7.4.3 Causality Determination

The relationship of specific adverse events to intravenous bisphosphonate use have been described. No new relationships were revealed during this review.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The rationale for the suboptimal fracture efficacy noted with ibandronate 0.5mg iv q3 months and 1 mg iv q3 months (study MF4380) is thought to be an insufficient dose of ibandronate and/or an inappropriately long dosing interval. This interpretation is 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 in the relevant skeletal compartments, which may be achieved by more frequent injections, the administration of a higher dose, or both.

Study MF4470 was a randomized, double-blind, placebo-controlled, 2-year trial evaluating 1??mg ibandronate i.v. q3 month, 2mg ibandronate i.v. q3 month and placebo i.v. q3 month. The study was terminated by the company after the suboptimal results of MF4380 were known. The original primary efficacy variable was relative change in lumbar spine BMD at 2 years. However, the study was terminated after all subjects completed Year 1 and the analysis was changed to the Year 1 endpoint. The mean change in lumbar supine BMD at 1 year was 0.0% for placebo, 2.8% for 1mg ibandronate ($p<0.01$ compared with placebo) and 5.0% for 2mg ibandronate ($p<0.01$ compared with placebo). The lumbar spine BMD increase with 2mg ibandronate iv q3 months was superior to the increase seen with the 1mg q3 month regimen and numerically greater than those seen in study MF4411 for 2.5mg ibandronate daily. Based on these data, it appeared that the 2 mg iv q3 month regimen might be sufficient and comparable to the 2.5 mg daily oral regimen. 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 extrapolation of the dose-response curves, the company felt that another dose doubling would not be necessary, and that a moderate dose increase to 3mg iv q3 months should be at least comparable to 2.5mg daily oral. This would be true unless the top of the dose response curve is reached with the 2mg iv q3 month dose. If the top of the dose-response curve is reached with 2mg, a reduction of the dosing interval may be necessary. Therefore, Roche decided to study both the 3mg iv q3 month dose and a 2mg iv q2 month dose.

COMMENT: Of note, both of the doses chosen for evaluation in study BM16550 have an annualized dose of 12mg ibandronate. The 2mg i.v. q3month dose would have an annualized dose of 8mg. The approved 150mg monthly oral dose of ibandronate, which was superior to 2.5mg daily oral ibandronate, would have an annualized dose of 10.8mg, assuming a 0.6% bioavailability. The 100mg monthly oral dose of ibandronate, an annualized dose of 7.2 assuming a 0.6% bioavailability, was noninferior but not superior to the daily oral dose. Taking into account the fracture efficacy of the 2.5mg daily oral dose (annualized dose of 5.5mg, assuming a 0.6% bioavailability) and the suboptimal fracture

efficacy exhibited by the 0.5mg and 1mg ibandronate i.v. q3 month doses (annualized doses of 2mg and 4mg respectively), this reviewer finds the doses studied acceptable. The 2mg i.v. q3month dose may well be an acceptable dose, but would require a fracture study for certainty.

8.2 Drug-Drug Interactions

A specific study was performed evaluating the interaction of ibandronate and tamoxifen in healthy postmenopausal women. There was no evidence of a pharmacokinetic interaction between these two drugs. Nor was there evidence of new unexpected adverse event signals. A study investigating the interaction of i.v. ibandronate with melphalan/prednisone in patients with multiple myeloma was also conducted. A small reduction in ibandronate AUC was noted although the 90% CI of 93.7% remained within the acceptable range and no dosing adjustment is required. Ibandronate did not influence the pharmacokinetics of melphalan and prednisolone.

8.3 Special Populations

Ibandronate is intended for the treatment and prevention of postmenopausal 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.

8.4 Pediatrics

The proposed indication in this NDA is restricted to postmenopausal women. The efficacy and safety of ibandronate have not been evaluated in the pediatric population.

8.5 Advisory Committee Meeting

This New Drug Application was not presented before the Metabolic and Endocrine Advisory Committee.

8.6 Literature Review

A MEDLINE review was conducted for ibandronate. The majority of the articles were included in the sponsor's references. The information included in the articles found upon review of the literature does not add materially to the information provided in the NDA.

8.7 Postmarketing Risk Management Plan

The sponsor proposes a risk management plan that predominantly focuses on product labeling, regular review of cumulative data and periodic safety updates. Roche proposes 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.

8.8 Other Relevant Materials

None

9 OVERALL ASSESSMENT

9.1 Conclusions

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. 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 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 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.

Both intermittent i.v. ibandronate regimens have an annualized dose of 12mg ibandronate, which is higher than the approved 150mg monthly oral dose (10.8mg, assuming a 0.6% bioavailability) and more than twice the annualized dose of the approved 2.5mg daily oral dose (5.5mg, assuming a 0.6% bioavailability). These higher doses may amplify the documented safety profile of ibandronate. 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 occurring 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 is 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 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. Over the two year study period of 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. 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 an insufficient number of subjects with baseline creatinine of 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 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 with bisphosphonate use. 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 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 the rate of ibandronate administration in the postmenopausal 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 3month 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. Some patients may experience acute phase reaction symptoms that will limit use of the medication. This 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.

9.2 Recommendation on Regulatory Action

This reviewer recommends approval of ibandronate 3mg i.v. delivered as a 15 to 30 second i.v. bolus every 3 months for treatment of postmenopausal osteoporosis.

9.3 Recommendation on Postmarketing Actions

9.3.1 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.

9.3.2 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 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.

9.3.3 Other Phase 4 Requests

None

9.4 Labeling Review

see separate document

9.5 Comments to Applicant

[redacted]

The following comments were provided to the sponsor on 12/11/05:

1) Animal studies with intravenous ibandronate clearly show renal toxicity is proportional to the dose AND rate of administration.

2) While there is no clear evidence that i.v. ibandronate in the doses and administration regimen studied adversely effects renal function in the population of postmenopausal women included in the pivotal noninferiority study, it is concerning that no subjects in the daily oral group, 4 subjects in the 2mg iv q2month group and 2 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. In addition, 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). There w ere an insufficient number of subjects with baseline creatinine values of greater than 1.4mg/dL to adequately assess the impact of ibandronate in this potentially higher - risk population - many of whom will be found in the target population for ibandronate .

3) In the postmenopausal osteoporotic population, there are no trials comparing the effects of i.v. bolus drug administration and i.v. infusion drug administration for the proposed doses.

4) 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. It is not possible to completely attribute the results to the lab methods. Doses higher than 3mg were given as i.v. infusions.

5) 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 and the 6mg dose was given as an i.v. infusion over 60-120 minutes.

6) 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 hour time period of the study, whether these results can be ascribed to the postmenopausal population is not clear. Again, 3mg ibandronate dosing was not evaluated.

