar spine was also higher in the i.v. treatment groups than the oral daily group (25% in the 2.5mg daily group, 36% in the 2mg i.v. q2 month group, and 36% in the 3mg i.v. q3month group).

At the total hip, 73% of subjects were responders in the 2.5mg daily group, while 84% in the 2mg i.v. q2 month group, and 82% in the 3mg i.v. q3month group were considered responders. As well, the percentage of subjects with ≥ 3% increase in BMD at the total hip was higher in the i.v. treatment groups than the oral daily group (31% in the 2.5mg daily group, 40% in the 2mg i.v. q2 month group, and 37% in the 3mg i.v. q3month group).

BM16550: Percentage of Responders (ITT)			
	2.5 po qd	**2mg iv q2mo**	**3mg iv q3mo**
N	458	442	458
Lumbar Spine			
Above Baseline	359 (82.7)	374 (90.8)	386 (90.0)
Below Baseline	75 (17.3)	38 (9.2)	43 (10.0)
≥ 6% Increase	110 (25.3)	150 (36.4)	153 (35.7)
Total Hip			
Above Baseline	312 (72.6)	383 (83.5)	298 (82.3)
Below Baseline	118 (27.4)	67 (16.5)	81 (19.1)
≥ 3% Increase	135 (31.4)	164 (40.5)	156 (36.7)
Femoral Neck			
Above Baseline	359 (82.7)	374 (90.8)	386 (90.0)
Below Baseline	75 (17.3)	38 (9.2)	43 (10.0)
Trochanter			
Above Baseline	329 (76.5)	347 (85.7)	363 (85.4)
Below Baseline	101 (23.5)	58 (14.3)	62 (14.6)

6.1.4.4 Serum CTx: Relative and Absolute Change from Baseline: Samples for serum CTX measurements were collected immediately prior to their i.v. dosing and represent trough values taken at the end of the dosing interval. As outlined in the table below, mean baseline serum CTX values were comparable in the three treatment groups. The percent change from baseline in CTx was slightly higher in the daily oral treatment group (-53%) compared to the two i.v. ibandronate treatment groups (-48% and -49%).

BM16550: Change in CTx at Month 12 (ITT)			
	2.5 po qd	**2mg iv q2mo**	**3mg iv q3mo**
N	458	442	458
n	413	383	397
Baseline CTx (g/cm^2)	0.55 ± 0.25	0.53 ± 0.24	0.52 ± 0.25
Month 12 CTx (g/cm^2)	0.24 ± 0.18	0.21 ± 0.147	0.24 ± 0.15
Absolute Change (g/cm^2)	-0.31 ± 0.26	-0.32 ± 0.22	-0.29 ± 0.22
% Change from Baseline	-52.9 ± 34.2	-48.3 ± 91.1	-48.7 ± 35.9
95% CI		-7.104 , 1.569	-0.614 , 8.957

6.1.4.6 Comparison of efficacy findings between studies BM16550, BM16549, MF4411 and MF4380

6.1.4.6.1 Lumbar spine BMD: Comparison of lumbar spine BMD changes at one year for the ITT analysis populations for the pivotal ibandronate trials are outlined in the table below. All active treatment groups in this comparison across studies showed a significantly higher mean increase in BMD than the placebo groups. In study BM16550, lumbar spine BMD increases were 3.6% in the 2.5mg daily oral ibandronate group, 4.8% in the 2mg i.v. q2month group and 4.6% in the 3mg i.v. q3month group. These increases are similar to those seen in the monthly oral ibandronate non-inferiority trial, BM16549, where LS spine increases were 3.7% in the 2.5mg daily oral ibandronate group, 3.9% in the 100mg monthly oral group and 4.8% in the 150mg monthly oral group. The highest i.v. ibandronate dose in study MF4380, the unsuccessful i.v. fracture trial, showed LS BMD increases of 3.3% at one year. Daily 2.5mg oral ibandronate had LS BMD increases of 4.9% in study MF4411, 3.6% in study BM16550, and 3.7% in study BM16549.

A responder analysis showed similar percentages of patients achieving a greater than 6% increase in LS BMD in the i.v. ibandronate treatment groups of BM16550 and the 2.5mg daily treatment group from MF441 (36%, 36% and 37% respectively). Of note, both the non-responder rate (decrease in BMD) and >6% response rate for the 2.5mg daily treatment group from both BM16550 and BM16549 and the 1mg i.v. q3month ibandronate group from MF4380 that failed to show fracture efficacy were similar. The reason for the apparent lesser efficacy in the 2.5mg daily group from these two noninferiority studies is unclear. Given the lower baseline BMD, one would have expected to see a larger relative increase in BMD.

Lumbar Spine BMD: Mean Relative Change from Baseline, One Year Data (ITT)						
		Baseline T-score	Baseline BMD (g/cm^2)	% Change from Baseline	BMD decreased (%)	BMD increase >6% (%)
BM16550	2.5mg po qd	-3.25	0.75	3.6	17%	25%
	2mg iv q2m	-3.27	0.75	4.8	9%	36%
	3mg iv q3m	-3.27	0.75	4.6	10%	36%
MF4380	placebo	-2.84	0.80	0.88	41%	9%
	1mg iv q3m	-2.76	0.80	3.27	19%	23%
MF 4411	placebo	-2.76	0.83	1.28	39%	12%
	2.5mg po qd	-2.75	0.83	4.87	12%	37%
BM16549	2.5mg po qd	-3.28	0.76	3.69	18%	24%
	100mg po qm	-3.27	0.76	3.91	14%	32%
	150mg po qm	-3.28	0.75	4.81	10%	35%

6.1.4.6.2 Total hip BMD: Comparison of total hip BMD changes at one year for the ITT analysis populations are outlined in the table below. All active treatment groups showed a significantly higher mean increase in BMD than the placebo groups. In study BM16550, total hip BMD increases were 1.6% in the 2.5mg daily oral ibandronate group, 2.4% in the 2mg i.v. q2month group, and 2.2% in the 3mg i.v. q3month group. The highest dose in study MF4380 showed hip BMD increases of 2.1% at one year. Placebo subjects in studies MF4411 and MF4380 showed a mean increase in total hip BMD of 0.6% and 0.1% respectively. A responder analysis showed similar percentages of patients achieving a greater than 3% increase in total hip BMD in the intermittent ibandronate treatment groups from BM16550 (40% in the 2mg i.v. q2month group and 37% in the 3mg i.v. q3month group), compared to 31% in the 2.5mg daily group.

Total Hip BMD: Mean Relative Change from Baseline, One Year Data (ITT)						
		Baseline T-score	Baseline BMD (g/cm^2)	% Change from Baseline	BMD decreased (%)	BMD increase >3% (%)
BM16550	2.5mg po qd	-2.00	0.73	1.6	27%	31%
	2mg iv q2m	-1.90	0.74	2.4	16%	40%
	3mg iv q3m	-1.96	0.74	2.2	19%	37%
MF4380	placebo	-1.80	0.72	0.13	40%	10%
	1mg iv q3m	-1.83	0.73	2.08	20%	32%
MF 4411	placebo	-1.73	0.74	0.59	40%	16%
	2.5mg po qd	-1.73	0.74	2.55	17%	37%
BM16549	2.5mg po qd	-1.78	0.75	1.90	23%	35%
	100mg po qm	-1.84	0.74	2.50	13%	43%
	150mg po qm	-1.84	0.74	2.90	10%	48%

6.1.4.6.3 C-telopeptide: Although the bone resorption marker CTx was assessed in all studies, a direct comparison of the data is not possible because in MF4411 and MF4380 CTx was measured in the urine, and in studies BM16550 and BM16549 CTx was measured in serum samples. However, in study BP16331 (reviewed previously), the pattern for the urinary CTx was similar to the serum CTx (-56% for urine CTx and -52% for serum CTx at Day 91). The mean decreases in serum CTx was -53% in the 2.5mg daily oral group, -48% in the 2mg i.v. q2month

group and -49% in the 3mg i.v. q3month group. While the mean decreases in serum CTx in the i.v. noninferiority trial are not as robust as those seen with in the pivotal 2.5mg daily fracture trial (MF4411, -58% in the 2.5mg daily group) or the monthly non-inferiority trial (-58% in the 2.5mg daily group and -67% in the 150mg monthly group), they are clearly lower than the mean relative decrease in CTx achieved by the 1mg i.v. q3month ibandronate dose from study MF4380 (-36%).

C-telopeptide: Mean Relative Change from Baseline, One Year Data (ITT)						
		Baseline, urine (µg/µmol Cr)	**Baseline serum (ng/ml)**	**% Change from Baseline**	**CTx decrease > 50% (%)**	**CTx decrease > 70% (%)**
BM16550	2.5mg po qd		0.55	-52.9	64%	38%
	2mg iv q2m		0.53	-48.3	71%	39%
	3mg iv q3m		0.52	-48.7	63%	26%
MF4380	placebo	0.34		-31.0	49%	21%
	1mg iv q3m	0.33		-36.5	30%	8%
MF 4411	placebo	0.25		-19.0	21%	3%
	2.5mg po qd	0.26		-58.5	69%	45%
BM16549	2.5mg po qd		0.51	-57.7	74%	44%
	100mg po qm		0.54	-56.6	71%	48%
	150mg po qm		0.52	-67.3	84%	63%

6.1.5 Clinical Microbiology

Ibandronate sodium has no antimicrobial properties, therefore, there are no clinical microbiology issues.

6.1.6 Efficacy Conclusions

Both ibandronate i.v. dosing regimens evaluated in study BM16550 were statistically, and presumably clinically, non-inferior to the daily oral 2.5mg dosing regimen, based on relative change in lumbar spine BMD at one year. Both i.v. regimens were also found to be statistically, and perhaps clinically, superior to the daily oral regimen. Increases in lumbar spine BMD ranged from 3.6% in the 2.5mg daily group, 4.6% in the 3mg i.v. q3month group, and 4.8% in the 2mg i.v. q2month group. The percentage of responders correlated with the increases in BMD, 83% in the 2.5mg daily group, 90% in the 3mg i.v. q3month group, and 91% in the 2mg i.v. q2month group. Twenty-five percent of subjects in the 2.5mg daily group, 36% in the 3mg i.v. q3month group, and 36% in the 2mg i.v. q2month group had LS BMD increases greater than 6%.

Increases in total hip BMD ranged from 1.6% in the 2.5mg daily group, 2.2% in the 3mg i.v. q3month group, and 2.4% in the 2mg i.v. q2month group. Again, the percentage of responders correlated with the increases in BMD, occurring in 73% in the 2.5mg daily group, 82% in the 3mg i.v. q3month group, and 84% in the 2mg i.v. q2month group with 31% in the 2.5mg daily

group, 37% in the 3mg i.v. q3month group, and 40% in the 2mg i.v. q2month group having LS BMD increases greater than 3%..

Serum CTX values decreased in all treatment groups, with a slightly higher decrease seen in the 2.5mg daily group (-53%), compared to -49% in the 3mg i.v. q3month group, and -48% in the 2mg i.v. q2month group.

The major difficulty in assessing the efficacy of intermittent intravenous ibandronate dosing is the validity of the surrogate endpoint lumbar spine BMD, in predicting fracture efficacy. The focus of this issue is study MF4380, the original pivotal trial for i.v. ibandronate, which showed lack of significant fracture reduction efficacy for the 0.5mg i.v. q3month and 1.0mg i.v. q3month regimens. The lack of fracture efficacy was attributed to insufficient dose or insufficient dose frequency. While it is possible to attribute the differences seen in BMD increases with these i.v. dosing regimens to insufficient dose with the every 3 month regimens used for the original fracture trial and adequate dosing with the current non-inferiority trial, there is insufficient information to state this definitively. Therefore, despite non-inferiority to the approved 2.5mg ibandronate dose, this reviewer believes that superiority to the approved 2.5mg daily oral dose is required for approval.

The increase in lumbar spine (L2 – L4) BMD seen with both the 2mg i.v. q2month and the 3mg i.v. q3month ibandronate regimens was non-inferior to the increase seen with 2.5mg daily regimen. Additional statistical analyses showed that both doses were also, in fact, superior to the 2.5mg daily dose with respect to increases in lumbar spine BMD ($p < 0.0001$). When compared to the highest dose in the terminated i.v. ibandronate fracture study MF4380, 1.0mg i.v., ibandronate showed mean lumbar spine BMD increases of 3.3% at one year, whereas the 2mg i.v. q2month dose had a mean increase of 4.8%, and the 3mg i.v. q3month dose had a mean increase of 4.6%. When compared to Year 1 data from study MF4411, the successful, pivotal 2.5mg fracture efficacy trial, lumbar spine BMD increases were comparable (4.8% with 2mg i.v. q2month dose, 4.6% with the 3mg i.v. q3month dose and 4.9% with 2.5mg daily). Therefore, these data suggest that both the 2mg i.v. q2month dose and the 3mg i.v. q3month dose of ibandronate are clinically comparable and may be clinically superior to ibandronate 2.5mg daily. This provides more reassurance that treatment with intravenous ibandronate every 3 months would confer fracture reduction efficacy.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety data have not been pooled. The bulk of the safety data presented here are from the pivotal study BM16650, as well as previously reviewed studies MF4411 and MF4380. Adverse events were graded on a four-point intensity scale: mild, moderate, severe, and life-threatening. The definition and reporting requirements for serious adverse events, as defined by the ICH guidelines, were adhered to.

7.1.1 Deaths

Four subjects died during the first year of this trial. A 72-year-old woman receiving placebo i.v. q2month and oral 2.5mg ibandronate daily was admitted to the hospital on study Day 35 with pulmonary edema and dehydration. She died on study Day 47. A 77-year-old woman receiving 2mg i.v. ibandronate q2month and daily oral placebo was hospitalized on study Day 21 with severe abdominal pain. She was diagnosed with multiple cholelithiasis, hemorrhagic pancreatitis and died on study Day 22. A 75-year-old woman receiving 3mg i.v. ibandronate q3month and daily oral placebo presented to her physician on study Day 102 and was diagnosed with acute myocardial infraction. She was sent to hospital for further care but died en route. A 72-year-old woman receiving 3mg i.v. ibandronate q3month and daily oral placebo was hospitalized on study Day 288 with severe arrhythmia, which was treated with cardiac pacemaker insertion. On study Day 307, she suffered a myocardial infarction, underwent angiogram with stent placement but subsequently died on study Day 311.

COMMENT: The causes of death are consistent with this population's baseline age and related comorbid conditions and similar to causes of death in the general population of postmenopausal patients at high risk for or with osteoporosis.

7.1.2 Other Serious Adverse Events

As outlined in the table below, the overall incidence of serious adverse events was the same in each treatment group (8% in the 2.5mg po daily group, 8% in the 2mg i.v. q2month group and 8% in the 3mg i.v. q3month group). Fracture was the most commonly reported serious adverse event. Serious events in the gastrointestinal and cardiac systems occurred in slightly more patients receiving ibandronate 2mg i.v. q2month.

