CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-455

MEDICAL REVIEW

CLINICAL REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #: 21-455 **Application Type:** Original NDA

Sponsor: Hoffman-La Roche, Inc **Proprietary Name:** Boniva

Pharmaceutical Category: Bisphosphonate **Route of Administration:** Oral, tablet

Indication: Prevention and Treatment of Postmenopausal Osteoporosis **Dosage:** 2.5 mg daily

Reviewers: Theresa Kehoe, MD
Eric Colman, MD **Date Review Completed:** April 21, 2003

Chemistry Reviewer: Elsbeth Chikhale, Ph.D.
Pharmacology Reviewer: Gemma Kuijpers, Ph.D.
Biopharmaceutics Reviewer: S.W. Johnny Lau, Ph.D., Wei Qui, Ph.D.
Statistical Reviewer: Japo Chaudhury, Ph.D.

REVIEW SUMMARY: See Executive Summary

OUTSTANDING ISSUE: None

RECOMMENDED REGULATORY ACTION: N drive location:

New clinical studies	_____	**Clinical Hold**	_____ **Study May Proceed**
NDA, Efficacy/Label supplement:	_____	**Approvable**	_____ **Not Approvable**
	X	**Approve**	

SIGNATURES: **Medical Reviewer:** Theresa Kehoe, M.D. **Date:** _____

Medical Team Leader: Eric Colman, M.D. **Date:** _____

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Clinical Review for NDA 21-455

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Approve

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

Future studies of oral ibandronate should include measurement of serum magnesium levels.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The clinical development program for oral ibandronate as a therapy for the prevention and treatment of postmenopausal osteoporosis included 5 placebo-controlled and 2 active-controlled phase 2/3 trials of 1 to 3 years duration. Four of these studies compared the effects of ibandronate 2.5 mg daily to placebo, 2 compared 2.5 mg daily to alternative active-control dosing regimens, and one compared weekly ibandronate to placebo. The pivotal treatment trial 4411 was a 3-year study of nearly 3000 postmenopausal osteoporotic women randomized 1:1:1 to therapy with ibandronate 2.5 mg daily, ibandronate 20 mg intermittently, or placebo. The primary efficacy endpoint was the percent of patients with new morphometric vertebral fractures after 3 years of treatment. The pivotal prevention trial 4499 was a 2-year study of more than 600 postmenopausal non-osteoporotic women randomized equally to daily therapy with ibandronate 0.5 mg, 1.0 mg, 2.5 mg, or placebo. The primary efficacy endpoint was percent change in lumbar spine bone mineral density after 2 years of therapy. Roche is seeking approval only for the 2.5 mg daily dose for both the prevention and treatment indications.

B. Efficacy

Treatment of Postmenopausal Osteoporosis: A phase 2 dose-ranging study in osteoporotic women indicated that increases in bone mineral density and suppression of biochemical markers of bone turnover were similar for the 2.5 mg and 5.0 mg daily doses of ibandronate; however, the adverse event profile of the 2.5 mg dose was clearly superior than that for the 5.0 mg dose. In the pivotal treatment trial 4411, relative to placebo, therapy with 2.5 mg daily ibandronate reduced the 3-year risk for morphometric vertebral fracture from approximately 10.0% to 5.0% ($p<0.0003$). The risk for clinical or symptomatic vertebral

fractures was reduced from 5.3% in placebo-treated women to 2.8% in ibandronate 2.5 mg-treated women (p=0.01). Ibandronate failed to reduce, however, the risk for non-vertebral osteoporotic fractures (8.0% vs. 9.0%, placebo vs. 2.5 mg). Treatment with 2.5 mg ibandronate relative to placebo was associated with significant increases in bone mineral density of the lumbar spine and total hip (5.0% and 4.0%, respectively) and significant reductions in biochemical markers of bone turnover.

Prevention of Postmenopausal Osteoporosis: In the pivotal prevention trial 4499, relative to placebo, therapy with 2.5 mg daily ibandronate increased lumber spine bone mineral density by approximately 3.0% ($p<0.001$) and total hip bone mineral density by roughly 2.0% ($p<0.05$). Biochemical markers of bone turnover in the subjects treated with ibandronate 2.5 mg daily were significantly reduced relative to placebo-treated women by Month 3 of the study and remained suppressed thereafter.