Therefore

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 different rates of ibandronate administration in the postmenopausal population, and the lack of data in postmenopausal women at greater risk of renal toxicity (i.e. baseline creatinine > 1.4mg/dL), suggest that an infusion time of at least 15 minutes, such as that used for zoledronic acid, would ensure greater safety than i.v. bolus administration.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Study BM16550: Randomized, double-blind, parallel groups, multi-center study to compare the efficacy and safety of two i.v. ibandronate dose regimens (2mg q2mo and 3mg q3mo) with 2.5 mg daily oral ibandronate in postmenopausal osteoporosis: Year 1 results

Objectives: The objectives of this study were:
The primary objective of this study were to:

1. To determine if the ibandronate dose regimens of either 2mg q2mo or 3mg q3mo, given as an i.v. injection over 15 to 30 seconds were not inferior to ibandronate 2.5 mg orally daily for BMD efficacy
2. To assess the overall tolerability and safety of the treatment regimens

Study Design: This was a randomized double-blind, parallel group, multi-center study. Eligible subjects were randomized into one of four treatment groups at a ratio of 2:1:2:1. To ensure blinding, two placebo formulations, a placebo tablet and a placebo injection, were used. The study was unblinded as to the schedule of the injections. All subjects were to receive active treatment for 24 months:

- Group A: Daily 2.5mg placebo p.o. and 2mg iv ibandronate q2mo
- Group B: Daily 2.5mg ibandronate p.o. and 2mg iv placebo q2mo
- Group C: Daily 2.5mg placebo p.o. and 3mg iv ibandronate q3mo
- Group D: Daily 2.5mg ibandronate p.o. and 3mg iv placebo q3mo

The primary endpoint was to demonstrate non-inferiority of lumbar spine BMD changes at one year. The study is continuing blinded for a second year. A confirmatory analysis will be performed after 24 months of treatment as well as safety analysis on bone biopsy specimens.

Population: This study enrolled women with postmenopausal osteoporosis who met the specified inclusion and exclusion criteria. The presence of a prevalent vertebral fracture was not a requirement for this study.

Subjects were stratified in to one of three strata, based on lumbar spine BMD:

- T-score < -2.5 and ≥ -3.0
- T-score < -3.0 and ≥ -3.5
- T-score < -3.5 and ≥ -5.0

Inclusion Criteria

- Women, at least five years after menopause
- Age 55-80 years
- Patients must be ambulatory at the beginning of the trial. It must not be anticipated that the patient becomes hospitalized, immobilized, or bedridden during the course of the trial

- Measurable BMD of the spine and hip BMD (no metal devices or osteoarthritis etc. that could interfere with measuring sites); artifacts would in most cases be assessed on the DXA scan
- Mean* lumbar spine BMD (L2-L4): ≤ -2.5 and ≥ -5.0 SD T-score [*mean BMD of at least two vertebrae (L2-L4) that are not fractured and not affected by an osteoarthritic process to such a degree that accurate measurement of BMD would be considered jeopardized by the central reading center]
- Patients who, in the opinion of the investigator, are able and willing to comply with the protocol for its duration
- Written informed consent

Exclusion Criteria

- Significant medical disease that in the medical opinion of the investigator was likely:
    - To interfere with the patient's ability to complete the entire two-year study period or to participate in all aspects of the trial
    - To require, during the study, administration of a treatment that would affect bone metabolism
- Malignant disease diagnosed within the previous 10 years (except successfully resected basal cell cancer), breast cancer diagnosed within the previous 20 years
- Allergy to bisphosphonates
- Contra-indications for calcium or vitamin D therapy
- Serum total Ca2+ > 10.5 mg/dL or < 8.0 mg/dL (equivalent to 2.63 and 1.99 mmol/L respectively)
- Vitamin D deficiency (serum 25-hydroxy vitamin D < 10 ng/mL, equivalent to 24 nmol/L)
- WBC < 2500/μL
- ALT > twice upper limit of normal range
- Serum albumin < 3.0 g/dL
- Renal impairment (serum creatinine > 2.4 mg/dL, equivalent to 216 μmol/L)
- History of major upper GI disease defined by:
    - Significant upper GI bleeding within the last year requiring hospitalization or transfusion.
    - Recurrent peptic ulcer disease documented by radiographic or endoscopic means
    - Dyspepsia or gastroesophageal reflux that is uncontrolled by medication
    - Abnormalities of the esophagus that delay esophageal emptying, such as stricture, achalasia, or dysmotility, and
    - Active gastric/duodenal ulcers.

  Patients were not excluded because of previous or active gastrointestinal disease, except as outlined above (e.g., symptoms of dyspepsia controlled by daily medication or prior history of non-recurrent peptic ulcer disease were not considered exclusionary).
- Disease/disorder known to influence bone metabolism e.g.,: Chronic gastrointestinal or liver disease, chronic alcoholism, severe malabsorption syndrome, primary hyperparathyroidism (patients with surgically treated hyperparathyroidism with documented normal serum calcium and PTH will be eligible for enrollment), Paget's disease of bone, histologically documented osteomalacia, or documented active thyroid disease without treatment
- Administration of any investigational drug within 30 days preceding the first dose of the study drug
- Previous treatment with an oral bisphosphonate for more than 24 months (total duration) and/or treatment within the last 12 month
- Previous treatment with an i.v. bisphosphonate at any time
- Treatment with fluoride for osteoporosis (dose greater than 10 mg/day) within the last 12 months, or past treatment for more than a total of 2 years
- Treatment with strontium for osteoporosis within the last 12 months
- Treatment with PTH or similar anabolic agent for osteoporosis within the last 2 years
- Treatment with other drugs affecting bone metabolism within the last 6 months
    - chronic systemic (oral, parenteral or long-term high-dose inhaled) corticosteroid (glucocorticoid or mineralocorticoid) treatment
    - hormones (e.g., estrogens/"natural estrogen preparations" [except for topical treatment at a frequency of up to twice per week], progestins, selective estrogen receptor modulators (SERMs,

such as raloxifene), anabolic steroids/androgens (such as dehydroepiandrosterone (DHEA), or its sulfated form (DHEAS), nandrolone), tibolone, active vitamin D analogs/metabolites (1,25 dihydroxy vitamin D (calcitriol) or 1-alpha-hydroxy vitamin D3 (1-alpha hydroxycholecalciferol)), calcitonin

- Calcineurin inhibitors (e.g., cyclosporine, tacrolimus) or methotrexate

Additional Exclusion Criteria, ECG Substudy: Subjects enrolled in the ECG substudy were recruited from patients randomized to the 3-month injection schedule (Groups C and D). Approximately 225 patients were planned for enrollment. Subjects who met any of the following criteria were not eligible for ECG substudy participation:

- Myocardial infarction or invasive cardiac procedure within 3 months of enrollment
- Cardiac pacemaker
- Personal or family history of congenital QT prolongation
- Treatment with antiarrhythmic agents (Class IA: procainamide, quinidine, disopyramide; IC: flecainide; III: amiodarone, ibutilide) or bepridil or sotalol
- Treatment with systemic macrolide antibiotics (e.g., clarithromycin, erythromycin) or fluoroquinolones (e.g., gatifloxacin, levofloxacin, moxifloxacin, sparfloxacin) within 4 weeks
- Initiation or change (e.g., withdrawal, change in dose, or frequency) in medications known to cause QT interval prolongation and/or torsades de pointes within 4 weeks
- QTc interval >450 msec on predose ECG(s) at Visit 1 (baseline)
- Atrial fibrillation or flutter on predose ECG(s) at Visit 1 (baseline)
- (Right/left) bundle branch block, Wolff-Parkinson White syndrome on predose ECG(s) at Visit 1 (baseline).