BM16550: Serious Adverse Events, by Body System			
	2.5 po qd	**2mg iv q2m**	**3mg iv q3m**
N, safety population	**465**	**448**	**469**
Subjects Reporting AEs	37 (8)	40 (9)	35 (8)
Events:	40	47	42
Body as a whole	0 (0)	1 (<1)	2 (<1)
Gastrointestinal	4 (1)	11 (2)	2 (<1)
Injury*	8 (2)	3 (1)	6 (1)
Nervous	3 (1)	3 (1)	3 (1)
Cardiovascular	3 (1)	7 (2)	4 (1)
Hepatobiliary	2 (<1)	1 (<1)	3 (1)
Neoplasms	2 (<1)	2 (<1)	4 (1)
Respiratory	5 (1)	1 (<1)	3 (1)
Endocrine/Metabolic	1 (<1)	0 (0)	1 (<1)
Musculoskeletal	2 (<1)	4 (1)	1 (<1)
Infectious	2 (<1)	3 (1)	3 (1)
Immune	1 (<1)	0 (0)	0 (0)
Blood and Lymphatic	0 (0)	1 (<1)	0 (0)
Skin and Appendages	0 (0)	1 (<1)	0 (0)

BM16550: Serious Adverse Events, by Body System			
	2.5 po qd	**2mg iv q2m**	**3mg iv q3m**
Renal / Urinary Disorders	1 (<1)	3 (1)	0 (0)
Reproductive	2 (<1)	2 (<1)	2 (<1)
Vascular Disorders	1 (<1)	1 (<1)	1 (<1)
Vision Disorders	1 (<1)	0 (0)	2 (<1)
Psychiatric	1 (<1)	1 (<1)	0 (0)
* including fractures			

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts: Overall, approximately 85% of subjects enrolled in study BM16550 completed one year of treatment. Of the 1395 subjects enrolled, 9 (<1%) subjects received no treatment and 197 (14%) prematurely withdrew from the study. Rates of withdrawal were slightly higher in the intravenous treatment groups (12% in the 2.5mg daily group, 15% in the 2mg i.v. q2month group, and 16% in the 3mg i.v. q3month group). Adverse events were the most common reason for early withdrawal, accounting for 50% of withdrawn subjects, with the rates balanced among the groups. The predominant other reasons for withdraw from the study was refused treatment, which occurred in 72 (36%) subjects. No subjects were withdrawn for insufficient therapeutic response.

7.1.3.2 Adverse events associated with dropouts: Overall, 114 subjects withdrew from the trial due to adverse events, including serious adverse events (35 (8%) in the 2.5mg po daily group, 33 (7%) in the 2mg i.v. q2month group, and 46 (10%) in the 3mg i.v. q3month group). The most common adverse events leading to withdrawal were due to gastrointestinal (20 (4%) in the 2.5mg po daily group, 16 (4%) in the 2mg i.v. q2month group, and 18 (4%) in the 3mg i.v. q3month group); musculoskeletal (3 (1%) in the 2.5mg po daily group, 7 (2%) in the 2mg i.v. q2month group, and 6 (1%) in the 3mg i.v. q3month group); and body as a whole (3 (1%) in the 2.5mg po daily group, 5 (1%) in the 2mg i.v. q2month group, and 6 (1%) in the 3mg i.v. q3month group).

7.1.3.3 Other significant adverse events - Dose alteration: Investigators were allowed to modify or interrupt treatment doses when necessary for medical reasons. Modification or interruption of the intermittent intravenous dose due to adverse events or i.v. administration difficulties occurred in 25 subjects (9 (2%) in the 2.5mg po daily group, 8 (2%) in the 2mg i.v. q2month group, and 8 (2%) in the 3mg i.v. q3month group). Modification or interruption of the daily oral dose due to adverse events occurred in 203 subjects (73 (16%) in the 2.5mg po daily group, 64 (14%) in the 2mg i.v. q2month group, and 66 (14%) in the 3mg i.v. q3month group). The most commonly affected categories were gastrointestinal disorders (25 (5%) in the 2.5mg po daily group, 25 (6%) in the 2mg i.v. q2month group, and 26 (6%) in the 3mg i.v. q3month group) and infections (20 (4%) in the 2.5mg po daily group, 14 (3%) in the 2mg i.v. q2month group, and 17 (4%) in the 3mg i.v. q3month group).

7.1.4 Other Search Strategies

No special search algorithms were utilized in this safety review.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program: Adverse events were assessed continuously during the study at each visit with directed questions and recorded in the case report form. During scheduled study visits, subjects were also instructed to, whenever they experienced an adverse event or any discomfort they thought was associated with study drug intake between visits, to call the investigator for advice. The investigator was to provide the patient with his/her recommendation concerning stopping or modifying treatment. Events were to be followed up until they returned to baseline status or stabilized.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms: An adverse event (AE) was appropriately defined as any untoward medical occurrence in a patient administered a pharmaceutical product and which did not necessarily have to have a causal relationship with the treatment. Pre-existing conditions that worsened during the study were to be reported as adverse events. The intensity of adverse events was graded on a four-point scale (mild, moderate, severe, life threatening). Serious adverse events were appropriately defined. Adverse events listings utilized MedDRA preferred terms.

7.1.5.3 Incidence of common adverse events: As outlined in the section below, the overall number of subjects experiencing adverse events was comparable across the treatment groups (360 (77%) in the 2.5mg po daily group, 365 (81%) in the 2mg i.v. q2month group, and 357 (76%) in the 3mg i.v. q3month group). Of note, subjects in the 2mg i.v. q2month group had two more study visits per year than the 3mg i.v. q3month group and thus had more opportunity to report adverse events. The most common disorders reported were infections and infestations (158 (34%) in the 2.5mg po daily group, 165 (37%) in the 2mg i.v. q2month group, and 118 (25%) in the 3mg i.v. q3month group), musculoskeletal and connective tissue disorders (122 (26%) in the 2.5mg po daily group, 151 (34%) in the 2mg i.v. q2month group, and 136 (25%) in the 3mg i.v. q3month group), and gastrointestinal disorders (125 (27%) in the 2.5mg po daily group, 148 (33%) in the 2mg i.v. q2month group, and 110 (23%) in the 3mg i.v. q3month group).

The most frequent adverse events were arthralgia (40 (9%) in the 2.5mg po daily group, 42 (9%) in the 2mg i.v. q2month group, and 45 (10%) in the 3mg i.v. q3month group), back pain (35 (8%) in the 2.5mg po daily group, 38 (8%) in the 2mg i.v. q2month group, and 33 (7%) in the 3mg i.v. q3month group), nasopharyngitis (28 (6%) in the 2.5mg po daily group, 30 (7%) in the 2mg i.v. q2month group, and 16 (3%) in the 3mg i.v. q3month group), and constipation (19 (4%) in the 2.5mg po daily group, 30 (7%) in the 2mg i.v. q2month group, and 16 (3%) in the 3mg i.v. q3month group.

Adverse events that were consistently more frequently reported in the intravenous dose groups were influenza-like illness (5 (1%) in the 2.5mg po daily group, 20 (4%) in the 2mg i.v. q2month group, and 19 (4%) in the 3mg i.v. q3month group), fatigue (5 (1%) in the 2.5mg po daily group,

11 (2%) in the 2mg i.v. q2month group, and 13 (3%) in the 3mg i.v. q3month group) and myalgia (4 (1%) in the 2.5mg po daily group, 19 (4%) in the 2mg i.v. q2month, and 13 (3%) in the 3mg i.v. q3month group).

7.1.5.4 Common adverse event tables

BM16550: Adverse Events, by Body System			
	2.5 po qd	**2mg iv q2m**	**3mg iv q3m**
N, safety population	**465**	**448**	**469**
AE, total (n)	360 (77)	365 (81)	357 (76)
Infectious	158 (34)	165 (37)	118 (25)
Musculoskeletal	122 (26)	151 (34)	136 (29)
Gastrointestinal	125 (27)	148 (33)	110 (23)
Body as a whole	29 (6)	61 (14)	62 (13)
Nervous	56 (12)	54 (12)	61 (13)
Injury, Poisoning*	33 (7)	39 (9)	40 (9)
Respiratory	39 (8)	31 (7)	23 (5)
Endocrine/Metabolic	37 (8)	29 (6)	23 (5)
Vascular Disorders	51 (11)	41 (9)	43 (9)
Vision Disorders	27 (6)	19 (4)	17 (4)
Cardiovascular	12 (3)	24 (5)	15 (3)
Skin and Appendages	27 (6)	25 (6)	34 (7)
Psychiatric	30 (6)	17 (4)	18 (4)
Renal / Urinary Disorders	10 (2)	15 (3)	11 (2)
Hearing / Vestibular	7 (2)	16 (4)	11 (2)
Hepatobiliary	6 (1)	3 (1)	4 (1)
Neoplasms	9 (2)	4 (1)	7 (1)
Immune	7 (2)	3 (1)	5 (1)
Blood and Lymphatic	5 (1)	5 (1)	4 (1)
Reproductive	8 (2)	7 (2)	8 (2)
* including fractures			

7.1.5.5 Identifying common and drug-related adverse events: Based on experience with currently approved oral and intravenous bisphosphonates, adverse events of special interest that may be related to drug include fracture, gastrointestinal disorders, acute phase reactions, musculoskeletal pain, eye disorders, renal disease, hypocalcemia and osteonecrosis of the jaw.

7.1.5.5.1 Fracture: A total of 43 subjects sustained fractures during the first year of this trial (17 (4%) in the 2.5mg po daily group, 13 (3%) in the 2mg i.v. q2month group, and 13 (3%) in the 3mg i.v. q3month group). Fractures that could be considered clinical osteoporotic fractures (excluding hand, foot and facial bones) occurred in 35 subjects (15 (3%) in the 2.5mg po daily group, 10 (2%) in the 2mg i.v. q2month group, and 12 (3%) in the 3mg i.v. q3month group). Clinical vertebral fractures were reported in 10 subjects (3 in the 2.5mg po daily group, 2 in the 2mg i.v. q2month group, and 5 in the 3mg i.v. q3month group). Hip fractures were reported in 3 subjects (2 in the 2.5mg po daily group and 1 in the 3mg i.v. q3month group).

7.1.5.5.2 Gastrointestinal disorders: Oral, nitrogen-containing bisphosphonates are well known to cause gastroesophageal irritation. In this study, a total of 383 (125 (27%) in the 2.5mg po daily group, 148 (33%) in the 2mg i.v. q2month group, and 110 (23%) in the 3mg i.v. q3month group) subjects experienced adverse events related to the gastrointestinal tract. Event rates were comparable among the treatment groups even though two treatment groups received no oral bisphosphonate medication. The most common adverse events were dyspepsia and nausea.

BM16550: Gastrointestinal Adverse Events			
	2.5 qd	**2mg iv q2m**	**3mg iv q3m**
N, safety population	**465 (%)**	**448**	**469**
Abdominal pain	27 (6)	26 (6)	26 (6)
Diarrhea	12 (3)	17 (4)	14 (3)
Dyspepsia/ GERD	26 (6)	28 (6)	23 (5)
Esophagitis/Esoph erosion	5 (1)	3 (1)	1 (<1)
Gastritis	10 (2)	10 (2)	9 (2)
Gastric Ulcer	1 (<1)	3 (1)	0 (0)
Duodenitis	3 (1)	2 (<1)	0 (0)
Nausea	20 (4)	20 (4)	10 (2)
Vomiting	8 (2)	7 (2)	6 (1)
Melena	0 (0)	0 (0)	0 (0)

COMMENT: These findings would support the hypothesis that the gastroesophageal side effects of nitrogen containing bisphosphonates are a consequence of their mechanism of action – inhibition of the mevalonate pathway and thus suppression of epithelial cell growth, rather than direct pill-related tissue irritation.

7.1.5.5.3. Acute phase reactions: Symptoms consistent with acute phase reaction have been reported with intravenous bisphosphonate use. Symptoms considered possibly related to an acute phase reaction include flu-like symptoms such as fatigue, fever, chills, myalgia, arthralgia, pain and generalized body aches, occurring within 3 days of i.v. dosing and lasting less than 7 days. Acute phase reaction symptoms occurred in 127 subjects. The overall incidence of patients with APR-like events (as pre-defined) was higher in the intravenous treatment groups (18 (4%) in the 2.5mg po daily group, 64 (14%) in the 2mg i.v. q2month group, and 45 (10%) in the 3mg i.v. q3month group). There were no serious adverse events related to APR-like symptoms. A total of 18 subjects (2 (0.4%) in the 2.5mg po daily group, 4 (1%) in the 2mg i.v. q2month group, and 12 (3%) in the 3mg i.v. q3month group) withdrew from the study due to APR-like symptoms. Four subjects, 1 in the 2mg i.v. q2month group, and 3 in the 3mg i.v. q3month group had dose modifications made due to APR-like symptoms and 32 subjects (5 (1%) in the 2.5mg po daily group, 21 (5%) in the 2mg i.v. q2month group, and 6 (1%) in the 3mg i.v. q3month group) required concomitant medical therapies for symptom relief.

As outlined in the table below, the majority of APR-like events occurred after the first two injections of study drug. Of those reporting APR-like symptoms, approximately 17% of subjects in the 2mg i.v. q2month group and 20% of subjects in the 3mg i.v. q3month group had a repeat event.

Study BM16550: Subjects with APR-like Events, by Injection Number							
		Injection Number					
	N	1	2	3	4	5	6
2.5mg qd	226	6 (3)	4 (2)	2 (1)	0 (0)	0 (0)	1 (<1)
2mg q2mo	448	50 (11)	15 (4)	4 (1)	9 (2)	3 (1)	1 (<1)
2.5mg qd	239	5 (2)	2 (1)	1 (<1)	2 (1)	-------	-------
3mg q3mo	469	39 (8)	13 (3)	8 (2)	2 (<1)	-------	-------

7.1.5.5.4 Musculoskeletal pain: An increased incidence of bony pain has been reported with bisphosphonate use. Overall, musculoskeletal pain symptoms occurred in 201 subjects (59 (13%) in the 2.5mg po daily group, 74 (17%) in the 2mg i.v. q2month group, and 66 (14%) in the 3mg i.v. q3month group). Specifically, bone pain occurred in 31 subjects and was slightly higher in the 2mg i.v. q2month group (7 (1%) in the 2.5mg po daily group, 17 (4%) in the 2mg i.v. q2month group, and 7 (1%) in the 3mg i.v. q3month group).

7.1.5.5.5 Eye disorders: An increased incidence of inflammatory eye diseases, such as uveitis and scleritis, has been reported with bisphosphonate use. Overall, 64 subjects (27 (6%) in the 2.5mg po daily group, 20 (4%) in the 2mg i.v. q2month group, and 17 (4%) in the 3mg i.v. q3month group) experienced adverse events related to the eye. Symptoms related to eye inflammation (including pain, erythema, irritation, blepharitis, conjunctivitis, episcleritis, iridocyclitis, iritis, keratitis, scleritis and uveitis) occurred in 16 subjects and evenly distributed through all treatment groups (4 in the 2.5mg po daily group, 7 in the 2mg i.v. q2month group, and 5 in the 3mg i.v. q3month group).