C. **Safety**

The majority of the placebo-controlled safety data for ibandronate come from the pivotal fracture trial 4411, in which approximately 3000 women were randomized to 3 years of treatment. Ancillary placebo-controlled safety information on the 2.5 mg ibandronate dose is provided by 3 much smaller studies of 1 to 2 years duration. No significant safety issues were noted during the review of this NDA. As with other oral bisphosphonates, there was a slightly higher incidence of some GI adverse events in active compared with placebo-treated patients: Dyspepsia and diarrhea were reported by approximately 11.0% and 7.5% of subjects who received ibandronate 2.5 mg compared with 9.0% and 5.0% of placebo-treatment women. Esophagitis was diagnosed in 1.5% of subjects randomized to the 2.5 mg group vs. 1.0% of placebo subjects. Concomitant therapy with NSAIDS increased the incidence of dyspepsia to 15% for women in the 2.5 mg group and to 11.0% in placebo-treated participants, but did not affect the rates for diarrhea or esophagitis. Very few women developed hypocalcemia or hypophosphatemia, two established adverse effects of bisphosphonate treatment (hypocalcemia: 0.3% vs. 0.2%; ibandronate vs. placebo) and (hypophosphatemia: 0.9% vs. 0.6%; ibandronate vs. placebo). Examination of bone biopsies in a subgroup of women treated with ibandronate for 22 and 34 months did not reveal any qualitative abnormalities such as osteomalacia or woven bone.

D. **Dosing**

Sufficient evidence has been provided in this NDA that the 2.5 mg daily dose of ibandronate has the most favorable benefit – risk ratio and is the most appropriate dose for the prevention and treatment of postmenopausal osteoporosis. In addition, it is clear that, relative to a 30-minute post-dose fast, a 60-minute fasting period enhances bioavailability and thus efficacy.

Clinical Review

I. Introduction and Background

I.A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Hoffman-La Roche, Inc. has submitted this new drug application for ibandronate sodium [1-hydroxy-3-(methylpentyl-amino) propylidene] bis-phosphonic acid)], proposed trade name Boniva. Ibandronate is a member of the bisphosphonate class of medications. Roche proposes to market a single oral dose of 2.5 mg ibandronate daily for the prevention and treatment of postmenopausal osteoporosis (PMO).

I.B. State of Armamentarium for Indication(s)

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

I.C. Important Milestones in Product Development

Ibandronate has been studied in both oral and intravenous (i.v.) formulations. Both formulations were examined for therapeutic benefit in the prevention and treatment of PMO. Ibandronate was initially developed by Boehringer Mannheim, Inc. and then, in 1998, acquired by Hoffman-La Roche. Important agency/sponsor interactions include:

- June 1996 – End-of-Phase 2 Meeting: The phase 3 development programs for i.v. and p.o. ibandronate were reviewed. A recommendation was made that treatment studies in postmenopausal osteoporosis should be 3 years duration.

- July 1998 – End-of-Phase 2 Meeting: A second meeting was held to introduce the new Roche development team and review the development program. It was noted that the dose of calcium taken by patients in the Phase 2 (1000mg calcium) and Phase 3 (500mg calcium + 400 IU vitamin D) treatment studies were different. The sponsor's explanation for the change in dose was:

"Calcium was supplemented to ensure that patients were not calcium deficient, as calcium deficiency might have led to increased bone resorption and loss of bone mass. In the dose finding studies MF 4348 and MF 4361, patients were not supplemented with vitamin D but received 1000 mg/day of calcium supplements. Patients participating in subsequent PMO treatment studies received 500 mg/day of supplemental calcium and 400 IU/day of supplemental vitamin D. The recommended total daily intake of calcium for postmenopausal women is 1000-1500 mg. Vitamin D was provided to optimize calcium absorption and the calcium supplement of 500 mg/day together with average

spontaneous dietary sources of calcium was expected to be at least as efficacious as the 1000 mg provided in the Phase 2 studies where vitamin D was not supplemented."

- August, 1999 – Pre-NDA CMC meeting.
- September, 1999 – Pre-NDA meeting.
- May 2000 – a type A meeting was held. Analysis of the pivotal i.v. study MF 4380 determined that it failed to reach statistical significance in its primary endpoint. The study was terminated prematurely due to lack of efficacy. It was agreed that the ongoing oral ibandronate program may be sufficient for filing of an NDA for ibandronate in the treatment and prevention of PMO, if the data were sufficiently positive (i.e., small p-value for fracture efficacy and strong inverse correlation between change in BMD and fracture risk).
- October 2000 – The Data Analysis Plan was submitted for pivotal oral treatment of PMO study MF4411.
- October 2001 – Pre-NDA meeting to discuss Phase 3 data from the pivotal oral studies of ibandronate in the prevention and treatment of PMO.