COMMENT: The inclusion and exclusion criteria appear appropriate. Of note, subjects were excluded for major gastrointestinal disease but subjects with active or a prior history of dyspepsia or gastrointestinal reflux disease were not excluded. As well, except for corticosteroids, subjects taking medications known to worsen gastrointestinal reflux disease were not excluded.

Study Medication:
Rationale for Dose Selection: The reason for the suboptimal fracture efficacy noted with ibandronate 0.5mg iv q3 months and 1 mg iv q3 months (study MF4380) is thought to be an insufficient dose of ibandronate and/or an inappropriately long dosing interval. This interpretation is 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 in the relevant skeletal compartments which may be achieved by more frequent injections, the administration of a higher dose, or both.

Study MF4470 was a randomized, double-blind, placebo-controlled, 2-year trial evaluating 1mg ibandronate iv q3months, 2mg ibandronate iv q3months and placebo. The study was terminated by the company after the suboptimal results of MF4380 were known. The original primary efficacy variable was relative change in lumbar spine BMD at 2 years. However, the study was terminated after all subjects completed Year 1 and the analysis was changed to the Year 1 endpoint. The mean change in lumbar supine BMD at 1 year was 0.0% for placebo, 2.8% for 1mg ibandronate ($p<0.01$ compared with placebo) and 5.0% for 2mg ibandronate ($p<0.01$

compared with placebo). The lumbar spine BMD increase with 2 mg ibandronate iv q3 months was superior to the increase seen with the 1mg q3 month regimen and numerically greater than those seen in study MF4411 for 2.5mg ibandronate daily. Based on these data, it appeared that the 2 mg iv q3 month regimen might be sufficient and comparable to the 2.5 mg daily oral regimen. 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 extrapolation of the dose-response curves, the company felt that another dose doubling would not be necessary, and that a moderate dose increase to 3mg iv q3 months should be at least comparable to 2.5mg daily oral. This would be true unless the top of the dose response curve is reached with the 2mg iv q3 month dose. If the top of the dose-response curve is reached with 2mg, a reduction of the dosing interval may be necessary. Therefore, Roche
decided to study both the 3mg iv q3 month dose and a 2mg iv q2 month dose.

COMMENT: Of note, both of the doses chosen have an annualized dose of 12mg ibandronate. The 2mg iv q3months dose would have an annualized dose of 8mg. The approved 150mg monthly oral dose of ibandronate, which was superior to 2.5mg daily oral ibandronate, would have an annualized dose of 10.8, assuming a 0.6% bioavailability. The 100mg monthly oral dose of ibandronate, an annualized dose of 7.2 assuming a 0.6% bioavailability, was noninferior but not superior to the daily oral dose. Taking into account the fracture efficacy of the 2.5mg daily oral dose (annualized dose of 5.5mg, assuming a 0.6% bioavailability) and the suboptimal fracture efficacy exhibited by the 0.5mg and 1mg ibandronate iv q3 months doses (annualized doses of 2mg and 4mg respectively), this reviewer finds the doses studied acceptable. The 2mg iv q3months dose may well be an acceptable dose, but would require a fracture study for certainty.

All subjects received one daily study drug tablet (either 2.5mg ibandronate or placebo) and one i.v. ibandronate dose (either 2mg or placebo i.v. every 2 months or 3mg ibandronate of placebo every 3 months), as outlined in the table below.

Study BM16550: Study Drug Dosing Schedule			
Group	Daily Dose	i.v. dose q 2mo	i.v. dose q 3mo
A	placebo	2mg	
B	2.5mg	placebo	
C	placebo		3mg
D	2.5mg		placebo

Subjects were instructed to take their daily study tablets were in the morning, after an overnight fast (6 hours or more), in an upright position, with a full glass of plain water (240 mL/8 oz.) and to remain in an upright position and remain fasting for 60 minutes after dosing. Plain water was allowed. Intravenous study medication was administered as a bolus injection over 15 to 30 seconds followed by a normal saline flush of the i.v. line.

All subjects received vitamin D 400 IU/day and elemental calcium 500mg/day and were instructed to take the supplements in the evening. If a subject had previously been taking calcium supplements that provided greater than 500mg of calcium daily (but no more than 1500mg daily), and wished to continue on this dose, she was permitted to do so using her own

supplements. 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.

Vitamin D supplementation was limited to the provided 400 IU/day and, therefore, patients were advised not to take additional supplements. Based on a request by the Canadian Therapeutics Products Directorate, the vitamin D dose remained at 400 IU daily. However, additional monitoring at Months 3 and 12 was to be implemented to assess 25-hydroxy vitamin D levels. At the three month time point it was expected that patients who had a 25-hydroxy vitamin D at screening in the low normal range would show a trend towards increasing levels. Provided this was the case, patients were allowed to continue on vitamin D 400 IU daily. 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. At one year, all subjects were to have a serum 25-hydroxy vitamin D level of at least 40 nmol/L (16.7 ng/mL). Subjects who had not achieved this threshold level for 25-hydroxy vitamin D were either to be withdrawn or provided with 800 IU vitamin D daily. The decision to increase the dose of vitamin D or remove a subject from study was to be made on a case by case basis, in conjunction with the treating physician and the sponsor.

COMMENT: A total of 66 subjects were recruited in Canada. Thirty four subjects increased their daily dose of vitamin D at some point during the study. Two subjects required increases in vitamin D dose per the protocol requirements. Of the 66 subjects enrolled, 62 had at least one follow-up value for serum 25-hydroxyvitmina D. Twenty four subjects had 25 hydroxyvitamin D levels below the normal range (<16.7 ng/mL) at screening. No subjects were withdrawn from the study due to a low serum 25-hydroxyvitamin D concentration.

Efficacy Measures

Primary Efficacy Endpoint

- The relative change from baseline in mean BMD of the lumbar spine (L2 – L4) at 12 months

Secondary Efficacy Endpoints

- The absolute change (g/cm^2) from baseline in mean* lumbar spine (L2-L4) BMD at 12 months
- The relative (%) and absolute (g/cm^2) change from baseline in mean* lumbar spine (L2-L4) BMD at 24 months
- The relative (%) and absolute (g/cm^2) change from baseline in total hip, trochanter, femoral neck BMD at 12 months
- The relative (%) and absolute (g/cm^2) change from baseline in total hip, trochanter, femoral neck BMD at 24 months
- Percentage of Responders, defined as
  - Patients with mean* lumbar spine BMD changes above baseline at Month 12
  - Patients with mean* lumbar spine BMD changes above baseline at Month 24
  - Patients with hip (i.e., total hip, trochanter, femoral neck) BMD above at Month 12

  - Patients with hip (i.e., total hip, trochanter, femoral neck) BMD above at Month 24
  - Patients with both hip (i.e., total hip, trochanter, femoral neck) and mean* lumbar spine BMD above baseline at Month 12
  - Patients with both hip (i.e., total hip, trochanter, femoral neck) and mean* lumbar spine BMD above baseline at Month 24
- The relative and absolute change from baseline in fasting serum CTX at 3, 6, 12 & 24 months

* mean BMD of at least two vertebrae (L2-L4) that are not fractured and not affected by an osteoarthritic process to such a degree that accurate measurement of BMD would be considered jeopardized by the central reading center

Safety Measures: Safety was assessed by adverse events (including vertebral and non-vertebral fractures), laboratory measurements (WBC, platelets, hemoglobin, hematocrit, ALT (SGPT), creatinine, BUN, albumin, sodium, chloride, potassium, total calcium, phosphate, and magnesium), height, weight, and physical exams. A subset of subjects will have histomorphometric analysis of transiliac bone biopsies at 21 or 22 months. Intact PTH and 25 hydroxyvitamin D will also be analyzed at screening and at the time of biopsy. A subset of subjects will have ECGs analyzed at baseline and 6 months. Fractures, symptoms suggestive of acute phase reactions (APRs) and renal events were identified as adverse events of special interest.