7.1.5.5.6 Renal disease: Intravenous bisphosphonates have been associated with increased renal function abnormalities (e.g., increases in serum creatinine), most notably in the setting of rapid i.v. administration. In study BM16550, i.v. ibandronate administration was by rapid bolus. The number of subjects with adverse events attributable to the renal tract were similar in all three dose groups (10 (2%) subjects in the 2.5 mg oral group, 15 (3%) subjects in the 2mg i.v. q2month group, and 11 (2%) subjects in the 3mg i.v. q3month group). The most common adverse events were nephrolithiasis (5 (1%) subjects in the 2.5 mg oral group, 2 (<1%) subjects in the 2mg i.v. q2month group, and 2 (<1%) subjects in the 3mg i.v. q3month group) and urinary incontinence (2 (<1%) subjects in the 2.5 mg oral group, no subjects in the 2mg i.v. q2month group, and 4 (1%) subjects in the 3mg i.v. q3month group). Six subjects (four in the 2mg i.v. q2month group and two in the 3mg i.v. q3month group) were reported to have either chronic renal failure, renal impairment or blood creatinine increased as an adverse event. Renal function laboratories for these subjects are outlined in the table below. Two subjects withdrew from the study prior to Month 12. A 59 year-old woman with a history of hypertension was randomized to i.v. ibandronate 3mg i.v. q3month. She withdrew from the study on Day 165 stating she did not want to continue. Her baseline creatinine was 0.8 mg/dL with a follow-up of 1.4 mg/dL on study Day 165. No further laboratory data is available. A 79 year-old woman with a history of acromegaly and panhypopituitarism was randomized to i.v. ibandronate 2mg i.v. q2month. Her baseline creatinine of 1.0 mg/dL was stable at 0.9 mg/dL on study Day 123 and increased to 1.5mg/dL on study Day 242. She withdrew from the study for unclear reasons. No further

laboratory data is available, however, her renal insufficiency reportedly resolved after 4 months off of study drug. See the laboratory results section for further discussion of increased creatinine with intravenous ibandronate use.

BM16550: Subjects with Reported AE of Renal Impairment/Insufficiency						
Subject	446	932	1255	334	280	931
Age	59	66	79	63	76	79
Dose	3mg q3m	3mg q3m	2mg q2m	2mg q2m	2mg q2m	2mg q2m
Creatinine (mg/dL)						
Baseline	0.8	1.3	1.0	1.0	0.8	1.1
Month 3		1.2				
Month 4	1.4		0.9	1.2	0.9	1.7
Month 6		1.2		1.2		
Month 8			1.5	1.1	0.8	1.4
Month 9		1.5				
Month 12		1.3		1.2	0.8	2.1
Month 15		1.5				
Month 16				1.2	1.8	1.4
Month 18		1.5				
Month 20				1.2	1.4	1.3
Month 21		1.7				
Month 24		1.7		1.2		1.3

7.1.5.5.7 Hypocalcemia: Bisphosphonate use, most notably intravenous bisphosphonates, have been associated with hypocalcemia. There were no adverse events directly related to low blood calcium levels. See the laboratory results section for further discussion of hypocalcemia with intravenous ibandronate use.

7.1.5.5.8 Osteonecrosis of the jaw: Some intravenous (and rarely, oral) bisphosphonates have been associated with osteonecrosis of the jaw. In this study 2 subjects experienced jaw pain/inflammation during the study. A 60-year-old subject in the 3mg i.v. q3month group experienced moderate left jaw and ear pain on Day 2. The symptoms resolved 18 days later without further treatment. A 69 year-old subject in the 2mg i.v. q2month group developed moderate jaw pain on Day 16. The symptoms resolved without further treatment.

7.1.5.6 Additional analyses and explorations: No additional analyses or explorations were performed.

7.1.6 Less Common Adverse Events

See discussions above for the rare, but important adverse events that have been shown to be related to bisphosphonate therapy.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program: Basic laboratory safety testing was performed in all studies. Except for creatinine levels, all laboratory results from study BM16550 were reviewed based on data from the first year of the study. Creatinine levels for both the first and second year of the study were provided by the sponsor and reviewed in depth. Because ibandronate is not metabolized by the liver, hepatic function was evaluated with only SGPT in study BM16550. A table of all normal laboratory ranges and pre-defined limits of change can be found in Appendix 10.3.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values: Study BM16550 is the focus of the laboratory evaluation. However, the timing of the mineral laboratories in study BM16550 did not allow for assessment of the expected calcium nadir. Therefore, other studies which had appropriately timed calcium assessments (study MF4328) were reviewed.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency: The mean relative change in laboratories from baseline to Month 12 are outlined in the table below. The increase in SGPT in the 3mg i.v. q3month group was significant compared to the 2.5mg daily oral group (p=0.03). Creatinine increased with all dosing regimens. The 2.5mg daily groups mean value increased by 0.9 ± 7.7 µmol/L, while the 2.0mg i.v. q2month group had an increase of 2.3 ± 10.3 µmol/L (p=0.04, compared with the daily group) and the 3mg i.v. q3month group increased by an average of 1.7 ± 8.6 µmol/L (p=0.26, compared with the daily group). Serum calcium fell -0.02 ± 0.1 mmol/L in the 2.5mg daily oral group, which was significantly different from the i.v. dose groups (-0.00 ± 0.10 mmol/L in the 2.0mg i.v. q2month group, p=0.02; and -0.00 ± 0.10 mmol/L in the 3mg i.v. q3month group, p=0.001). Phosphate levels decreased in all treatment groups, with the greatest decrease in the 2.5mg daily group.

BM16550: Laboratory Values: Mean Change at Month 12

	2.5 po qd	2mg iv q2m	3mg iv q3m
N, safety population	465	448	469
SGPT (U/L)	-0.4 ± 7.8	0.2 ± 7.8	0.8 ±8.4*
Albumin (g/L)	0.1 ± 2.3	0.1 ± 2.5	0.3 ± 2.3
BUN (mmol/L)	0.0 ± 1.2	0.0 ± 1.4	-0.1 ± 1.3
Creatinine (µmol/L)	0.9 ± 7.7	2.3 ± 10.3*	1.7 ± 8.6
Calcium (mmol/L)	-0.02 ± 0.10	-0.00 ± 0.10*	0.00 ± 0.10*
Phosphate (mmol/L)	-0.04 ± 0.17	-0.02 ± 0.16	-0.01 ± 0.17*
Magnesium (mmol/L)	-0.0 ± 0.1	-0.0 ± 0.1	-0.0 ± 0.1
Sodium (mmol/L)	0.8 ± 3.2	0.7 ± 3.2	0.9 ± 3.3
Potassium (mmol/L)	-0.1 ± 0.4	-0.1 ± 0.4	-0.1 ± 0.4

BM16550: Laboratory Values: Mean Change at Month 12			
	2.5 po qd	2mg iv q2m	3mg iv q3m
Chloride (mmol/L)	0.4 ± 2.8	0.2 ± 2.8	0.4 ± 2.8
WBC (10^9/L)	-0.5 ± 1.3	-0.4 ± 1.3	-0.6 ± 1.3
Hemoglobin (g/dL)	-0.1 ± 0.8	-0.2 ± 0.8	-0.1 ± 0.8
Hematocrit (fraction)	-0.0 ± 0.02	-0.0 ± 0.02	-0.0 ± 0.02
Platelets (10^9/L)	-10 ± 37	-9 ± 34	-9 ± 40
* p≤0.05 compared with 2.5mg daily, analysis by students t-test			

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal: The majority of patients had laboratory values for all parameters that remained in the normal range during the trial. As outlined in the table below, decreases of the WBC count from normal into the low range was the most common laboratory shift, occurring in 74 (16%) in the 2.5 mg daily groups, 76 (17%) in the 2.0mg i.v. q2month group, and 89 (19%) in the3mg i.v. q3month group. SGPT was the only laboratory parameter evaluated to assess liver function. Increases in SGPT above the normal range occurred in 44 (9%) subjects in the 2.5 daily groups, 38 (8%) subjects in the 2.0mg i.v. q2month group, and 59 (13%) subjects in the 3mg i.v. q3month group. With regard to renal function, the number of patients with increases in BUN above the normal range was similar across treatment groups (22 (5%) in the 2.5 mg daily groups, 27 (6%) in the 2.0mg i.v. q2month group, and 19 (4%) in the 3mg i.v. q3month group). The number of subjects with increases in serum creatinine above the normal range was low (4 (1%) in the 2.5 mg daily groups, 5 (1%) in the 2.0mg i.v. q2month group, and 1 (<1%) in the 3mg i.v. q3month group). Only one subject in the 2.0mg i.v. q2month group had a decrease in serum calcium below the normal range. A decrease in WBC count into the low range was the most common laboratory shift, occurring in 22 (5%) in the 2.5 mg daily groups, 27 (6%) in the 2.0mg i.v. q2month group, and 19 (4%) in the 3mg i.v. q3month group

BM16550: Pertinent Laboratory Values: Shift Table			
	2.5 po qd	2mg iv q2m	3mg iv q3m
N, safety population	465	448	469
SGPT, Nl to Hi	44 (11)	38 (10)	59 (14)
BUN, Nl to Hi	22 (5)	27 (6)	19 (4)
Creatinine, Nl to Hi	4 (1)	5 (1)	1 (<1)
Calcium, Nl to Hi	40 (9)	38 (8)	40 (9)
Calcium, Nl to Low	0 (0)	1 (<1)	0 (0)
Phosphate, Nl to Hi	34 (7)	42 (9)	46 (10)
Phosphate, Nl to Low	16 (3)	7 (2)	11 (2)
Magnesium, Nl to Low	9 (2)	11 (2)	10 (2)
WBC, Nl to Low	74 (16)	76 (17)	89 (19)
Hematocrit, Nl to Low	41 (9)	37 (8)	44 (9)
Hemoglobin, Nl to Low	38 (8)	41 (9)	41 (9)

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities: As outlined in the table below, a total of 23 (7 (2%) in the 2.5mg daily group, 8 (2%) in the 2.0mg i.v. q2month group and 7 (1.5%) in the 3mg i.v. q3month group) subjects developed marked laboratory abnormalities during the study. The most common abnormality was marked increases in SGPT,

which occurred in 9 (2%) subjects in the 2.5mg daily group, 8 (2%) subjects in the 2.0mg i.v. q2month group and 9 (2%) subjects in the 3mg i.v. q3month group). One subject in the 2.0mg i.v. q2month dose group developed a markedly elevated creatinine. No abnormalities in calcium metabolism were noted.

BM16550: Marked Laboratory Abnormalities at Month 12			
	2.5 po qd	**2mg iv q2m**	**3mg iv q3m**
N, safety population	465	448	469
Albumin (35 – 50 gm/L)			
Value < 27	0 (0)	1 (<1)	0 (0)
Calcium (2.15 – 2.55 mmol/L or 8.6 – 10.2 mg/dL)			
Value < 2.0 mmol/L (8.0 mg/dL)	0 (0)	0 (0)	0 (0)
Value > 2.9 mmol/L (11.6 mg/dL)	0 (0)	0 (0)	0 (0)
Phosphate (0.87 – 1.45 mmol/L)			
Value < 0.75	3 (1)	3 (1)	0 (0)
Value > 1.6	6 (1)	1 (<1)	5 (1)
Blood Urea Nitrogen (1.7 – 8.3 mmol/L)			
Value > 14.3	0 (0)	2 (<1)	0 (0)
Creatinine (0 – 133 µmol/L or 0 – 1.5 mg/dL)			
Increase ≥ 75% and value >133 µmol/L	0 (0)	1 (<1)	0 (0)
Sodium (135 – 145 mmol/L)			
Value < 130	0 (0)	0 (0)	0 (0)
Value > 150	0 (0)	0 (0)	0 (0)
Potassium (3.5 – 5.1 mmol/L)			
Value < 3	0 (0)	1 (<1)	0 (0)
Value > 6	0 (0)	0 (0)	0 (0)
Chloride (98 – 106 mmol/L)			
Value < 95	0 (0)	0 (0)	2 (<1)
Value > 115	1 (<1)	0 (0)	0 (0)
SGPT (0 – 30 IU/L)			
Value > 60	8 (2)	8 (2)	9 (2)
WBC (3.6 – 11.0 10^9/L)			
Value < 3.0	1 (<1)	3 (1)	2 (<1)
Value > 18.0	0 (0)	1 (<1)	1 (<1)
Hematocrit (0.35 – 0.47)			
Value < 0.36	0 (0)	1 (<1)	3 (1)
Value > 0.60	0 (0)	0 (0)	1 (<1)
Hemoglobin (11.5 – 16.5 gm/dL)			
Value < 11	1 (<1)	3 (1)	4 (1)
Value > 20	0 (0)	1 (<1)	1 (<1)
Platelets (150 – 400 10^9/L)			
Value < 100	1 (<1)	0 (0)	1 (<1)
Value > 700	0 (0)	0 (0)	1 (<1)

7.1.7.4 Additional analyses and explorations

7.1.7.4.1 Serum Creatinine: In study BM16550, serum creatinine levels were measured at baseline and Months 4, 8, 12, 16, 20 and 24 for subjects on a q2month injection schedule; and

Months 3, 6, 9, 12, 15, 18, 21 and 24 for subjects on a q3month injection schedule. As outlined in the table below, the mean change in serum creatinine was comparable between the three treatment groups: - 0.01 to 0.02 mg/dL at Month 12 and 0.05 to 0.07 mg/dL at Month 24. A total of 18 subjects shifted from a normal creatinine at baseline to a high creatinine at some point during the two years of the study (6 (2%) in the 2.5mg oral daily group, 9 (2%) in the 2mg i.v. q2month group and 3 (1%) in the 3mg i.v. q3month group).

During the two years of the study, thirteen subjects developed a markedly elevated creatinine, defined as > 154 µmol/L or >1.7 mg/dL (4 in the 2.5mg oral daily group, 5 in the 2mg i.v. q2month group and 4 in the 3mg i.v. q3month group). Three subjects, all in the 2mg i.v. q2month group had markedly elevated creatinine when defined as a creatinine >1.5 mg/dL and > 75% increase from baseline.

When evaluated as a clinically relevant change (defined as an increase of 0.5 mg/dL in subjects with a baseline creatinine of <1.4 mg/dL, or an increase of 1.0 mg/dL in subjects with a baseline creatinine of ≥ 1.4 mg/dL, or any value at least 2 fold higher than baseline), a total of thirteen subjects (3 in the 2.5mg daily oral group, 7 in the 2mg i.v. q2month group and 3 in the 3mg i.v. q3month group) with baseline creatinine of <1.4 mg/dL exhibited a clinically significant increase in creatinine during the study (six in the first year and an additional seven in the second year) Very few subjects with a baseline creatinine ≥ 1.4.mg/dL were enrolled into the study and none had a clinically relevant change in creatinine during the 24 month study period.