I.D. Other Relevant Information

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

I.E. Important Issues with Pharmacologically Related Agents

Bisphosphonate are used in the prevention and treatment of postmenopausal and corticosteroid-induced osteoporosis, Paget's disease, hypercalcemia of malignancy, and bony metastases. Safety concerns with oral bisphosphonates include esophageal and gastric irritation and ulceration. Recently the Division has raised concern regarding the use of these drugs in women of childbearing age and the potential for fetal toxicity after remote exposure to the drug. The Division is currently discussing these issues with the various bisphosphonate manufacturers.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

II.A. Chemistry

(Please see Dr. Chikhale's review for complete details) The drug product is an immediate release film coated tablet for oral administration with a strength of 2.5 mg/tablet. The drug will be packaged in HDPE bottles containing 30, 90, or 500 tablets. The proposed storage is at 25°C

(room temperature), and the proposed expiry date is 36 months. The batches used for clinical trials were round tablets, made in Mannheim, Germany, and the commercial batches are oblong tablets, made in Basel, Switzerland. These batches all have the exact same composition and are considered equivalent from a chemical stand point. However, the site specific stability data on these batches are incomplete.

II.B. Animal Pharmacology and Toxicology)
(Please see Dr. Kuijpers' review for complete details)

II.C. Biopharmaceutics
(Please see Dr. Lau's review for complete details) No difference existed between the to-be-marketed formulation and the pivotal clinical study formulation. However, the manufacture of the product was transferred from the development site, Mannheim (Germany), to the commercial manufacturing site, Base (Switzerland). The tablet was also changed from round (pivotal clinical study) to oblong (to-be-marketed) shape. This change had no influence either on the manufacturability of the tablets or their dissolution properties.

II.D. Statistics
(Please see Dr. Choudhury's review for complete details) A discussion of the pertinent findings has been incorporated into the appropriate sections of the efficacy review.

III. Human Pharmacokinetics and Pharmacodynamics

(please see Dr. Lau's and Dr. Qiu's review for complete details)

III.A. Pharmacokinetics

II.A.1. PK Properties
The oral bioavailability of ibandronate is low (~ 0.6%), highly variable (inter subject CV: > 70% and intra subject CV: estimated as 46%) and markedly reduced (~ 90%) in the presence of food. There is no reduction in bioavailability provided ibandronate is taken 60 minutes before a meal. Reducing the post-dose fast period from 60 minutes to 30 minutes results in a decrease in bioavailability of about one-third. After oral administration ibandronate is rapidly absorbed with median peak concentrations reached by 1 hour. Plasma profiles of ibandronate are multiphasic and terminal concentrations are low, sustained and variable. The range of observed apparent half-lives was broad (10-60 hours). Renal clearance was found on average to be 3.6 L/h. Steady-state appears to be reached after 8 days of dosing with no unexpected accumulation (< 2-fold) during chronic treatment. Ibandronate is initially widely distributed throughout the body then redistributed to the bone or excreted in the urine. Plasma protein binding is approximately 85% at therapeutic concentrations and is unlikely to result in any significant drug interactions. Approximately 40-50% of the circulating dose is taken up in bone.

II.A.2. PK: Potential for Interactions
In vitro studies indicate that the potential for drug-drug interactions through competition for binding to plasma proteins or biotransformation by cytochrome P450 or other drug-metabolizing enzymes is minimal.

II.A.3. PK: Effects on impaired renal and hepatic function

There is no evidence that ibandronate is metabolized in animals or humans. The pharmacokinetics of ibandronate are unlikely to be affected in patients with liver disease and dose adjustment is not necessary. Circulating ibandronate is excreted into urine and about half of the absorbed oral dose is found in urine within 24 hours. There is a linear relationship between creatinine clearance and renal clearance of ibandronate. Renal clearance appears to involve both glomerular filtration and a specialized secretory pathway. In patients with severe renal impairment (CLcr < 30 mL/min), exposure to ibandronate increases approximately 2-3 fold.

II.A.4. PK Effects of size, body weight, gender, race

Bioavailability and pharmacokinetics of ibandronate are similar in men and women. There is no evidence for clinically relevant inter-ethnic differences between Asians and Caucasians in ibandronate disposition. The pharmacokinetics of ibandronate were not studied in other races. Bioavailability and disposition are similar in elderly and younger patients. There are no data on the use of ibandronate in the pediatric patient population (less than 18 years old).