Study Methods:
Bone Mineral Density: BMD of the lumbar spine (at least two vertebrae L2 – L4) was measured by a single DXA scan at screening, Month 12 and Month 24 in all treatment groups. BMD of the hip (total hip, femoral neck, trochanter) was measured at baseline, Month 12 and Month 24. All DXA scans were read by a central reading center [redacted] A longitudinal instrument quality control (IQC) correction factor was calculated for each site at the one-year analysis.

Biochemical Markers of Bone Turnover: Serum CTX, a biochemical marker of bone resorption, was investigated at baseline, Months 2, 4, 6, 12 and 24 for subjects randomized to Groups A and B (every 2 month injection schedule); and at baseline, Months 3, 6, 12 and 24 for subjects randomized to Groups C and D (every 3 month injection schedule). Samples were obtained prior to i.v. injection or oral tablet intake and analyzed in a central laboratory [redacted] using the [redacted] technique).

Safety Laboratories: Blood for safety labs was collected prior to i.v. injection or po tablet intake. Samples were analyzed Laboratory tests will be processed through a centralized safety laboratory [redacted]). Blood collection for laboratory tests was done at screening and Months 4, 8, and 12 for the q2 month i.v. dosing groups and at screening and Months 3, 6, 9, and 12 for the q3 month i.v. dosing groups.

COMMENT: Of note, intravenous bisphosphonate use has been associated with a fall in serum calcium levels, with the nadir occurring one to two weeks post dose. The timing of

the post-dose laboratory studies in this trial is not adequate to evaluate any acute changes in calcium levels.

ECG: ECGs were collected at baseline and 6-month visits. At those visits, subjects had two 12-lead ECGs recorded before (at -60 minutes and -30 minutes) and after (+5 minutes and +120 minutes) study drug administration. All ECGs were reviewed in a blinded manner by an experienced cardiologist at [redacted] and were assessed for heart rate, P-R interval, QRS interval and QT interval. The presence of the following was also to be noted: abnormal U-waves, negative or biphasic T-waves (combined), ST depression, atrial fibrillation, left anterior hemiblock, right bundle branch block, left bundle branch block, and any myocardial infarction pattern.

Bone biopsy: Single transiliac bone biopsies will be performed at month 22 or subjects randomized to Groups C and D (every 3 month injection schedule) or month 23 for subjects randomized to Groups A and B (every 2 month injection schedule).

Withdrawal criteria: Patients had the right to withdraw from the study at any time for any reason. The investigator could also withdraw patients if it was in the best interest of the patient. In the case of a patient showing significant BMD loss that was confirmed by a repeated measurement as soon as possible after the previous DXA scan (i.e., lumbar spine BMD decrease of greater than 6% over 1 year and/or hip BMD decrease of greater than 8% over 1 year), the BMD central reading center was to inform the investigator. The investigator was to inform the patient and perform appropriate follow-up. The investigator was to encourage the patient to remain in the study and continue the study medication, unless he/she thought it might present a safety concern. In the latter case the patient could be withdrawn from the study drug and another treatment for osteoporosis prescribed by the patient's primary physician. If a patient suffered a clinical osteoporotic fracture, the patient was to be referred for additional medical attention. The investigator was to encourage the patient to remain in the study and continue the study medication.

Patients were withdrawn from the ECG substudy under the following circumstances:

- Introduction of any medication known to cause QT interval prolongation and/or torsades de pointes during the study prior to the ECG assessment at month 6 (exception of macrolide antibiotics or fluoroquinolones when the last dose was at least 4 weeks prior to the ECG)
- Any change (e.g., withdrawal, change in dose, or frequency) in established baseline therapy with any medication known to cause QT interval prolongation and/or torsades de pointes.

Statistical Analyses: The primary hypothesis was that the difference in the effects of daily oral ibandronate and i.v. ibandronate (2mg q2mo or 3mg q3mo) on the relative change in lumbar spine BMD after 12 months of treatment was small, no more than the 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 . To account for non-compliant patients and drop-out of 20%, the sample size was calculated to be approximately 1194 patients. For efficacy analyses the two daily ibandronate 2.5 mg oral groups (Groups B and D) were combined. This approach assumes that the effect of the injection schedule on efficacy is negligible.

The following ordered set of null hypotheses were to be tested sequentially to maintain an overall alpha level of 0.025:

H01: There is a difference of more than 1% in favor of the daily oral dose of 2.5 mg, comparing it with the IV regimen of 2 mg every 2 months.

H02: There is a difference of more than 1% in favor of the daily oral dose of 2.5 mg, comparing it with the IV regimen of 3 mg every 3 months.

These hypotheses were to be tested sequentially and H02 tested only if H01 was rejected

Efficacy data were analyzed for two analysis populations: an intent-to-treat (ITT) population and a Per Protocol (PP) population. The primary efficacy analysis was based on the PP population. Both the primary and secondary efficacy endpoints were also analyzed using the ITT population to demonstrate the robustness of the results. Subjects were included in the ITT population if they were randomized, received at least one dose of the trial medication and had at least one efficacy follow-up data point. The per-protocol population consisted of all those patients in the intent-to-treat population who had no major violations of the protocol (see discussion of protocol violations in the section below).

To determine non-inferiority, a one-sided 97.5% confidence interval of the difference of the means between each of the two i.v. dose regimens and the active-control, oral ibandronate 2.5 mg daily regimen was constructed using an ANOVA model controlling for geographic location and baseline BMD effects (BMD lumbar spine (L2 – L4) T-score $\geq$ -3, <-3 $\geq$ -3.5 and <-3.5). The i.v. dosing regimens were considered as comparable (as judged by non-inferiority) to the 2.5 mg daily regimen if the lower bound of the one-sided 97.5% confidence interval was greater or equal to –1 percentage point. If non-inferiority was demonstrated, the ANOVA model was to be used to test for superiority.

Protocol Amendments: The protocol was amended twice with changes noted below:
BM16550-B (April 18, 2002, in response to FDA Special Protocol Assessment)

- Inclusion criteria for BMD of the lumbar spine (L2 – L4) was changed from $\leq$ -2.0 and $\geq$ 5.0 SD T-score to < -2.5 and $\geq$ 5.0 SD T-score. As well, one of the four stratum: BMD of the lumbar spine (L2 – L4) with a baseline T-score $\leq$ -2.0 and $\geq$ 2.5, was removed
- For the primary confirmatory analysis, the overall alpha level was changed to 0.025 rather than the 0.05 originally specified.
- Discontinuation criteria were changed to a BMD loss of greater than 6% over 1 year for lumbar spine and/or greater than 8% over 1 year for hip

- Following FDA recommendations, the potential for QT interval prolongation would be assessed in an ECG substudy of patients using 8 ECGs: 2 ECGs preceding and 2 ECGs following the IV injection at baseline (Visit 1) and month 6 (Visit 3)

BM16550-C (January 21, 2003)

- If into the ECG substudy was inadequate when recruitment completed for the main study, additional required patients would be enrolled solely to Groups C and D (the three-month injection groups)
- To ensure that sufficient (96) evaluable bone biopsies would be available at the end of the study, the number of patients allowed to consent to the bone biopsy procedure was increased from 138 to 240
- To clarify how the IV study drug was to be administered, the term "bolus injection" was changed to "15-30 second injection".