BM16550: Renal Safety						
	2.5 po qd		**2mg iv q2m**		**3mg iv q3m**	
	M12	**M24**	**M12**	**M24**	**M12**	**M24**
	465		448		469	
Creatinine (0 – 1.5mg/dL)						
N	409	387	382	363	395	377
Baseline Cr (mg/dL)	0.9	0.9	0.9	0.9	0.9	0.9
Follow-up Cr (mg/dL)	0.9	1.0	0.9	1.0	0.9	1.0
Mean change (mg/dL)	0.01	0.05	0.02	0.06	0.02	0.07
Shift normal to high (n (%))	4 (1)	6 (2)	5 (1)	9 (2)	1 (<1)	3 (1)
Cr > ULN (≥1.5 mg/dL) (n (%))	6 (1)	10 (2)	7 (2)	14 (3)	2 (<1)	9 (2)
Cr marked (≥1.7 mg/dL) (n (%))	1 (<1)	4 (1)	2 (<1)	5 (1)	2 (<1)	4 (1)
Cr marked ≥1.5mg/dL + 75% increase (n (%))	0 (0)	0 (0)	2 (<1)	3 (1)	0 (0)	0 (0)
Cr increase ≥50% (n (%))	2 (<1)	5 (1)	5 (1)	10 (2)	1 (<1)	2 (<1)
Cr increase ≥75% (n (%))	0 (0)	1(<1)	3 (<1)	4 (1)	0 (0)	0 (0)
Cr increase 2 x baseline (n (%))	0 (0)	1 (<1)	1 (<1)	2 (<1)	0 (0)	0 (0)
Cr base < 1.4mg/dl (N)	**449**		**427**		**451**	
increase ≥0.5 mg/dL (n (%))	0 (0)	3 (1)	4 (1)	7 (2)	2 (<1)	4 (1)
Cr base ≥ 1.4 mg/dL (N)	**4**		**6**		**8**	
increase ≥1.0 mg/dL (n (%))	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

The table below outlines the pattern of serum creatinine levels for subjects noted to have a clinically significant increase in creatinine. Most increases were transient, although creatinine

did not return to baseline values. Of concern is the one subject with a baseline creatinine of 1.7 mg/dL. After one dose of i.v. ibandronate, her creatinine increased to 2.3 mg/dL. No further laboratory data is available as the patient withdrew from the study due to worsening glycemic control.

BM16550: Subjects with Clinically Significant Increases in Creatinine

Dose	2.5 po qd			2mg iv q2m							3mg iv q3m			
Pt*	5	161	508	114	2111	2553	2563	2571	6052	8731	1814	2200	3070	4710
Age	72	75	67	59	79	64	58	68	72	76	63	67	59	73
Month														
0	0.6	0.9	1.3	0.9	1.1	0.7	0.7	0.9	1.0	0.8	1.3	1.7	0.8	1.0
3		0.9									1.2	2.3		1.4
4	0.6		1.6	0.9	1.7	0.6	0.5	0.9	0.9	0.9				
6		0.9									1.4		1.4	1.2
8	0.8		1.5	0.8	1.4	0.7	0.7	0.9	1.5	0.8				
9		0.9									1.9			1.2
12	0.7	0.9	1.5	1.0	2.1	1.3	1.7	0.9		0.8				1.3
15		1.5									1.6			1.5
16	0.8		2.2	1.5	1.4		0.7	1.2		1.8				
18		0.9												1.4
20	0.7		2.1	0.9	1.3		0.6	1.4		1.4				
21		0.9												1.2
24	1.2	0.9	2.1	1.1	1.3		0.7	1.2						1.2

*patient numbers from the second year dataset were used

Study MF4328 was an open-label, non-controlled multicenter study to evaluate the safety and efficacy of single i.v. injections of ibandronate in doses of 0.5, 1, 2, and 3mg as well as infusions of ibandronate in doses of 4 and 6mg conducted in 148 normocalcemic subjects with breast cancer and osteolytic bone metastases. Serum creatinine levels were drawn on Days 2, 4, 7, 14, 21, and 28. Urinary protein evaluations also occurred on Days 2, 4, 7, 14, 21, and 28.

Changes in serum creatinine from baseline to last value are listed in the table below. The were no significant changes in serum creatinine in any dose group over the 28 days of the trial.

Study MF4328: Serum creatinine

	0.5 mg iv bolus	1.0 mg iv bolus	2.0 mg iv bolus	3.0 mg iv bolus	4.0 mg iv infusion	6.0 mg iv infusion
N	14	23	54	15	16	25
age	58.9 ± 12.6	58.6 ± 10.6	55.8 ± 11.3	67.0 ± 11.9	49.5 ± 10.6	51.2 ± 11.5
Baseline (mmol/L)	0.08 ± 0.01	0.08 ± 0.02	0.08 ± 0.02	0.09 ± 0.03	0.08 ± 0.01	0.07 ± 0.01
Last value (mmol/L)	0.08 ± 0.01	0.08 ± 0.02	0.08 ± 0.02	0.09 ± 0.03	0.07 ± 0.01	0.07 ± 0.01
Change (mmol/L)	0.01 ± 0.01	0.00 ± 0.01	0.00 ± 0.01	0.00 ± 0.01	0.00 ± 0.01	0.00 ± 0.01
Relative Chnge (%)	9.1 ± 20.4	-1.2 ± 10.4	0.6 ± 11.4	-0.6 ± 12.6	-0.4 ± 9.4	-2.0 ± 12.4

Increases in urinary protein may represent the earliest signs of renal damage with bisphosphonate use. At baseline, 118 of 147 subjects had negative urinary protein dipstick. Investigators reported proteinuria in eight subjects (one in the 2.0mg i.v. bolus group and 7 in the 3.0mg i.v.

bolus group). Based on recorded laboratory results, a total of 22 subjects (3 in the 0.5mg i.v. bolus group, 3 in the 1.0mg i.v. bolus group, 5 in the 2.0mg i.v. bolus group, 5 in the 3.0mg i.v. bolus group, 2 in the 4.0mg i.v. infusion group, and 4 in the 6.0mg i.v. infusion group) had an increase in urinary total protein at some point during the 28 days following ibandronate administration. Three subjects (two in the 2mg i.v. bolus group and one in the 3mg i.v. bolus group) developed greater than 5 g/L urinary total protein following ibandronate dosing.

Study MF4265 was a double-blind, placebo-controlled, randomized multicenter study to evaluate the efficacy and safety of long-term treatment with 2 mg (i.v. bolus) or 6 mg (i.v infusion) ibandronate administered intravenously at 4-week intervals for at least 60 weeks in patients with metastatic bone disease due to breast cancer. Subjects could be enrolled for a total of 96 weeks. Serum creatinine was measured at baseline and Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84 and 96. The protocol was amended to include an evaluation of renal function in a subset of subjects. As outlined in the table below, the change in serum creatinine level was comparable between the treatment groups.

Study MF4265: Serum creatinine

	Placebo			2mg i.v. bolus			6mg i.v. infusion		
Week	n	Value µmol/L	Change µmol/L	n	Value µmol/L	Change µmol/L	n	Value µmol/L	Change µmol/L
0	155	93 ± 30		153	91 ± 22		151	92 ± 24	
4	151	92 ± 26	-1 ± 20	144	91 ± 24	-0 ± 11	147	90 ± 23	-3 ± 16
8	142	96 ± 41	2 ± 30	146	91 ± 22	0 ± 13	138	92 ± 28	-0 ± 17
12	135	91 ± 30	-1 ± 19	138	92 ± 23	1 ± 15	131	92 ± 32	-0 ± 19
24	108	91 ± 27	-2 ± 25	120	92 ± 23	-0 ± 18	115	93 ± 23	2 ± 17
36	93	93 ± 26	-0 ± 26	109	95 ± 27	3 ± 17	101	96 ± 26	4 ± 19
48	79	91 ± 31	0 ± 34	101	97 ± 27	5 ± 18	99	93 ± 24	0 ± 18
60	67	90 ± 27	-1 ± 30	84	93 ± 23	2 ± 16	87	97 ± 28	5 ± 23
72	52	88 ± 22	-3 ± 33	70	94 ± 24	4 ± 18	72	93 ± 19	2 ± 17
84	39	97 ± 3	6 ± 44	44	96 ± 30	4 ± 20	42	92 ± 19	4 ± 14
96	19	88 ± 23	3 ± 24	31	97 ± 32	2 ± 19	24	92 ± 19	1 ± 16
Last	153	99 ± 39	6 ± 36	151	94 ± 26	3 ± 19	149	95 ± 34	3 ± 23

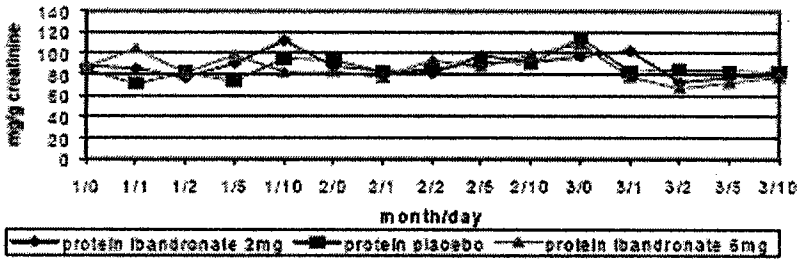
When evaluated by shift tables, 7 (4%) subjects in the placebo group, 9 (6%) subjects in the 2mg i.v. bolus group and 6 (4%) of subjects in the 6mg i.v. infusion group had serum creatinine values that shifted from normal (baseline) to high (last available assessment).

In the subgroup further evaluated with urinary markers, 74 (23 in the placebo group, 23 in the 2mg ibandronate group and 28 in the 6mg ibandronate group) subjects had levels of total protein, albumin, α1- microglobulin, and β-acetyl-β-D-glucosaminidase (β-NAG) measured before treatment and on Days 1, 2, 5, and 10 after treatment for three successive 4-week dose intervals.

Results for urinary total protein did not show a consistent pattern. As outlined in the Figure below, the placebo group showed an increase in proteinuria in Month 1 and a decrease during Months 2 and 3. It is concerning that the 2mg i.v. bolus group, where there was a marked increase in proteinuria between Day 0 and Day 10 during Month 1, a smaller increase during

Month 2, and a decrease in proteinuria in Month 3. The 6 mg i.v. infusion group showed a slight decrease in proteinuria in Month 1, an increase in Month 2 and a decrease in Month 3. The patterns for albumin and α-microglobulin were also inconsistent. There were no significant changes in β-NAG values over time for any treatment group.

Study MF4265: Mean Total Protein over Time



Study MF7141 was a randomized double-blind, placebo controlled, cross-over study evaluating the renal effects of 2mg ibandronate delivered as an i.v. bolus over 30 seconds in 16 healthy male volunteers with a mean age of 31 years. Subjects received 2 treatments: A) 2mg ibandronate i.v. over 30 seconds, given 15 minutes after a 5 minute inulin infusion; and B) placebo i.v. over 30 seconds, given 15 minutes after a 5 minute inulin infusion. Laboratory parameters including urinary albumin, α1- microglobulin, β2- microglobulin, and β-acetyl-β-D-glucosaminidase (β-NAG) were measured before injection and at urine collected at 2 – 4 hours and 12 – 24 hours post injection. The mean baseline serum creatinine was 74 ± 8 μmol/L (0.84 mg/dL) and 75 ± 8 μmol/L (0.85 mg/dL) 14 hours post dose. As outlined in the table below, in the short time period of observation, there was no definitive evidence of renal damage in young healthy men given 2mg ibandronate by 30 second i.v. bolus.

Study MF7141: Renal Safety Parameters

	Albumin	α1- microglobulin	β2- microglobulin	β-NAG
Placebo				
2-4hr postdose	0.865 ± 0.665	0.278 ± 0.279	0.026 ± 0.010	0.084 ± 0.029
12-24hr post dose	4.535 ± 3.890	1.409 ± 1.378	0.131 ± 0.042	0.381 ± 0.101
Ibandronate				
2-4hr postdose	0.757 ± 0.461	0.342 ± 0.307	0.027 ± 0.008	0.075 ± 0.020
12-24hr post dose	3.209 ± 2.118	1.821 ± 2.051	0.149 ± 0.046	0.397 ± 0.103

7.1.7.4.1 Creatinine Clearance: To further investigate the potential for changes in renal function, creatinine clearance values were calculated for each serum creatinine measurement using the Cockcroft-Gault equation. As outlined in the table below, the number of subjects with a decrease in creatinine clearance from normal (≥ 90 mL/min) to mild impairment (60 - < 90 mL/min) at any timepoint in the first year of treatment was small (13 (3%) in the 2.5mg oral daily group, 9 (2%) in the 2mg iv q2month group and 14 (3%) in the 3mg iv q3month group).

The number of subjects with a decrease in creatinine clearance from mild impairment (60 - < 90 mL/min) to moderate impairment (30 - < 60 mL/min) was slightly higher in the 3mg iv q3month group 62 (13%), compared to 50 (11%) in the 2.5mg daily oral group and 49 (11%) in the 2mg iv q2month group. The number of subjects with a decrease from moderate impairment to the severe impairment (< 30 mL/min) was again, quite small (1 (<1%) in the 2.5mg oral daily group, 3 (<1%) in the 2mg iv q2month group and 2 (<1%) in the 3mg iv q3month group).

BM16550: Creatinine Clearance: Shift Table			
	2.5 po qd	**2mg iv q2m**	**3mg iv q3m**
N, safety population	465	448	469
Creatinine Clearance, estimated			
≥ 90 mL/min to ≥ 90 mL/min	12	9	10
≥ 90 mL/min to 60 - < 90 mL/min	13	9	14
60 - < 90 mL/min to 60 - < 90 mL/min	140	145	145
60 - < 90 mL/min to 30 - < 60 mL/min	50	49	62
30 - < 60 mL/min to 30 - < 60 mL/min	224	209	206
30 - < 60 mL/min to < 30 mL/min	1	3	2

COMMENT: Overall, there is no clear evidence that i.v. ibandronate in the doses studied adversely effects renal function in the population of postmenopausal women included in the pivotal noninferiority study. However, during the two years of the study, fourteen subjects (3 in the 2.5mg daily oral group, 7 in the 2mg iv q2month group and 4 in the 3mg iv q3month group) with baseline creatinine less than 1.4mg/dL did have elevations in creatinine of more than 0.5mg/dL. Most significant creatinine increases were transient, although levels frequently did not return to baseline. There were insufficient subjects with baseline creatinine of greater than 1.4mg/dL to adequately assess the impact of ibandronate in this higher-risk population.

Animal studies with intravenous ibandronate clearly showed renal toxicity that was proportional to the dose and rate of administration. In the postmenopausal osteoporotic population, there are no trials comparing effects of i.v. bolus drug administration and i.v. infusion drug administration. In oncology study MF4328, which used i.v. bolus infusion for ibandronate doses up to 3mg, there were more subjects in the 3mg ibandronate group who had increases in urinary total protein, possibly an early sign of renal damage with bisphosphonates. In oncology study MF4265, no clear decrease in renal function was found. However, in the subset of subjects with specific renal evaluations, the increase in proteinuria following the 2mg i.v. bolus remains concerning. The dose of 3mg i.v. was not studied. Study MF7141 evaluated the renal safety of 2mg ibandronate by i.v. bolus over 30 seconds in young, healthy male patients. Though there was no definitive evidence of renal damage in the short 24 time period of the study, whether these results are applicable to the postmenopausal population is not clear. Again, 3mg ibandronate dosing was not evaluated.

Lessons learned from the intravenous zoledronate trials for the treatment of bone metastases support the findings in animals that rate of infusion affects renal toxicity. When i.v. zoledronate infusion times were lengthened from 5 minutes to 15 minutes, the absolute and relative risks of renal deterioration were lowered, though not completely

ameliorated. Of note, with the longer infusion time, the time-to-first episode of renal function deterioration also increased.

The knowledge of renal toxicity seen with i.v. bisphosphonate administration and the benefit of longer infusion times for preserving renal function, coupled with lack of adequate data comparing rates of ibandronate administration in the postmenopsaul population at greater risk of renal toxicity (i.e. baseline creatinine > 1.4mg/dL) leads this reviewer to recommend a long infusion time than i.v. bolus administration. The smallest time of ibandronate infusion in other protocols was 15 minutes. Therefore, 15 minute i.v. infusion, rather than i.v. bolus would be acceptable.

7.1.7.4.3 Serum Calcium: In study BM16550, serum calcium levels were measured at baseline and Months 4, 8, 12, 16, 20 and 24 for subjects on a q2month injection schedule; and Months 3, 6, 9, 12, 15, 18, 21 and 24 for subjects on a q3month injection schedule. There was no evidence of hypocalcemia in study BM16550. However, the calcium nadir following i.v. bisphosphonate therapy occurs between 1 and 2 weeks post dose. Therefore, the timing of the safety laboratories in this trial do not allow for assessment of the perturbations in calcium homeostasis that may occur following ibandronate dosing.

Study MF 4328 was an open-label, non-controlled multicenter study to evaluate the safety and efficacy of single i.v. ibandronate in doses of 0.5, 1, 2, and 3mg as well as infusions of 4 and 6mg. This study was conducted in 148 normocalcemic subjects with breast cancer and osteolytic bone metastases. Serum calcium levels were drawn on Days 2, 4, 7, 14, 21, and 28. As noted in the table below, calcium nadir occurred at approximately Day 7. With the exception of the 3mg i.v. ibandronate group, there was a dose related decrease in serum calcium levels. The main difference between the 3mg dose group and all other dose groups was patient age – 67 years for the 3mg group compared to 50 – 59 years for all other dose groups. Calcium levels fell below 8.5mg/dl in 65 (44%) of subjects; below 8.0mg/dL in 24 subjects (1 (4%) in the 1mg dose group, 5 (10%) in the 2mg dose group, 10 (67%) in the 3mg dose group and 8 (32%) in the 6mg dose group) and below 7.5mg/dL in 8 subjects (3 (6%) in the 2mg dose group, 4 (27%) in the 3mg dose group and 1 (4%) in the 6mg dose group).

Study MF4328: Serum calcium, corrected for albumin							
		0.5 mg iv bolus	1.0 mg iv bolus	2.0 mg iv bolus	3.0 mg iv bolus	4.0 mg iv infusion	6.0 mg iv infusion
N		14	23	54	15	16	25
age		58.9 ± 12.6	58.6 ± 10.6	55.8 ± 11.3	67.0 ± 11.9	49.5 ± 10.6	51.2 ± 11.5
		Calcium (mg/dL)					
Baseline	mean ± SD	9.2 ± 0.4	9.4 ± 0.5	9.5 ± 0.5	9.1 ± 0.6	9.8 ± 0.5	9.3 ± 0.6
Day 2	mean ± SD	9.1 ± 0.3	9.1 ± 0.5	9.0 ± 0.5	8.1 ± 0.5	9.2 ± 0.4	8.5 ± 0.4
Day 4	mean ± SD	9.0 ± 0.5	8.9 ± 0.6	8.8 ± 0.5	8.2 ± 0.4	9.0 ± 0.3	8.5 ± 0.6
Day 7	mean ± SD	9.1 ± 0.5	9.1 ± 0.4	9.0 ± 0.7	8.2 ± 0.4	9.4 ± 0.3	8.8 ± 0.6
Day 14	mean ± SD	9.3 ± 0.5	9.3 ± 0.6	9.2 ± 0.8	8.4 ± 0.5	9.4 ± 0.3	8.9 ± 0.5
Day 21	mean ± SD	9.5 ± 0.4	9.3 ± 0.5	9.3 ± 0.6	8.6 ± 0.5	9.6 ± 0.6	9.0 ± 0.5

Study MF4328: Serum calcium, corrected for albumin							
		0.5 mg iv bolus	1.0 mg iv bolus	2.0 mg iv bolus	3.0 mg iv bolus	4.0 mg iv infusion	6.0 mg iv infusion
Day 28	mean ± SD	9.4 ± 0.7	9.4 ± 0.5	9.4 ± 0.7	8.7 ± 0.4	9.5 ± 0.3	9.1 ± 0.6
Absolute Change (mg/dL)							
Day 2	mean ± SD	-0.1 ± 0.4	-0.3 ± 0.5	-0.4 ± 0.4	-1.0 ± 0.5	-0.6 ± 0.6	-0.8 ± 0.5
Day 4	mean ± SD	-0.1 ± 0.5	-0.5 ± 0.6	-0.6 ± 0.4	-0.9 ± 0.5	-0.6 ± 0.5	-0.8 ± 0.6
Day 7	mean ± SD	-0.1 ± 0.5	-0.4 ± 0.5	-0.4 ± 0.4	-0.9 ± 0.5	-0.3 ± 0.5	-0.5 ± 0.5
Day 14	mean ± SD	0.1 ± 0.5	-0.1 ± 0.5	-0.2 ± 0.6	-0.6 ± 0.5	-.03 ± 0.5	-0.4 ± 0.4
Day 21	mean ± SD	0.3 ± 0.4	-0.2 ± 0.5	-0.1 ± 0.5	-0.5 ± 0.5	-0.1 ± 0.4	-0.3 ± 0.4
Day 28	mean ± SD	0.3 ± 0.7	0.0 ± 0.5	-0.1 ± 0.5	-0.4 ± 0.6	-0.4 ±	-0.2 ± 0.4
Relative Change (%)							
Day 2	mean ± SD	-1.4 ± 4.7	-3.1 ± 5.3	-4.4 ± 4.0	-10.3 ± 5.0	-6.0 ± 5.4	-8.6 ± 4.6
Day 4	mean ± SD	-1.3 ± 5.1	-5.1 ± 6.6	-6.7 ± 4.6	-9.5 ± 4.8	-6.2 ± 4.5	-8.4 ± 6.2
Day 7	mean ± SD	-0.8 ± 5.5	-3.6 ± 4.8	-4.2 ± 4.6	-9.7 ± 4.6	-2.7 ± 5.3	-4.9 ± 5.1
Day 14	mean ± SD	1.6 ± 5.8	-1.4 ± 5.2	-2.6 ± 6.1	-6.9 ± 5.7	-2.6 ± 4.7	-3.9 ± 4.2
Day 21	mean ± SD	3.7 ± 4.3	-1.5 ± 5.3	-1.4 ± 4.8	-4.8 ± 5.9	-1.4 ± 4.4	-2.9 ± 4.6
Day 28	mean ± SD	3.5 ± 7.8	0.2 ± 5.4	-0.9 ± 5.5	-3.6 ± 6.2	-3.5 ± 3.7	-2.2 ± 4.4
Calcium < 8.5mg/dL		4 (29)	9 (39)	20 (37)	15 (100)	2 (12)	15 (60)
Calcium < 8.0 mg/dL		0 (0)	1 (4)	5 (10)	10 (67)	0 (0)	8 (32)
Calcium < 7.5 mg/dL		0 (0)	0 (0)	3 (6)	4 (27)	0 (0)	1 (4)
All calcium values converted from mmol/L to mg/dL							

COMMENT: The age of the 3mg dose group in study MF4328 corresponds to expected age of patients requiring treatment for postmenopsaul osteoporosis. However, the subjects enrolled in this study, while normocalcemic, do have breast cancer metastases to bone, which places them at a higher risk of hypocalcemia following bisphosphonate therapy. Therefore, while it is not possible to fully attribute the findings of this study to the postmenopausal osteoporotic patient population, it is of concern that the 3mg dose group exhibits a substantial rate of hypocalcemia. Regardless, the majority of subjects in all dose groups had normalized their serum calcium by Day 28 following ibandronate dosing.

7.1.7.4.3 Liver Function: In BM16550, a total of five subjects (four in the 2mg i.v. q2month group and one in the 3mg i.v. q3month group) had elevations in liver function tests reported as adverse events. Liver function was evaluated in all enrolled subjects by serum glutamic pyruvic transaminase (SGPT) levels, which were measured at baseline and Months 4, 8, 12, 16, 20 and 24 for subjects on a q2month injection schedule; and Months 3, 6, 9, 12, 15, 18, 21 and 24 for subjects on a q3month injection schedule. The SGPT values at scheduled visits for the subjects with adverse event reports are outlined in the table below. Two subjects had study drug dosing held due to the liver function abnormalities.

BM16550: Subjects with Reported AE of Increased Liver Enzymes					
Subject	224	915[$]	1068	1302	1004
Age	66	73	67	69	71
Dose	**2mg iv**	**2mg iv**	**2mg iv**	**2mg iv**	**3mg iv**
SGPT, (normal 0 – 30 U/L)					
Baseline	14	14	48	15	33
Month 3					63
Month 4	13	12	61	107	62
Month 6					47**
Month 8	129*	8	70	21	
Month 9					28
Month 12	10		60	33	31

[$] Enzyme elevations based on local laboratory results
* Study drug dose not given at Month 10
** Study drug dose not given at Months 6 and 9

As outlined in the table below, the mean change in serum SGPT at Month 12 was small for all treatment groups (-0.2 – 1.0 IU/L) with a statistically significant difference between the 3.0mg i.v. q3month group compared to the daily oral placebo group (p=0.03). A total of 141 subjects shifted from a normal SGPT at baseline to a high SGPT at some point during the first year of the study (44 (9%) in the 2.5mg oral daily group, 38 (8%) in the 2mg iv q2month group and 59 (13%) in the 3mg iv q3month group). Approximately 9% of the enrolled population had a baseline SGPT above the upper limit of normal. On subsequent laboratory evaluations, a total of 223 subjects had SGPT above the upper limit of normal (79 (17%) in the 2.5mg oral daily group, 61 (14%) in the 2mg iv q2month group and 83 (18%) in the 3mg iv q3month group), while 25 subjects had SGPT elevations greater than 60 IU/L or 2 times the upper limit of normal (8 (2%) in the 2.5mg oral daily group, 8 (2%) in the 2mg iv q2month group and 9 (2%) in the 3mg iv q3month group). One subject had a baseline SGPT greater than 90 IU/L (3 times the ULN) at baseline and six subjects developed elevations in SGPT greater than 90 IU/L (2 in the 2.5mg oral daily group, 3 in the 2mg iv q2month group and 1 in the 3mg iv q3month group), with the highest level of 180 IU/L occurring in a subject receiving 2.5mg daily oral ibandronate.

BM16550: Hepatic Function			
	2.5 po qd	**2mg iv q2m**	**3mg iv q3m**
	M12	**M12**	**M12**
	465	448	469
SGPT (0 – 30 U/L)			
N	409	382	395
Baseline SGPT (U/L)	20	20	19
M12 SGPT (U/L)	20	20	19
Mean change (U/L)	-0.2	0.4	1.0*
Shift normal to high (n (%))	44 (9)	38 (8)	59 (13)
baseline SGPT > ULN (≥30 IU/L) (n (%))	45 (10)	43 (10)	35 (7)
f//u SGPT > ULN (≥30 IU/L) (n (%))	79 (17)	61 (14)	83 (18)
SGPT > 2x ULN (≥60 IU/L) (n (%))	8 (2)	8 (2)	9 (2)
SGPT > 3x ULN (≥90 IU/L) (n (%))	3 (1)	3 (1)	1 (<1)
* p = 0.028 compared to the 2.5mg daily group			

The SGPT values for subjects with any SGPT value exceeding three times the upper limit of normal are shown in the table below. In most cases, the significant SGPT elevations were transient. Only one subject had study drug held due to the SGPT elevation.

BM16550: Subjects with Reported AE of Increased Liver Enzymes

Subject	391	708	712	224	537	1302	842
Age							
Dose	**2.5mg po**	**2.5mg po**	**2.5mg po**	**2mg iv**	**2mg iv**	**2mg iv**	**3mg iv**
SGPT, (normal 0 – 30 U/L)							
Baseline	32	126 / 49*	44	14	49	15	31
Month 3	87		130				31
Month 4		51		13	66	107	
Month 6	118		29				123
Month 8		42		129*	67 / 89*	21	
Month 9	21		180				49
Month 12	18	42	36	10	108	33	49

* Repeated measurement approximately one week later
** Study drug dose not given at Month 10

COMMENT: Ibandronate is not metabolized by the liver. Increases in SGPT were predominantly isolated, with levels of 1 - 2 times the upper limit of the normal range. This level of SGPT is not clinically significant. Few subjects experienced increases greater than 3 times the upper limit of normal and most had subsequent values that had normalized.

7.1.7.5 Special assessments

No further special laboratory assessments were performed.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program: The pivotal study BM16550 required measurement of only weight and height at screening and Month 12. Other vital sign assessments may have been done, but were not required or routinely recorded.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons: Study BM16550 was the focus of the vital sign analysis. However, weight and height were the only vital signs recorded.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies: As outlined in the table below, there was little change in height or weight in any treatment group at the end of the first year of the study.

BM16550: Vital Signs: Change from Baseline (Safety)			
	2.5 po qd	**2mg iv q2mo**	**3mg iv q3mo**
N	458	442	458
Baseline Height (cm)	149 ± 29	151 ± 26.2	148 ± 29.8
Month 12 Height (cm)	150 ± 26	151 ± 25.1	149 ± 29.2
Absolute Change (cm)	0.06 ± 0.90	-0.04 ± 1.41	-0.02 ± 0.60
% Change from Baseline	0.03 ± 0.61	-0.03 ± 0.93	-0.02 ± 0.45
Baseline Weight (kg)	71 ± 26.5	70 ± 28.4	72 ± 27.3
Month 12 Weight (kg)	71 ± 26.3	70 ± 23.8	72 ± 27.2
Absolute Change (kg)	-0.19 ± 3.50	-0.21 ± 2.98	-0.29 ± 3.38
% Change from Baseline	-0.37 ± 4.70	-0.48 ± 4.26	-0.43 ± 4.00

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal: A total of 30 subjects (14 in the 2.5mg po qd group, 10 in the 2mg iv q2month group and 6 in the 3mg iv q3month group) had a decrease in weight of ≥ 10% during the first year of the study, while a total of 20 subjects (5 in the 2.5mg po qd group, 6 in the 2mg iv q2month group and 9 in the 3mg iv q3month group) had a ≥ 10% increase in weight. Two subjects, both in the 2mg i.v. q2month group, lost 7cm of height from baseline to Month 12. Two additional subjects, in the 2mg i.v. q2month group, lost 5cm of height from baseline to Month 12. None of the four subjects sustained a fracture during the first year of the study, although radiologic evaluation to detect morphometric vertebral fractures was not performed.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities: Twelve subjects were reported to have adverse events related to changes in vital signs. Four subjects, none with a history of high blood pressure, had increased blood pressure (one in the 2.5mg po qd group, two in the 2mg iv q2month group and one in the 3mg iv q3month group). One subject in the 2.5mg daily oral group reported feeling an increased heart rate around 5pm on Study days 54 and 89. Symptoms lasted 2 – 3 days and resolved spontaneously. Two subjects (one in the 2.5mg po qd group reported and one in the 3mg iv q3month group) had increased body temperature. Both qualified as symptoms of an APR and resolved within 3 days. A total of 11 subjects reported changes in weight as adverse events. Seven subjects (two in the 2.5mg po qd group, two in the 2mg iv q2month group and three in the 3mg iv q3month group) reported weight gain and four (one in the 2.5mg po qd group, two in the 2mg iv q2month group and one in the 3mg iv q3month group) reported weight loss.