Results

Patient Disposition: As shown in the table below, 1804 subjects were screened and 1395 subjects were enrolled and randomized this study. Subjects were recruited at 58 centers in North America (14%), Eastern and Western Europe (68%) and other parts of the world (18%). Approximately 85% of subjects completed one year of treatment. Adverse events were the most common reason for early withdrawal, with the rates balanced between the groups. Overall, 1382 (99%) patients were included in the safety population, 1358 (97%) patients in the intent-to-treat population, and 1104 (~ 79%) patients in the per-protocol population. The most common reason for exclusion from the per protocol analysis population was lack compliance with daily oral medication (248 (18%) subjects), non compliance with the i.v. dosing schedule (165 (12%) subjects), and no reliable BMD value (81 (6%) subjects).

Study BM16550: Patient Disposition				
	2.5 qd*	2mg q2mo	3mg q3m	Total
Enrolled	470	454	471	1395
No treatment	2 (<1)	5 (1)	2 (<1)	9 (<1)
At least one dose	468	449	469	1386
At least one follow-up (Safety population)	465 (99)	448 (99)	469 (99)	1382 (99)
ITT population	458 (97)	442 (97)	458 (97)	1358 (97)
PP population	381 (81)	355 (79)	368 (78)	1104 (79)
Withdrew - Total	56 (12)	66 (15)	75 (16)	197 (14)
Deaths	1 (<1)	1 (<1)	2 (<1)	4 (<1)
Adverse Events	30 (6)	30 (7)	39 (8)	99 (7)
Refused treatment	22 (5)	23 (5)	27 (6)	72 (5)
Failure to return	0 (0)	5 (1)	4 (1)	9 (1)
Other	3 (<1)	7 (2)	3 (<1)	13 (1)
Completed 1 year of treatment	409 (87)	382 (84)	394 (84)	1185 (85)
*Groups B and D pooled				

Protocol Violations: Major protocol violations were defined as follows:

- Patients with a biased follow-up (and baseline) BMD assessment as defined by the central DXA reading facility [redacted]
- Patients with a baseline T-score ≥ -2.5 SD
- Patients with one of the following diseases present at baseline or developed during the first year: Paget's disease, liver disease, hyperparathyroidism, medically significant malabsorption, osteomalacia, malignant disease, metastatic bone disease, end-stage renal disease, or active thyroid disease without treatment
- Patients who received a bone effective treatment before and/or after randomization into the study. All visits occurring after treatment with a therapeutic class affecting the bone were excluded from the PP analysis. These classes include bisphosphonates, sex hormones, anabolic agents, SERMs, parathyroid hormone, calcitonins, and corticosteroids
- Patients with a vitamin D deficiency at screening (serum 25-hydroxy vitamin D <10 ng/mL, equivalent to 24 nmol/L)
- Lack of compliance during the first year, defined as subjects who missed more than 25% of their daily tablets per 6 months and/or more than one injection in the first year; or patients that received less than 2.25 mL of the 3 mL IV injection for more than one injection during the first year
- Patients who did not take 50% of the same IV or daily treatment during the first year (i.e., the number of IV injections or daily tablets taken during the first year had to exceed 50% of the total number administered)
- Patients whose menopausal status was not confirmed (i.e., patients that had a missing age at menarche and an unknown duration of menopause). If only the duration of menopause was missing and the patient was aged ε 60 years old, the patient was assumed to be menopausal

Major entry or protocol deviations occurred in 4 subjects who were subsequently withdrawn from the study (1 in 2.5mg po daily group, 3 in 2mg iv q2month group, and none in 3mg iv q3month group).

As outlined in the table below, protocol violations leading to exclusion from the per protocol analysis populations occurred in 282 subjects (87 (19%) in 2.5mg po daily group, 94 (21%) in 2mg iv q2month group, and 101 (22%) in 3mg iv q3month group). The main reasons for excluding patients from the per-protocol analysis population were lack of daily oral study medication compliance (18%), non-compliance with intravenous study medication (12%), and no reliable BMD values (6%).

Study BM16550: Protocol Violations Leading to Exclusion from the PP Analysis				
	2.5 qd*	2mg q2mo	3mg 3qm	Total
Enrolled	470 (%)	454 (%)	471 (%)	1395 (%)
At least one dose	468	449	469	1386
PP population	381 (81)	355 (79)	368 (78)	1104 (79)
Excluded from PP, total	87 (19)	94 (21)	101 (22	282 (20)
Baseline BMD ≥ 2.5 SD	7 (1)	5 (1)	6 (1)	18 (1)
Concomitant Disease	3 (1)	2 (<1)	2 (<1)	7 (1)

Excluded medication	3 (1)	6 (1)	12 (3)	21 (2)
Vitamin D deficiency	1 (<1)	0 (0)	0 (0)	1 (<1)
Noncompliance, oral study med	74 (16)	86 (19)	88 (19)	248 (18)
Noncompliance, iv study med	47 (10)	55 (12)	63 (13)	165 (12)
No reliable BMD values	25 (5)	27 (6)	29 (6)	81 (6)
No valid Efficacy Follow-up	11 (2)	7 (2)	10 (2)	28 (2)
*Groups B and D pooled				

The Sponsor conducted audits of study centers to evaluate investigator site compliance and the systems used in the protocol. One of nine sites audited was reported to have major GCP findings. These included a) failure to add the investigator to the US IND and b) inability to confirm the investigator blinding with respect to patient BMD measurements. However, the company reports there was no evidence that the investigator had knowledge of any of the patient's BMD measurements. As this is a non-inferiority study with three active dose groups, the potential for knowledge of an individual BMD measurement to unblind the investigator is extremely low. Thus the data
from this site are considered valid for inclusion in the primary analysis.

COMMENT: Overall, study subjects were excluded from the per protocol analysis because of major protocol violations including lack of compliance with study medication or inappropriate timing of efficacy assessments. The numbers of major protocol violations and per protocol exclusions were balanced between treatment groups and it is unlikely that the protocol violations affected the principal efficacy or safety results.

Demographics: 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 in 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
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)

BM16550: Patient Demographics				
	2.5 qd*	2mg q2mo	3mg 3qm	Total
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				

Concomitant Medications: Overall, 74% of study participants received concomitant medications during the trial. The most frequently reported medications were non-steroidal anti-inflammatories (23%), analgesics (22%), and salicylates (17%). Vitamin and mineral preparations were used by 12% of study participants. Anti-inflammatory agents were used by 29 % of study participants while COX-2 inhibitors were used by 8%. Medication use to control gastric acid secretion included antacids (4%), H2 receptor antagonists (5%), and proton pump inhibitors (9%). Concomitant medications that could affect bone metabolism are listed in the table below. Approximately 11% of subjects received some form of glucocorticoids during the first year of the study. Approximately 2% of subjects were receiving concomitant anticonvulsant medications.