7.1.8.4 Additional analyses and explorations: No additional analyses were performed.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons: An ECG substudy was performed as part of studies BM16550 and JM16651. In study BM16550, the effect of iv ibandronate on the QT and corrected QT intervals compared with baseline values was evaluated. ECG recordings were made at baseline and at six months. The ECG safety population included 157 subjects who received ibandronate 3mg iv q3month and 87 subjects who received ibandronate 2.5mg po daily. ECG recordings were sent to a central laboratory for measurement of cardiac intervals and assessment of morphological changes. A cardiologist blinded to study treatment reviewed and interpreted the results.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency: In study BM16550, ECG recordings were obtained, in duplicate, pre-dose and 5 minutes and 2 hours after the iv drug dose at the initial visit and again at Month 6. The mean ECG intervals at baseline, post dose number 1, trough dose number 3 and post dose number 3 are outlined in the table below. A small increase in heart rate was noted post 1st dose in the 2.5mg daily oral ibandronate group. There were no significant changes in heart rate, PR interval or QRS interval. Both Bazett's (QT_cB) and Fridericia's (QT_cF) formulae were used to correct the QT interval for heart rate. The mean QT_cB intervals at baseline were 410 ms and 414 ms in the 2.5mg oral daily and 3mg iv q3month ibandronate groups, respectively. After the first ibandronate dose, the mean change in QT_cB from baseline was 2.7 ms in the 2.5mg oral daily group and -0.7 ms in the 3mg iv q3month ibandronate group. At Month 6 pre-dose (presumed trough), the mean change in QT_cB from baseline was -3.2 ms in the 2.5mg oral daily group and -4.2 ms in the 3mg iv q3month ibandronate group. Post-dose mean changes from baseline were -1.9 ms in the 2.5mg oral daily group and -2.7 ms in the 3mg iv q3month ibandronate group.

BM16550 ECG Substudy: Results, Interval Parameters

	2.5 po qd				3mg iv q3m			
	87				157			
	Visit 1		Month 6		Visit 1		Month 6	
Endpoint	base	post	trough	post	base	post	trough	post
n	87	85	80	80	157	153	134	134
Heart Rate (bpm)								
mean	68	69	67	69	68	68	68	68
SD	10	10	9	8	10	10	11	11
change from baseline		1.7	-0.5	0.8		0.1	-0.1	0.4
PR Interval (ms)								
mean	159	160	156	155	165	167	162	162
SD	21	26	24	21	23	24	27	26
change from baseline		0.9	-2.0	-3.1		2.0	-4.1	-3.5

BM16550 ECG Substudy: Results, Interval Parameters								
	2.5 po qd				3mg iv q3m			
	87				157			
	Visit 1		Month 6		Visit 1		Month 6	
Endpoint	base	post	trough	post	base	post	trough	post
n	87	85	80	80	157	153	134	134
QRS Interval (ms)								
mean	85	86	85	85	87	86	86	86
SD	6	9	5	5	9	9	7	7
change from baseline		1.2	0.1	0.4		-0.1	-0.4	0.3
QT Interval (ms)								
mean	388	386	386	384	392	391	387	388
SD	25	25	24	25	29	28	28	30
change from baseline		-1.7	-2.2	-4.1		-0.4	-3.5	-3.1
QTcB Interval (ms)								
mean	410	412	407	408	414	412	409	410
SD	19	18	18	19	21	22	20	20
change from baseline		2.7	-3.2	-1.9		-0.7	-4.2	-2.7
QTcF Interval (ms)								
mean	402	404	399	400	406	405	401	402
SD	17	17	17	18	20	20	18	19
change from baseline		1.2	-2.8	-2.7		-0.7	-4.0	-3.0

In study JM16651, ECG recordings were obtained 30 and 60 minutes pre-dose and 5 and 120 minutes after the iv drug dose at the initial visit and again at Month 4. The mean ECG intervals at baseline, post dose #1, trough dose #3 and post dose #3 are outlined in the table below. At Month 4 pre-dose (presumed trough), the mean change in QT_cB from baseline was +5 msec in the placebo group, +2 msec in the 0.5mg i.v. q1month group, -6 msec in the 1.0mg q1month group and -7 ms in the 2mg iv q2month group. Post-dose mean changes from baseline were +4 msec in the placebo group, +5 msec in the 0.5mg i.v. q1month group, -5 msec in the 1.0mg q1month group and -5 msec in the 2mg iv q2month group.

JM16651: ECG Substudy: Results, Interval Parameters									
Param	**Dose**	**n**	**Visit 1**			**Month 4**			
			base	**post**	**chng**	**trough**	**chng**	**post**	**chng**
Heart Rate (bpm)	placebo	48	61 ± 8	60 ± 6		±		63 ± 8	
	0.5mg q1m	44	64 ± 9	63 ± 8		64 ± 8		63 ± 8	
	1.0mg q1m	52	62 ± 8	61 ± 8		61 ± 8		60 ± 8	
	2.0mg q2m	46	66 ± 9	66 ± 9		65 ± 10		62 ± 8	
PR (ms)	placebo	48	178 ± 19	178 ± 19		±		175 ± 23	
	0.5mg q1m	44	173 ± 21	176 ± 21		170 ± 21		172 ± 25	
	1.0mg q1m	52	172 ± 20	174 ± 22		171 ± 20		172 ± 21	
	2.0mg q2m	46	171 ± 16	170 ± 16		165 ± 15		168 ± 18	
QRS (ms)	placebo	48	86 ± 7	88 ± 6		±		85 ± 7	
	0.5mg q1m	44	85 ± 9	85 ± 7		85 ± 5		85 ± 5	
	1.0mg q1m	52	88 ± 8	89 ± 9		87 ± 8		88 ± 9	
	2.0mg q2m	46	90 ± 8	90 ± 8		87 ± 9		88 ± 8	

JM16651: ECG Substudy: Results, Interval Parameters									
Param	**Dose**	**n**	**Visit 1**			**Month 4**			
			base	**post**	**chng**	**trough**	**chng**	**post**	**chng**
QT (ms)	placebo	48	405 ± 28	407 ± 26		396 ± 27		401 ± 28	
	0.5mg q1m	44	397 ± 22	401 ± 21		394 ± 24		398 ± 25	
	1.0mg q1m	52	405 ± 27	409 ± 26		402 ± 24		407 ± 24	
	2.0mg q2m	46	394 ± 25	401 ± 23		393 ± 27		403 ± 24	
QTcB (ms)	placebo	48	406 ± 21	406 ± 18	4 ± 13	408 ± 15	5 ± 16	408 ± 19	4 ± 18
	0.5mg q1m	44	408 ± 19	410 ± 19	8 ± 12	403 ± 19	2 ± 18	406 ± 21	5 ± 18
	1.0mg q1m	52	409 ± 20	412 ± 18	1 ± 13	404 ± 23	-6 ± 15	406 ± 22	-5 ± 17
	2.0mg q2m	46	412 ± 18	416 ± 19	3 ± 13	406 ± 20	-7 ± 13	408 ± 20	-5 ± 17
QTcF (ms)	placebo	48	406 ± 20	406 ± 19	3 ± 12	404 ± 15	-0.4 ± 15	405 ± 18	0 ± 16
	0.5mg q1m	44	404 ± 15	407 ± 15	6 ± 11	400 ± 17	0.3 ± 15	403 ± 19	3 ± 15
	1.0mg q1m	52	407 ± 19	411 ± 17	1 ± 12	403 ± 20	-7 ± 15	406 ± 19	-4 ± 16
	2.0mg q2m	46	406 ± 16	411 ± 16	3 ± 10	401 ± 18	-7 ± 12	406 ± 18	-2 ± 15

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal: In study BM16550, as outlined in the table below, there were few outliers for the parameters of heart, PR interval or QRS interval. The QT_cB interval was increased 30 – 60 msec for 6% and 4% of subjects after the initial dose of 2.5mg daily oral ibandronate and 3mg iv q3month ibandronate, respectively. At the Month 6 pre-dose trough, 8% of the 2.5mg oral daily group and 4% of the 3mg iv q3month ibandronate group had an increase in the QT_cB interval of 30 – 60 msec. Post-dose at Month 6, 9% of the 2.5mg oral daily group and 8% of the 3mg iv q3month ibandronate group had an increase in QT_cB interval of 30 – 60 msec. Only one subject in the 3mg iv q3month ibandronate group had an increase in QT_cB interval of greater than 60 msec after the Month 3 dose. No subject developed QT_cB interval durations of greater than 500 msec.

BM16550 ECG Substudy: Outliers								
Endpoint	2.5 po qd				3mg iv q3m			
	87				157			
	Visit 1		Month 6		Visit 1		Month 6	
	base	post	trough	post	base	post	trough	post
n	87	85	80	80	157	153	134	134
Heart Rate (bpm)								
<50 + >25% decrease		0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)
>100 + >25% increase		1 (1)	0 (0)	0 (0)		0 (0)	0 (0)	1 (1)
PR Interval (ms)								
>200 + >25% increase		1 (1)	1 (1)	0 (0)		0 (0)	1 (1)	1 (1)
QRS Interval (ms)								
>100 + >25% increase		0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	1 (1)
QT Interval (ms)								
>500 with base <500		0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)
QTcB Interval (ms)								
Increase 30 – 60 ms		5 (6)	6 (8)	7 (9)		6 (4)	5 (4)	10 (8)
Increase > 60 ms		0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	1 (1)
> 500 ms		0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)

BM16550 ECG Substudy: Outliers								
Endpoint	2.5 po qd				3mg iv q3m			
	87				157			
	Visit 1		Month 6		Visit 1		Month 6	
	base	post	trough	post	base	post	trough	post
n	87	85	80	80	157	153	134	134
OTcF Interval (ms)								
Increase 30 – 60 ms		1 (1)	1 (1)	4 (5)		2 (1)	3 (2)	6 (5)
Increase > 60 ms		0 (0)	1 (1)	0 (0)		0 (0)	0 (0)	0 (0)
> 500 ms		0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)

In study JM16651, no subjects had increases in QTcB greater than 60 msec at any time during the study. At Visit 1, the QT_cB interval was increased 30 – 60 msec in five subjects (one in the placebo group, three in the 0.5mg i.v. q1month group and one in the 2mg i.v. q2month group) post dose. At Month 4, four subjects (two in the placebo group and 2 in the 0.5mg i.v. q1month group) had QT_cB interval increased 30 – 60 msec from baseline pre-dose (trough) while 10 subjects (four in the placebo group, four in the 0.5mg i.v. q1month group, one in the 1.0mg i.v. q1month group and one in the 2.0mg i.v. q2month group) had increased QT_cB intervals 30 – 60 msec above baseline post-dose. No subject had a QT interval greater than 500 msec recorded during the study.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities: The table below outlines important changes in ECG morphology from study BM16550. Nonspecific T-wave changes were the most common new abnormality seen, occurring in 5 – 6% of subjects post dose #1, 1 – 3% of subjects at the Month 6 trough, and 5 – 7% of subjects post-dose #3. One subject in the 3mg iv q3month group developed atrial fibrillation first noted pre-dose at Month 6 and a second patient, also receiving 3mg iv ibandronate q3month was noted to have ECG evidence of a myocardial infarction pre-dose at Month 6.

BM16550 ECG Substudy: Changes from Baseline in ECG Parameters						
Endpoint	2.5 po qd			3mg iv q3m		
	87			157		
	Visit 1	Month 6		Visit 1	Month 6	
	post	trough	post	post	trough	post
n	85	80	80	153	134	134
Abnormal U-wave	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Negative, biphasic or flat T-wave	5 (6)	1 (1)	4 (5)	8 (5)	4 (3)	9 (7)
ST depression	2 (2)	1 (1)	1 (1)	5 (3)	3 (2)	3 (2)
Atrial fibrillation	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)
L Anterior Hemiblock	3 (4)	1 (1)	4 (5)	0 (0)	5 (4)	5 (4)
R Bundle Branch block	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
L Bundle Branch block	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Myocardial Infarction	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)

COMMENT: Despite the ability to transiently lower serum calcium levels, there has been no indication to date that bisphosphonates, as a class, cause prolongation of the QT

interval. The ECG substudies from BM16550 and JM16651 did not show any apparent effect of intravenous ibandronate on QT prolongation for the 2 mg and 3 mg doses. However, the results should be cautiously interpreted since these studies did not follow the rigorous protocol necessary for a thorough QT study.

7.1.9.4 Additional analyses and explorations

No additional analyses or explorations were performed.

7.1.10 Immunogenicity

No immunogenicity data have been submitted. Ibandronate is a non-peptide xenobiotic that would not be expected to elicit an immune response when given to humans.

7.1.11 Human Carcinogenicity

Given that ibandronate has been marketed in the U.S. for only a short time and is being sold in a small number of foreign countries, there is no basis upon which to examine the human carcinogenic potential of this drug. Data from preclinical studies do not suggest that ibandronate is genotoxic or oncogenic. In fact some animal data suggest that bisphosphonates may have anti-angiogenic properties, which could reduce the metastatic potential of some primary tumors.

7.1.12 Special Safety Studies

7.1.12.1 Bone Histomorphometry: Bone safety was evaluated by quantitative histomorphometry evaluation at Month 22 (for q 3 month dosing groups) or Month 23 (for q 2 month dosing groups). A total of 254 subjects consented to bone biopsy at study initiation. However, only 109 subjects actually underwent transiliac biopsy at Month 22 or Month 23. Of those 109 samples, 89 were evaluable (32 in the pooled 2.5mg po daily group, 27 in the 2mg i.v. q2m group and 30 in the 3mg i.v. q3 month group). The labeling schedule for the bone biopsies consisted of 3 days of tetracycline, followed by 14 days off tetracycline, followed by 3 additional days of tetracycline and then a 5 - 14 day interval before the transiliac biopsy was performed. All subjects who were randomized, received at least one dose of the trial medication (whether withdrawn prematurely or not), and had a bone biopsy taken as scheduled were included in the analysis population. One subject in the 2mg i.v. q2month ibandronate group missed one dose of study drug and one subject in the 3mg i.v. q3month ibandronate group received daily oral ibandronate rather than the i.v. study drug dose for one three month period. This subject is summarized by the treatment received most frequently during the study (3mg i.v. q3month ibandronate). Histomorphometry results are outlined in the table below.

Osteoid thickness (OTh): Osteoid thickness can be used a marker of bone formation. The mean osteoid thickness at Month 22 or 23 was below the normal range for all three dose groups. This is an expected finding, given the anti-resorptive nature of bisphosphonate drugs. Increases in osteoid thickness would be expected in setting of a mineralization defect.

Osteoid volume/ Bone volume (OV/BV): Osteoid volume represents the percentage of bone volume that is non-mineralized osteoid. A clear increase in OV/BV would support the hypothesis of impaired mineralization. The mean OV/BV at Month 22 or 23 was well within the normal range for all three dose groups. There is no evidence of excessive reduction in bone turnover or lack of formation of new bone.

Osteoid surface / Bone surface (OS/BS): The osteoid surface/bone surface ratio reflects bone remodeling. Both iv ibandronate dosing groups exhibit mean OS/BS ratios below the normal range. this is an expected finding given the anti-resorptive nature of ibandronate. No subject had complete suppression of bone remodeling (OS/BS of 0). The lowest level of OS/BS was 0.39% in the 2.5mg daily group, 0.23% in the 2mg iv q2month group, and 0.64% in the 3mg iv q3month group.

Mineral apposition rate (MAR): The mineral apposition rate is an indicator of mineralized bone accrual at remodeling sites. A clear reduction in MAR during treatment in comparison with normal could indicate impairment of mineralization and the potential of a drug to induce osteomalacia. In this study, the mean MAR was slightly above the normal range for the 2.5mg po daily group and the 3mg iv q3month group, and in the normal range for the 2mg iv q2month group.

Mineralization Lag Time (MLT): Mineralization lag time represents the mean time interval between deposition of osteoid and its mineralization, and is the most sensitive index of abnormalities in mineralization. Frequently, it is the earliest change at the onset of osteomalacia. The mean MLT was in the normal range for all three treatment groups. However, outliers are also present. Overall, 4 (12%) of subjects in the 2.5mg daily group, 5 (18%) of subjects in the 2mg iv q2month group and 5 (17%) of subjects in the 3mg iv q3month group had MLTs greater than 80 days while 6 subjects (2 in the 2.5mg daily group, 1 in the 2mg iv q2month group and 3 in the 3mg iv q3month group) had MLTs greater than 100 days.

One subject, a 57-year-old woman with a baseline lumbar spine T-score of -2.45 receiving 2mg iv q2month ibandronate, had a MLT of 332 days. Her baseline CTx level was low at 0.13 g/cm^2 and her baseline vitamin D level was 22 ng/mL. She exhibited a 3.3% increase in LS BMD and a 3.8% decrease in total hip BMD by Month 12.

BM16550: Bone Histomorphometry

Parameter	Normal Range	2.5 po qd	2mg iv q2mo	3mg iv q3mo
N		32	27	30
Osteoid Thickness (μm)	5.5 – 12.0	5.23 ± 0.91	4.92 ± 0.88	5.61 ± 1.86
Osteoid Volume (%)	0.30 – 3.10	0.90 ± 0.98	0.62 ± 0.64	0.77 ± 0.90
Osteoid Surface (%)	7.0 – 25.0	8.05 ± 6.89	6.73 ± 6.51	5.96 ± 5.40
Mineral Apposition Rate (μm/d)	0.360 – 0.630	0.64 ± 0.16	0.60 ± 0.25	0.65 ± 0.28
Mineralizing Surface (%)	1.0 – 13.5	2.82 ± 3.28	1.19 ± 1.50	1.60 ± 1.90
Adjusted Apposition Rate (μm/d)	NA	0.21 ± 0.12	0.16 ± 0.12	0.19 ± 0.12
Mineralization Lag Time (days)	24 – 80	38 ± 28	58 ± 68	46 ± 38
Formation Period (years)	0.16 – 0.70	0.64 ± 0.49	1.00 ± 1.14	0.78 ± 0.68
Bone Volume (%)	14.0 – 30.0	20.2 ± 7.2	20.4 ± 6.7	18.8 ± 4.8
Trabecular Thickness (μm)	93 - 185	153 ± 42	160 ± 50	140 ± 27
Activation Frequency (per yr)	NA	0.21 ± 0.23	0.09 ± 0.10	0.12 ± 0.13

BM16550: Bone Histomorphometry				
Parameter	**Normal Range**	**2.5 po qd**	**2mg iv q2mo**	**3mg iv q3mo**
Cortical Thickness (μm)	NA	748 ± 316	872 ± 400	614 ± 250

COMMENT: Although mineralization lag time is increased in both ibandronate groups when compared to the daily oral ibandronate group, there is no overt evidence of impaired mineralization. Ibandronate treatment resulted in a modest reduction in the thickness and volume of osteoid compared to a normal reference population, which is consistent with a bisphosphonate effect. As well, the mineral apposition rate was normal compared to the normal reference data.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No abuse potential or withdrawal phenomena have been recognized for bisphosphonates.

7.1.14 Human Reproduction and Pregnancy Data

No human pregnancy data are available for ibandronate. This drug is indicated for treatment of postmenopausal osteoporosis. Concern regarding the use of bisphosphonates in women of childbearing age and the potential for fetal toxicity after remote exposure to the drug has led to class labeling precautions.

7.1.15 Assessment of Effect on Growth

Ibandronate has not been studied in children or adolescents and its effects on growing bone are unknown.

7.1.16 Overdose Experience

No subjects in study BM16550 received an overdose of intravenous ibandronate.

7.1.17 Postmarketing Experience

Ibandronate has been approved and is currently marketed in the U.S. for treatment of postmenopausal osteoporosis in a dose of 150mg once monthly. In addition, 2.5mg tablets once daily have been marketed outside the U.S. for treatment and prevention of postmenopausal osteoporosis. Ibandronate has also been approved and marketed outside the U.S. for i.v. use (1, 2, 4 or 6mg) and for oral use as 50mg tablets for treatment of malignancy associated bone diseases. Since its approval, an estimated 455,000 patients have been exposed to ibandronate. For the period ending December, 2003, a total of 39 adverse event reports were received (32 were reported in women and 7 in men). The age range of affected individuals was 33 to 89 years with a mean age of 60 years. The distribution of AEs per indication was as follows: PMO (29%), cancer (50%) and unknown (20%). The 39 case reports included 65 AEs of which 30 were considered serious. Five of the SAEs resulted in death and were assessed as due to the

underlying malignancy. The majority of AEs (73.8%) occurred with the i.v. formulation. The most frequently reported events for all indications were from the skin disorders (16%), body as a whole (13%), and musculoskeletal (7.6%). Gastrointestinal adverse event reports were rare. There were no reports of overdose, drug interaction, use in pregnancy or lactation, abuse, misuse, dependence and withdrawal.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Study BM16550 is a Phase III, randomized, double-blind, parallel group, multicenter, two-year study with a one-year interim analysis comparing the efficacy and safety of ibandronate 2mg i.v. q2month and 3mg i.v. q3month with 2.5mg daily oral ibandronate in women with postmenopsaul osteoporosis. This is the largest trial and provides most of the safety information reviewed, with a total of 1395 subjects enrolled and 1382 subjects evaluable in the safety population.

7.2.1.2 Demographics

Study BM16550: Baseline subject demographics are balanced across the treatment groups (see table below). The average age of enrollees is 66 years. The racial mix is predominantly Caucasian. The average time since menopause is approximately 18 years. Baseline bone density is well with the osteoporotic range and comparable in all groups. Approximately 33% of enrollees had a prevalent osteoporotic fracture at baseline. Approximately 15% of enrollees were vitamin D insufficient (< 15 ng/mL) at baseline, while 0.4% were frankly vitamin D deficient (< 9ng/mL) at baseline.

BM16550: Patient Demographics				
	2.5 qd*	**2mg q2mo**	**3mg 3qm**	**Total**
N	470	454	471	1395
Age (yrs.)	65.7 ± 6.1	66.6 ± 6.3	65.8 ± 6.3	66.0 ± 6.2
BMI	25.4 ± 4.3	25.8 ± 4.1	25.6 ± 4.3	25.6 ± 4.2
Race				
Caucasian	438 (94)	416 (93)	440 (94)	1294 (94)
Black	0 (0)	0 (0)	0 (0)	0 (0)
Oriental	0 (0)	3 (1)	1 (<1)	4 (<1)
Hispanic	26 (6)	26 (6)	25 (5)	77 (6)
Other	1 (<1)	3 (1)	3 (1)	7 (<1)
Time since menopause (yrs)	18.1 ± 8.0	19.3 ± 8.2	18.6 ± 8.1	18.7 ± 8.1
Baseline BMD, LS (gm/cm2)	0.747 ± 0.08	0.747 ± 0.07	0.745 ± 0.08	0.746 ± 0.07

BM16550: Patient Demographics				
	2.5 qd*	**2mg q2mo**	**3mg 3qm**	**Total**
Baseline BMD, LS (T-score)	-3.25	-3.27	-3.27	-3.26
Baseline Clinical OP Fracture	146 (31)	156 (35)	156 (33)	458 (33)
Baseline 25OH D (ng/mL)	24.5 ± 9.4	25.2 ± 12.2	24.3 ± 8.8	24.6 ± 10.3
Vit D range	8.9 – 57.6	7.9 – 193.2	6.8 – 60.2	6.8 – 193.2
< 9 ng/mL	1 (0.2)	2 (0.4)	3 (0.6)	6 (0.4)
< 15 ng/mL	66 (14)	72 (16)	67 (14)	205 (15)
Postmenopausal ERT	113 (24)	119 (27)	128 (27)	360 (26)
*pooled groups B and D				

7.2.1.3 Extent of exposure (dose/duration)

In study BM16550, the mean duration of treatment was 11.1 months for the 2.5mg oral daily group, 11.0 months for the 2mg iv q2mo group, and 10.9 months for the 3mg i.v. q3mo group (see table below).

BM16550: Dosing Schedule				
	plac po qd 2mg iv q2m	2.5 po qd plac iv q2m	plac po qd 3mg iv q3m	2.5 po qd plac iv q3m
N, safety population	448	226	469	239
Mean Treatment Duration (mo)	11.0 ± 2.6	11.1 ± 2.8	10.9 ± 2.8	11.1 ± 2.7
Total i.v. dose (mg)	11.0 ± 2.6	0.0 ± 0.0	10.9 ± 2.8	0.01 ± 0.194

The table below outlines the dose compliance rates at Month 12. In all treatment groups, the majority of subjects received ≥ 90% of their i.v. study medication. The incidence of subjects receiving < 80% of their i.v. study medication was 16% overall (54 (14) in the placebo po daily + 2mg i.v. q2month group, 26 (13) in the 2.5mg po daily + placebo i.v. q2month group, 72 (18) in the placebo po daily + 3mg i.v. q3month group and 33 (16) in the 2.5mg po daily + placebo i.v. q3month group). As well, the majority of subjects in each treatment group took ≥ 90% of their daily oral study medication. The incidence of < 80% compliance with the daily oral study medication was 16 (4) in the placebo po daily + 2mg i.v. q2month group, 10 (5) in the 2.5mg po daily + placebo i.v. q2month group, 13 (3) in the placebo po daily + 3mg i.v. q3month group and 5 (2) in the 2.5mg po daily + placebo i.v. q3month group.

BM16550: Exposure				
	plac po qd 2mg iv q2mo	2.5 po qd plac iv q2mo	plac po qd 3mg iv q3mo	2.5 po qd plac iv q3mo
N, safety population	448	226	469	239
Month 12, n	381	198	394	209
i.v. Dose, Number of Injections				
6	374 (84)	196 (87)	na	na
5	20 (4)	4 (2)	na	na
4	11 (2)	4 (2)	397 (85)	206 (86)
3	9 (2)	5 (2)	8 (2)	14 (6)
2	11 (2)	9 (4)	21 (4)	6 (2)
1	23 (5)	8 (4)	43 (9)	13 (5)

BM16550: Exposure				
	plac po qd 2mg iv q2mo	2.5 po qd plac iv q2mo	plac po qd 3mg iv q3mo	2.5 po qd plac iv q3mo
0	0 (0)	0 (0)	0 (0)	0 (0)
Oral Dose Compliance*				
100%	212 (56)	87 (44)	190 (48)	106 (51)
90 – 100%	138 (36)	81 (41)	170 (43)	85 (41)
80 – 90%	15 (4)	20 (10)	21 (5)	13 (6)
< 80%	16 (4)	10 (5)	13 (3)	5 (2)
* at Month 12				

One subject in the ibandronate 2.5mg daily oral group received 3mg ibandronate iv at study visit 2. She also received oral placebo tablets at that visit. Therefore, there was no over-exposure to ibandronate. At study Visit 3 onward, she received placebo iv and ibandronate 2.5mg daily.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Study JM16651 was a multi-center, randomized, placebo-controlled, blind, parallel inter-group comparative study conducted in Japan. The primary endpoint was change in lumbar spine BMD at Month 6. Treatment groups included placebo i.v., 0.5mg ibandronate i.v., 1.0mg ibandronate i.v. and 2.0mg ibandronate i.v. once monthly. Rate of administration was not specified. Review of this study focused on the ECG substudy.

Study MF4328 was an open-label, non-controlled multicenter study to evaluate the safety and efficacy of single i.v. injections of ibandronate in doses of 0.5, 1, 2, and 3mg as well as infusions of ibandronate in doses of 4 and 6mg conducted in 148 normocalcemic subjects with breast cancer and osteolytic bone metastases. Serum creatinine levels were drawn on Days 2, 4, 7, 14, 21, and 28. Urinary protein evaluations also occurred on Days 2, 4, 7, 14, 21, and 28. This study was reviewed for renal safety. In addition, this was the only study in which the timing of the laboratories allowed for adequate assessment of ibandronate induced calcium nadir.

Study MF4265 was a double-blind, placebo-controlled, randomized multicenter study to evaluate the efficacy and safety of long-term treatment with 2 mg (i.v. bolus) or 6 mg (i.v infusion) ibandronate administered intravenously at 4-week intervals for at least 60 weeks in patients with metastatic bone disease due to breast cancer. Subjects could be enrolled for a total of 96 weeks. This study was reviewed specifically for the renal safety parameters. Serum creatinine was measured at baseline and Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84 and 96. The protocol was amended to include an evaluation of renal function in a subset of subjects.

Study MF7141 was a randomized, double-blind, placebo controlled cross-over PK study evaluating the renal effects of 2mg ibandronate delivered as an i.v. bolus over 30 seconds in 16 healthy male volunteers with a mean age of 31 years. Subjects received 2 treatments: A) 2mg ibandronate i.v. over 30 seconds, given 15 minutes after a 5 minute inulin infusion; and B)

placebo i.v. over 30 seconds, given 15 minutes after a 5 minute inulin infusion. This study was reviewed specifically for the renal safety parameters. Laboratory parameters including urinary albumin, α1- microglobulin, β2- microglobulin, and β-acetyl-β-D-glucosaminidase (β-NAG) were measured at time intervals 2 – 4 hours and 12 – 24 hours post injection.