BM16550: Concomitant Medications Affecting Bone Metabolism				
	2.5 qd+	2mg q2mo	3mg 3qm	Total
N	465	448	469	1382
Sex Hormones	13 (3)	10 (2)	19 (4)	42 (3)
Raloxifene	1 (0.2)	1 (0.2)	4 (1)	6 (0.4)
Bisphosphonates	2 (0.4)	5 (1)	5 (1)	12 (1)
Steroids, total	44 (9)	43 (10)	60 (13)	147 (11)
Anticonvulsants	11 (2)	10 (2)	13 (3)	34 (2)
+ pooled groups B and D				

Primary Efficacy Outcomes

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 was 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 treatment group (3.6%). The ITT analysis is shown. Analyses with the per protocol population produced similar results. The increase in lumbar spine (L2 – L4) 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 which 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 (L2 – L4) 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.

The absolute change in lumbar spine BMD from baseline, a secondary efficacy parameter, was also greater in both i.v. dose groups.

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
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 $\geq$ -3.0, Group 3: < -3.0 and $\geq$ -3.5, and Group 4: < -3.5 and $\geq$ -5.0); continent; age (< 70 and $\geq$ 70 years); race; calcium compliance; cumulative calcium dose group based on tertiles (Group 1: $\leq$ 182 g, Group 2: > 182 g to $\leq$ 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.

Secondary Efficacy Outcomes

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 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			
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			

Percentage of Responders: Responders to treatment were defined as the incidence of patients who had an increase in BMD above or equal to baseline after one year of treatment. In addition, responders were also defined as: the incidence of 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 incidence 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, 82.7% of subjects were responders in the 2.5mg po daily group while 90.8% in the 2mg i.v. q2 month group, and 90.0% 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 (25.3% in the 2.5mg daily group, 36.4% in the 2mg i.v. q2 month group, and 35.7% in the 3mg i.v. q3month group).

At the total hip, 72.6% of subjects were responders in the 2.5mg daily group while 83.5% in the 2mg i.v. q2 month group, and 82.3% 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 also higher in the monthly treatment groups (31.4% in the 2.5mg daily group, 40.5% in the 2mg i.v. q2 month group, and 36.7% 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)

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

Efficacy Conclusions: Both iv dosing regimens were non-inferior and superior to the daily po 2.5mg dosing regimen, based on relative change in lumbar spine BMD at one year.

Safety

Events Rates: As shown in the table below, approximately 78% of subjects experienced adverse events during the study. Serious adverse event rates and withdrawals due to adverse events were

equally distributed between the oral and i.v. treatment groups. Subjects in the 2mg q 2mo i.v. group had two more study visits per year than the 3mg q 3mo i.v. group and thus had more opportunity to report adverse events. However, since all subjects had the opportunity to report events at all study visits, it is unlikely that a significant reporting signal was missed as a result of the difference in visit numbers.

BM16550: Event Rates

	2.5 po qd	**2mg iv q2m**	**3mg iv q3m**
N, safety population	465	448	469
Deaths	1 (<1)	1 (<1)	2 (<1)
Serious Adverse Events	37 (8)	40 (9)	35 (8)
Withdrawals due to SAE	6 (1)	5 (1)	7 (2)
Withdrawals due to AE	31 (7)	30 (7)	40 (8)
AE Leading to Dose Alteration	9 (2)	9 (2)	8 (2)
All Adverse Events	360 (77)	365 (81)	357 (76)

Exposure: The mean duration of treatment was 11.1 months for the two 2.5mg oral daily groups, 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, in 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)
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.

Deaths: Four subjects died during the first year of this trial. A 72 year-old woman receiving placebo iv q 2months 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 iv ibandronate q 2months 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 iv ibandronate q 3months 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 q 3months 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 patients.

Serious Adverse Events: As outlined in the table below, the overall incidence of serious adverse events was similar between the treatment groups (8% in the 2.5mg po daily group, 8% in the 2mg iv q2month group and 9% in the 3mg iv q3 month 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 iv q2 months.

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)
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			

Adverse Events Leading to Withdrawal: 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 iv q2 month group, and 46 (10%) in the 3mg iv q3 month 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 iv q2 month group, and 18 (4%) in the 3mg iv q3 month group); musculoskeletal (3 (1%) in the 2.5mg po daily group, 7 (2%) in the 2mg iv q2 month group, and 6 (1%) in the 3mg iv q3 month group); and body as a whole (3 (1%) in the 2.5mg po daily group, 5 (1%) in the 2mg iv q2 month group, and 6 (1%) in the 3mg iv q3 month group) disturbances.

Adverse Events Leading to 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 iv administration difficulties occurred in 25 subjects (9 (2%) in the 2.5mg po daily group, 8 (2%) in the 2mg iv q2 month group, and 8 (2%) in the 3mg iv q3 month 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 iv q2 month group, and 66 (14%) in the 3mg iv q3 month group). The most commonly affected categories were gastrointestinal disorders (25 (5%) in the 2.5mg po daily group, 25 (6%) in the 2mg iv q2 month group, and 26 (6%) in the 3mg iv q3 month group) and infections (20

(4%) in the 2.5mg po daily group, 14 (3%) in the 2mg iv q2 month group, and 17 (4%) in the 3mg iv q3 month group).

Adverse Events: As outlined in the table 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 iv q2 month group, and 357 (76%) in the 3mg iv q3 month group). Of note, subjects in the 2mg iv q2 month group had two more study visits per year than the 3mg i.v. q3 month 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 iv q2 month group, and 118 (25%) in the 3mg iv q3 month group), musculoskeletal and connective tissue disorders (122 (26%) in the 2.5mg po daily group, 151 (34%) in the 2mg iv q2 month group, and 136 (25%) in the 3mg iv q3 month group), and gastrointestinal disorders (125 (27%) in the 2.5mg po daily group, 148 (33%) in the 2mg iv q2 month group, and 110 (23%) in the 3mg iv q3 month group).

The most frequent adverse events were arthralgia (40 (9%) in the 2.5mg po daily group, 42 (9%) in the 2mg iv q2 month group, and 45 (10%) in the 3mg iv q3 month group), back pain (35 (8%) in the 2.5mg po daily group, 38 (8%) in the 2mg iv q2 month group, and 33 (7%) in the 3mg iv q3 month group), nasopharyngitis (28 (6%) in the 2.5mg po daily group, 30 (7%) in the 2mg iv q2 month group, and 16 (3%) in the 3mg iv q3 month group), and constipation (19 (4%) in the 2.5mg po daily group, 30 (7%) in the 2mg iv q2 month group, and 16 (3%).

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 iv q2 month group, and 19 (4%) in the 3mg iv q3 month group), fatigue (5 (1%) in the 2.5mg po daily group, 11 (2%) in the 2mg iv q2 month group, and 13 (3%) in the 3mg iv q3 month group) and myalgia (4 (1%) in the 2.5mg po daily group, 19 (4%) in the 2mg iv q2 month group, and 13 (3%) in the 3mg iv q3 month group).