7.2.2.2 Postmarketing experience

The post-marketing adverse events reported for ibandronate are mainly from the intravenous formulation used in the treatment of hypercalcemia of malignancy outside of the US. Approximately 48,000 patients received ibandronate treatment during the reporting period and a total of 26 medically confirmed adverse event reports, including 19 serious adverse events, were received. Of the events reported, the majority were GI events with the majority being nausea and vomiting. One case of osteonecrosis of the jaw and one case of osteomyelitis of the jaw was reported.

7.2.2.3 Literature

7.2.3 Adequacy of Overall Clinical Experience

The ibandronate clinical development program is adequate with respect to the number of subjects studied and the duration of exposure and follows the recommendations outlined in the Agency's osteoporosis guidance. The studies were almost exclusively conducted in postmenopausal women, which is the population for the proposed indication.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The pharmacology/toxicology program is adequate and specific testing of ibandronate's effects on bone in multiple animal models, as outlined in the osteoporosis guidance, has been done.

7.2.5 Adequacy of Routine Clinical Testing

Adequate investigation of known potential effects of bisphosphonate therapy was performed, particularly effects on serum creatinine and BUN. However, the Cockcroft-Gault formula was used to estimate creatinine clearance. This formula has been shown to underestimate GFR in patients older than age 65 years. In study BM16550, there was no assessment of urinary protein or other markers of renal toxicity. The timing of serum calcium measurements in study BM16550 did not allow for assessment of the calcium nadir.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Adequate in-vitro testing has been performed, as discussed in previous ibandronate NDA submissions.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Adequate investigation of known side effects of bisphosphonate therapy was performed.

7.2.8 Assessment of Quality and Completeness of Data

The data submitted and reviewed for safety were complete and of good quality.

7.2.9 Additional Submissions, Including Safety Update

A four-month safety update report was submitted in April, 2005, and covers events through January, 2005. Studies include the ongoing study BM16550 and two other newly initiated studies: study ML17904, an open-label long term extension of study BM16550, which will follows subject for up to five years of treatment, and study ML18058, an open-label study evaluating the adherence to 150mg monthly oral ibandronate and i.v. ibandronate 3mg every 3 months in postmenopausal osteoporotic women who are GI intolerant of daily and/or weekly alendronate or risedronate.

A major amendment, containing the requested Year 2 bone histomorphometry data was submitted in October, 2005. Review of that data can be found in Special studies (7.1.12)

Study BM16550: In study BM16550, 58% of subjects who completed the first year and continued into the second year of treatment completed Month 24 before the January, 2005 cut-off.

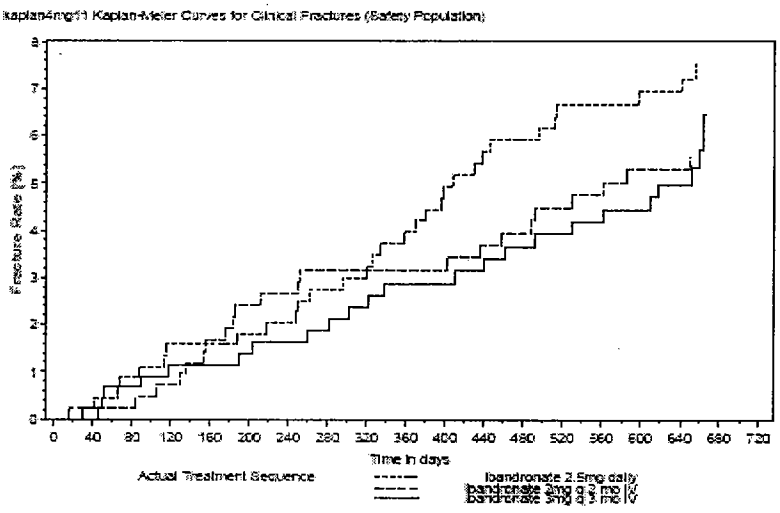
Four additional deaths of study subjects occurred during the reporting period. A 76-year-old woman receiving 2mg i.v. q2month ibandronate was diagnosed with colon cancer and underwent hemicolectomy on study Day 489. She was admitted with a GI hemorrhage on study Day 686 and died 2 days later. An autopsy revealed the cause of death to be pulmonary embolism. A 69-year-old woman, receiving 2.5mg oral daily ibandronate was admitted to hospital with acute biliary colic on study Day 476. She was found to have gall bladder cancer that had metastasized to the supraclavicular lymph nodes. She died on study Day 542. A 72-year-old woman with a history of coronary artery disease was randomized to receive ibandronate 2mg i.v. q2months. She had an episode of chest pain ten days after her 8th injection, an episode of syncope ten days prior to her 9th injection and a respiratory infection between the 11th and 12th injections. She died suddenly on study Day 675, five days after receiving her 12th ibandronate dose. The cause of death was reported as myocardial infarction. A 74-year-old woman with a history of hypertension and atrial fibrillation who was anticoagulated and maintained on digoxin, sotalol, and metoprolol was receiving 2.5mg oral daily ibandronate. She died suddenly on study Day 483 and the cause of death was reported to be a ventricular arrhythmia.

Serious adverse events were reported in 90 (6.5%) of subjects. Because of the continuation into Year 2 of the study, treatment group assignment remains blinded. The most frequently reported

adverse event categories were neoplasms (1%), nervous system, (1%) and cardiac disorders (1%). The frequency of reports of serious neoplasms was slightly higher in the second year (1%) than in the first year of the study (0.5%). Malignant neoplasms reported include four new cases of breast cancer, and one case each of colon, metastatic colon, gallbladder, bladder, and basal cell cancer, as well as one case of non-Hodgkin's lymphoma. The frequency of reports of serious nervous system disorders was also slightly higher in the second year (0.9%) than in the first year of the study (0.7%). Transient ischemic attacks were reported in three subjects and epilepsy was reported in two subjects, both of whom had a history of seizures. There were six reports of myocardial infarction.

An additional 56 (4%) subjects were withdrawn from the study, 31 (27 for adverse events and 4 deaths) for safety reasons and 25 (2%) for other reasons. Overall, 765 (55%) of patients experienced at least one adverse event during the safety update reporting period. The most commonly affected body categories were infections, musculoskeletal, and gastrointestinal disorders. The most frequently reported events were nasopharyngitis, hypertension, back pain, and arthralgia. There were no additional reports of APRs. However, two subjects did report influenza-like illness.

Fractures: A total of 79 subjects (31 (7%) in the 2.5mg po daily group, 23 (5%) in the 2mg iv q2 month group, and 25 (5%) in the 3mg iv q3 month group) sustained a clinical fractures since the start of treatment. The proportion of subjects in each treatment group experiencing a fracture is displayed in the Kaplan-Meier curve below.



Renal safety: Renal safety data for the period ending January, 2005, was reported using defined change criteria based on baseline serum creatinine: an increase of $\geq$ 0.5 mg/dL in subjects with a baseline serum creatinine of $<$ 1.4 mg/dL; or an increase of $\geq$ 1.0 mg/dL in subjects with a baseline serum creatinine of $\geq$ 1.4 mg/dL; or a 2 fold increase in baseline serum creatinine. Six

additional subjects (3 in the 2.5mg po daily group, 2 in the 2mg iv q2 month group, and 1 in the 3mg iv q3 month group) met the criteria of renal deterioration. When evaluated as calculated creatinine clearance, 42 (63%) subjects (14 (56%) in the 2.5mg po daily group, 12 (67%) in the 2mg iv q2 month group, and 16 (67%) in the 3mg iv q3 month group) shifted from normal to mild or moderate impairment; 203 (34%) subjects (64 (34%) in the 2.5mg po daily group, 65 (33%) in the 2mg iv q2 month group, and 74 (35%) in the 3mg iv q3 month group) shifted from mild impairment to moderate impairment; and 12 (2%) subjects (5 in the 2.5mg po daily group, 5 in the 2mg iv q2 month group, and 2 in the 3mg iv q3 month group) shifted from moderate impairment to severe impairment.

ML17904: As of the January, 2005, cut-off date, 410 subjects had been enrolled and randomized in this study. There were no deaths, serious adverse events or premature withdrawals in this extension study during the reporting period.

ML18058: As of the January, 2005, cut-off date, only eight subjects had been enrolled and randomized in this study. There were no deaths, adverse events, serious adverse events, or withdrawals in those enrolled subjects.

COMMENT: No new safety concerns were identified in the 4-month safety report. The renal safety data remain concerning.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Intermittent i.v. ibandronate tolerability was similar to daily oral ibandronate dosing. The nature and frequency of adverse events were similar for all treatment groups. Eight deaths have occurred thus far during the pivotal trial BM16550. The causes of death are consistent with this population's baseline age and related comorbid conditions and similar to causes of death in the general population of patients. The overall incidence of serious adverse events was similar between the treatment groups. Fracture was the most commonly reported serious adverse event. Serious events in the gastrointestinal and cardiac systems occurred in slightly more patients receiving ibandronate 2mg i.v. q2 months. The overall rates of study withdraw were slightly higher in the intravenous treatment groups (12% in the 2.5mg daily group, 15% in the 2mg i.v. q2month group, and 16% in the 3mg i.v. q3month group). Withdrawal due to adverse events occurred more frequently in the 3mg i.v. q3month group (10%, compared to 8% in the 2.5mg daily oral group and 7% in the 2mg i.v. q2month group). Gastrointestinal and musculoskeletal adverse events accounted for the majority of events leading to premature withdrawal from the study. These events were evenly distributed between the treatment groups. Adverse events that were consistently more frequently reported in the intravenous dose groups were influenza-like illness, fatigue and myalgia.

Symptoms consistent with APR have been reported with intravenous bisphosphonate use. Acute phase reaction-like symptoms were reported in all treatment groups. The overall incidence of subjects with APR-like events was higher in the intravenous treatment groups (4% in the 2.5mg

daily group, 14% in the 2mg i.v. q2month group, and 10% in the 3mg i.v. q3month group. A total of 18 subjects, 2 in the daily oral group and 16 in the intermittent i.v. groups, withdrew from the study due to APR-like symptoms. An additional four subjects, all in intermittent i.v. dose groups, had dose modifications made due to APR-like symptoms and 32 subjects (5 in the daily oral group and 27 in the intermittent i.v. groups) required concomitant medical therapies for symptom relief.

Clinical osteoporotic fractures were recorded as adverse events. The proportion of subjects sustaining a clinical osteoporotic fracture was similar among the treatment groups, occurring in 3% in the 2.5mg daily group, 2% in the 2mg i.v. q2month group, and 3% in the 3mg i.v. q3month group.

Some intravenous (and rarely, oral) bisphosphonates have been associated with osteonecrosis of the jaw. Between the ibandronate clinical development program and postmarketing adverse event reporting, there have been two reports of osteomyelitis/osteonecrosis of the jaw.

Bisphosphonate use, most notably intravenous bisphosphonates, has been associated with hypocalcemia. There were no adverse event reports attributable to hypocalcemia. There was no laboratory evidence of hypocalcemia in study BM16550. However, the timing of the mineral laboratories did not allow for assessment of the expected calcium nadir. In an open-label, non-controlled multicenter study in normocalcemic subjects with breast cancer and osteolytic bone metastases, there was a dose related decrease in serum calcium levels. In the 3mg i.v. ibandronate group, where the age of the subjects closely approximated the expected age of the postmenopausal population, calcium levels fell below 8.0mg/dL in 67% of subjects and below 7.5mg/dL in 27% of subjects.

Intravenous bisphosphonates have been associated with increased renal toxicity, that appears to be related to dose and rate of i.v. administration. In study BM16550, administration of intravenous study medications was by a 15 – 30 second i.v. bolus. Overall, the numbers of subjects with adverse events attributable to the renal tract were similar in all three dose groups. During the two years of the study, six subjects, all receiving i.v. ibandronate, were reported to have either renal insufficiency or renal impairment. Mean creatinine levels did increase minimally in all treatment groups. However, fourteen subjects (3 in the 2.5mg daily oral group, 7 in the 2mg iv q2month group and 4 in the 3mg iv q3month group) with baseline creatinine less than 1.4mg/dL did have elevations in creatinine of more than 0.5mg/dL. There were insufficient subjects with baseline creatinine of greater than 1.4mg/dL to adequately assess the impact of ibandronate in this higher-risk population. When looking at shift tables for creatinine clearance, a slightly higher percentage of subjects with mild renal impairment that received the 3mg dose shifted into moderate renal impairment (13% vs. 11% for the other 2 groups). Increases in urinary protein may represent the earliest signs of renal damage with bisphosphonate use. Urinary protein was not evaluated in study BM16550. Review of smaller Phase 2 and 3 studies in different treatment populations revealed a weak but concerning signal of increased proteinuria and other markers with bolus bisphosphonate doses of 2mg or higher. Doses 4mg and above were not given as i.v. bolus, but as i.v. infusion over 15minutes to 2 hours.

Lessons from the intravenous zoledronate trials for the treatment of bone metastases support the findings in animals that rate of infusion affects renal toxicity. When i.v. zoledronate infusion times were lengthened from 5 minutes to 15 minutes, the absolute and relative risks of renal deterioration were lowered, though not completely ameliorated. In the ibandronate clinical development program, there are no trials comparing effects of i.v. bolus drug administration and i.v. infusion drug administration.

Given the knowledge of renal toxicity seen with i.v. bisphosphonate administration and the benefit of lengthening infusion times for preserving renal function, coupled with lack of adequate data comparing rate of ibandronate administration in the postmenopsaul population at greater risk of renal toxicity (i.e. baseline creatinine > 1.4mg/dL), leads this reviewer to remain concerned with the safety of a 15 – 30 second i.v. bolus administration, especially in patients at high risk of renal insufficiency. A longer infusion time may be beneficial but further study would be required to assess this.

Year 2 bone biopsy data from study BM16550 revealed no safety signals with the 3mg i.v. q3month dose when compared to the 2.5mg daily oral dose.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Study BM16550 is the primary source of safety data predominantly because of the lack of comparable doses and schedules in the other intravenous ibandronate trials. No pooling of data has been performed. The sponsor did pool data from all of the ibandronate clinical trials for a discussion of renal safety. However, the analyses performed were based on the annualized dose of ibandronate and did not provide any additional information to differentiate the safety of the 2mg i.v q2month dose and the 3mg i.v. q3month dose, both of which have an annualized ibandronate dose of 12mg.

7.4.1.2 Combining data

Study BM16550 is the primary source of safety data predominantly because of the lack of comparable doses and schedules in the other intravenous ibandronate trials. Data have not been combined for this review.

7.4.2 Explorations for Predictive Factors

Adverse events relating to both intravenous and oral bisphosphonate use have been well described. Exploration of these events were performed and have been documented elsewhere in this review.