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)

BM16550: Adverse Events, by Body System			
	2.5 po qd	**2mg iv q2m**	**3mg iv q3m**
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			

Adverse Events of Special Interest:

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 iv q2 month group, and 13 (3%) in the 3mg iv q3 month 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 iv q2 month group, and 12 (3%) in the 3mg iv q3 month group). Clinical vertebral fractures were reported in 10 subjects (3 in the 2.5mg po daily group, 2 in the 2mg iv q2 month group, and 5 in the 3mg iv q3 month group). Hip fractures were reported in 3 subjects (2 in the 2.5mg po daily group and 1 in the 3mg iv q3 month group).

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 iv q2 month group, and 45 (10%) in the 3mg iv q3 month 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 iv q2 month group, and 12 (3%) in the 3mg iv q3 month group) withdrew from the study due to APR-like symptoms. Four subjects, 1 in the 2mg iv q2 month group, and 3 in the 3mg iv q3 month 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 iv q2 month group, and 6 (1%) in the 3mg iv q3 month 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 iv q2 month group and 20% of subjects in the 3mg iv q3 month 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)	-------	-------

Musculoskeletal Adverse Events: 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 iv q2 month group, and 66 (14%) in the 3mg iv q3 month group). Specifically, bone pain occurred in 31 subjects and was slightly higher in the 2mg iv q2 month group (7 (1%) in the 2.5mg po daily group, 17 (4%) in the 2mg iv q2 month group, and 7 (1%) in the 3mg iv q3 month group).

Jaw Pain: 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 iv q3 month group experienced moderate left jaw and ear pain on Day 2. The symptoms resolved 18 days later without further treatment. A 543 69 year-old subject in the 2mg iv q2 month group developed moderate jaw pain on Day 16. The symptoms resolved without further treatment.

Ocular Adverse Events: 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 iv q2 month group, and 17 (4%) in the 3mg iv q3 month 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 iv q2 month group, and 5 in the 3mg iv q3 month group).

Laboratory

Blood collection for laboratory tests was done at screening and Months 4, 8, and 12 for the q2 month iv dosing groups and at screening and Months 3, 6, 9, and 12 for the q3 month iv dosing groups.

Adverse Events: As outlined in the table below, thirteen subjects had adverse events related to laboratory parameters. Five subjects (one in the 3mg iv q3 month group and 4 in the 2mg iv q2 month group) were noted to have increased liver enzymes on either study or local laboratory testing. The one subject in the 3mg iv q3 month group discontinued from the study due to the hepatic enzyme elevations and 2 of the 4 subjects in the 2mg iv q2 month group had study drug interruptions.

BM16550: Laboratory Adverse Events					
Pt	Age	Grp	Day	Parameter	Comment
1004	71	3mg iv q3m	97	ALT increased	discontinued
334	63	2mg iv q2m	120	Creatinine increased	
446	59	3mg iv q3m	126	Glucose increased	on steroids
1302	69	2mg iv q2m	116	Liver enzyme (GGT) increased	
			43	Triglycerides increased	
			178	Triglycerides increased	
1294	59	2.5mg po qd	242	Uric acid increased	
357	68	2.5mg po qd	142	Glucose increased	
224	66	2mg iv q2m	251	Liver enzymes increased	tx interrupted
915	73	2mg iv q2m	372	Liver enzymes increased	tx interrupted 30d
1068	67	2mg iv q2m	92	Liver enzymes increased	
1082	55	3mg iv q3m	195	MCV, MCH increased	
1178	66	3mg iv q3m	46	Sed rate increased	discontinued

Marked Laboratory Abnormalities: As outlined in the table below, a total of 23 (7 (2%) in the 2.5mg daily group, 8 (2%) in the 2mg iv q2 month group and 7 (1.5%) in the 3mg iv q3 month group) subjects developed marked laboratory abnormalities during the study. The most common abnormality was marked increases in ALT, which occurred in 7 (2%) subjects in the 2.5mg daily group, 5 (1%) subjects in the 2mg iv q2 month group and 9 (2%) subjects in the 3mg iv q3 month group). One subjects in the 2mg iv q2 month dose group developed a markedly elevated creatinine. No abnormalities in calcium metabolism were noted.

BM16550: Marked Laboratory Abnormalities			
	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)			

BM16550: Marked Laboratory Abnormalities			
	2.5 po qd	**2mg iv q2m**	**3mg iv q3m**
Value < 95	0 (0)	0 (0)	2 (<1)
Value > 115	1 (<1)	0 (0)	0 (0)
ALT, SGPT (0 – 30 IU/L)			
Value > 60	7 (2)	5 (1)	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)

Mean Change from Baseline: The mean relative change in laboratories from baseline to Month 12 are outlined in the table below. there were no significant differences in liver function labs (ALT). Creatinine increased with all dosing regimens. The 2.5mg daily group increased 1.5 ± 9.9 µmol/L, while the 2.0mg iv q2 months group increased 3.0 ± 13.3 µmol/L (p=0.06, compared with the daily group) and the 3mg iv q3 months group increased 2.6 ± 10.6 µmol/L (p=0.18, compared with the daily group). Serum calcium fell -0.9 ± 4.2 mmol/L in the 2.5mg daily oral group, which was significantly different from the i.v. dose groups (-0.2 ± 4.2 mmol/L in the 2.0mg iv q2 months group, p=0.03; and 0.1 ± 4.3 mmol/L in the 3mg iv q3 months group, p=0.001). Phosphate levels in the 3mg iv q3 months group had a significantly lower decrease when compared to the 2.5mg daily group (p=0.05).

BM16550: Laboratory Values: Mean Change at Month 12			
	2.5 po qd	2mg iv q2m	3mg iv q3m
N, safety population	465	448	469
ALT	6.0 ± 26.3	4.5 ± 39.2	7.9 ± 48.5
Albumin	0.3 ± 5.3	0.3 ± 5.8	0.7 ± 5.3
BUN	2.2 ± 23.3	3.8 ± 28.1	1.7 ± 24.4
Creatinine	1.5 ± 9.9	3.0 ± 13.3	2.6 ± 10.6
Calcium	-0.9 ± 4.2	-0.2 ± 4.2*	0.1 ± 4.3*
Phosphate	-2.2 ± 14.3	-1.1 ± 13.7	-0.3 ± 15.0*
Magnesium	-2.8 ± 9.2	-2.4 ± 8.9	-2.3 ± 8.7
Sodium	0.6 ± 2.3	0.6 ± 2.3	0.7 ± 2.3
Potassium	-1.1 ± 8.8	-0.9 ± 8.9	-1.4 ± 9.0
Chloride	0.4 ± 2.6	0.3 ± 2.7	0.3 ± 2.7
WBC	-5.9 ± 19.2	-6.3 ± 19.3	-7.1 ± 20.1
Hemoglobin	-0.4 ± 5.4	-1.1 ± 4.9*	-0.4 ± 4.6

BM16550: Laboratory Values: Mean Change at Month 12			
	2.5 po qd	2mg iv q2m	3mg iv q3m
Hematocrit	-0.3 ± 5.0	-1.1 ± 5.2*	-0.4 ± 5.0
Platelets	-2.3 ± 12.7	-3.0 ± 11.8	33.6 ± 724.9
* p≤0.05 compared with 2.5mg daily, analysis by students t-test			

Shifts: 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 2mg iv q2 month group, and 89 (19%) in the 3mg iv q3 month group. SGPT is 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 2mg iv q2 month group, and 59 (13%) subjects in the 3mg iv q3 month 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 2mg iv q2 month group, and 19 (4%) in the 3mg iv q3 month 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 2mg iv q2 month group, and 1 (<1%). Only one subject in the 2mg iv q2 month group had a decrease in serum calcium below the normal range. A decease 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 2mg iv q2 month group, and 19 (4%) in the 3mg iv q3 month 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 (9)	38 (8)	59 (13)
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)

Renal Safety:

Adverse Events: Intravenous bisphosphonates have been associated with increased renal function abnormalities, most notably in the setting of i.v. bolus administration. In study BM16550, i.v. ibandronate administration was by i.v. 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). Three subjects (two in the 2mg i.v. q2month group and 1 in the 3mg i.v. q3month group) were reported to have either renal insufficiency or renal impairment. See the laboratory results section for further discussion of increased creatinine with intravenous ibandronate use.

Serum Creatinine: 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. A total of 10 subjects shifted from a normal creatinine at baseline to a high creatinine at some point during the first year of the study (4 (1) in the 2.5mg oral daily group, 5 (1) in the 2mg iv q2month group and 1 (<1) in the 3mg iv q3month group). A total of 8 subjects (3 in the 2.5mg oral daily group, 2 in the 2mg iv q2month group and 3 in the 3mg iv q3month group) had baseline creatinine > 1.5mg/dL, while an additional 9 subjects developed a creatinine above the upper limit of normal, > 1.5mg/dL, during the study (3 in the 2.5mg oral daily group, 5 in the 2mg iv q2month group and 1 in the 3mg iv q3month group). Five subjects developed a markedly elevated creatinine, defined as > 154 Umol/L or >1.7 mg/dL (1 in the 2.5mg oral daily group, 1 in the 2mg iv q2month group and 1 in the 3mg iv q3month group). Two subjects, both in the 2mg iv 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), 6 subjects (4 in the 2mg iv q2month group and 2 in the 3mg iv q3month group) with baseline creatinine of <1.4 mg/dL had an increase in creatinine more than 0.5 mg/dL.

BM16550: Renal Safety			
	2.5 po qd	**2mg iv q2m**	**3mg iv q3m**
	465	448	469
Creatinine (0 – 1.5mg/dL)			
baseline Cr mg/dL	0.9	0.9	0.9
M12 Cr mg/dL	0.9	0.9	0.9
mean change mg/dL at M12	0.01	0.02	0.02
shift nl to high (n (%))	4 (1)	5 (1)	1 (<1)
Cr > ULN (>1.5 mg/dL) (n (%))	6 (1)	7 (2)	2 (<1)
Cr marked (>1.7 mg/dL) (n (%))	1 (<1)	2 (<1)	2 (<1)
Cr marked >1.5mg/dL + 75% increase (n (%))	0 (0)	2 (<1)	0 (0)
Cr increase >50% (n (%))	2 (<1)	5 (1)	1 (<1)
Cr increase >75% (n (%))	0 (0)	3 (<1)	0 (0)
Cr increase 2 x baseline (n (%))	0 (0)	1 (<1)	0 (0)
Cr base < 1.4mg/dl (N)	**449**	**427**	**451**

BM16550: Renal Safety			
	2.5 po qd	**2mg iv q2m**	**3mg iv q3m**
	465	448	469
increase >0.5 mg/dL (n (%))	0 (0)	4 (1)	2 (<1)
Cr base >1.4 mg/dL (N)	**4**	**6**	**6**
increase >1.0 (n (%))	0 (0)	0 (0)	0 (0)

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 adversely effects renal function in the population of post menopausal women included in this study. However, 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.

Vital Signs: Height and weight were the only vitals signs recorded during the study visits. However, 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) increased body temperature. Both qualified as symptoms of an acute phase reaction and resolved within 3 days. A total of 11 subjects reported change 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.

ECG substudy: An ECG substudy was done to evaluate the effect of iv ibandronate on the QT and corrected QT intervals compared with baseline values. 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

As outlined in the table below, the demographics of the enrolled population was well matched, with a mean age of 65 years and BMI of 26. The percentages of subjects who were taking drugs that could potentially cause QT prolongation was small, and similar between the two groups. The number of subjects with a positive history of cardiovascular disease was also well matched, 15% in each treatment group.

BM16550 ECG Substudy: Patient Demographics		
	2.5 qd	**3mg 3qm**
N	87	157
Age (yrs.)	64.6 ± 6.4	65.2 ± 6.3
BMI	26.0 ± 4.5	26.5 ± 4.3
Race		
Caucasian	86(99)	153(97)
Black	0 (0)	0 (0)
Oriental	0 (0)	0 (0)
Hispanic	1 (1)	3 (2)
Other	0 (0)	1 (1)
Medications possibly affecting QTc		
Opioids	6 (7)	4 (3)
Selective Serotonin Reuptake Inhibitors	2 (2)	3 (2)
Tricyclic Antidepressants	2 (2)	3 (2)
Baseline positive cardiac history	13 (15)	24 (15)
Atherosclerosis	1 (1)	5 (3)
Diabetes mellitus	1 (1)	6 (4)

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 #1, trough dose #3 and post dose #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) 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
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

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)
OTcB 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)
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)

The table below outlines important changes in ECG morphology. 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: Use of intravenous bisphosphonates has been shown to decrease serum calcium levels. Therefore, one could predict that ibandronate may be associated with a prolongation of the QT interval. The data presented here suggests that it is unlikely that iv

ibandronate, in the proposed dose of 3mg iv q3months, has the potential to significantly prolong cardiac repolarization.

Safety 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. Four deaths have occurred during the first year of the study. 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. There were no reports of osteomyelitis/osteonecrosis of the jaw in this study.

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 this study. However, the timing of the mineral laboratories did not allow for assessment of the expected calcium nadir.

Intravenous bisphosphonates have been associated with increased renal toxicity, that appears to be related to dose and rate of i.v. administration. In this study, administration of intravenous

study medications was by i.v. bolus. Overall, the numbers of subjects with adverse events attributable to the renal tract were similar in all three dose groups. Three 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, six subjects (4 in the 2mg iv q2month group and 2 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).

Discussion and Conclusions: 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. 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 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 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.

Both intermittent i.v. ibandronate regimens have an annualized dose of 12mg ibandronate, which is higher than the approved 150mg monthly oral dose (10.8mg, assuming a 0.6% bioavailability) and more than twice the annualized dose of the approved 2.5mg daily oral dose (5.5mg, assuming a 0.6% bioavailability). These higher doses may amplify the documented safety profile of ibandronate.

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. The causes of death are consistent with the postmenopausal population's baseline age and related comorbid conditions and is 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 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. There were no adverse event reports or laboratory evidence of hypocalcemia in this study. However, the timing of the mineral laboratories did not allow for assessment of the expected calcium nadir.

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). In this study, i.v. ibandronate administration was by 15 – 30 second bolus injection. Mean creatinine levels did increase minimally in all treatment groups. However, six subjects (4 in the 2mg iv q2month group and 2 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.

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