III.B. Pharmacodynamics

III.B.1. Mechanism of action

Bisphosphonates are carbon-substituted analogs of pyrophosphate. They have a high affinity for mineralized tissue and bind tightly to hydroxyapatite (the mineral component of bone). Bisphosphonates act as inhibitors of osteoclast-mediated bone resorption. While the mechanism of action is not yet completely understood, evidence indicates an inhibitory effect on mature osteoclasts. Consequently, the generation of new bone remodeling units is reduced, as is the depth of the erosion cavities they generate. At the molecular level bisphosphonates interfere in the intracellular mevalonate pathway by inhibiting FPP synthase (farnesyl diphosphonate) and thus protein prenylation of small GTPases, which are important for osteoclast function and apoptosis.

III.B.2. Dosing

Ibandronate has been investigated in both oral and intravenous formulations. Biochemical markers were used to predict long-term response in bone mass during anti-resorptive therapy. During the Phase 2 dose-finding study MF4348, the decrease in urinary CTX was dependent on dose with maximum suppression occurring at about 3 months after the start of treatment. The greatest suppression occurred at the 2 highest doses (2.5 and 5 mg) with an overall magnitude of 80-90%. The effect was maintained throughout the remaining dosing period, but levels returned to baseline within 12 months after the discontinuation of treatment. Serum osteocalcin levels also declined in a dose-dependent manner to a maximum extent of about 40% of baseline values, although the time taken to reach peak inhibition was later (about 6 months) and the recovery at the end of the dosing period was slower – a indication of the primary mechanism of action of bisphosphonates on bone resorption, with the effects on markers of formation a consequence of the coupling of the two processes.

III.B.3. Interaction studies

Products containing calcium and other multivalent cations (such as aluminum, magnesium and iron), are likely to interfere with absorption of ibandronate. Ranitidine (i.v.) caused an increase in ibandronate bioavailability of about 20%, most likely by lowering gastric acidity. When co-administered with melphalan and prednisolone, there were minor changes in the pharmacokinetics of ibandronate. These changes are unlikely to be of clinical relevance. Ibandronate caused no changes in the pharmacokinetics of either melphalan or prednisolone.

IV. Description of Clinical Data and Sources

IV.A. Overall Data

The ibandronate clinical development program for the prevention and treatment of osteoporosis included treatment trials for both the i.v. formulation and the oral formulation as well as prevention trials for both formulations. This review focuses on the oral ibandronate trials.

IV.B. Tables Listing the Clinical Trials:

(i.v. studies are listed in *italics*)

Treatment of Postmenopausal Osteoporosis Trials

Ibandronate Osteoporosis Treatment Trials					
	dose (mg)		**subjects**	**duration**	**primary endpoint**
Randomized, Double Blind, Placebo-Controlled Trials					
MF 4411	(oral)		2946 (2929)	3 yrs	vertebral fractures
	placebo daily		982 (975)		
	2.5 daily		982 (977)		
	20 intermit		982 (977)		
MF 4433	(oral)		240	2 yrs	LS BMD (L1 – L4)
	plac qd (year 1)	2.5 qd	81	37	
		20 int		35	
	2.5 daily (2yr)		81		
	20 intermit (2yr)		78		
MF 4348	(oral)		180	1 yr.	LS BMD (L1 – L4)
	0.25 – 5.0 daily				
MF4380	*(iv)*		*2862*	*3 yrs*	*vertebral fractures*
	placebo q3mo		*950*		
	0.5 q3m0		*951*		
	1.0 q3mo		*961*		
MF4492	*(iv) crossover study from MF4380 completers n=194, early termination of study*				
	plac	*1.0 q3mo*	*65*	*2yrs*	*LS BMD (L1 – L4)*
	0.5 q3mo	*plac*	*34*		
		0.5 q3mo	*33*		
	1.0 q3mo	*plac*	*33*		
		1.0 q3mo	*30*		
MF4361	*(iv) q3mo*		*126*	*1 yr*	*LS BMD (L1 – L4)*
	0, 0.25, 0.5, 1.0, 2.0				
MF4470	*(iv) 2 yr early termination of 2 yr study*				
	0, 1.0, 2.0 q3mo		*520*		*LS BMD (L1 – L4)*
MF8306	*(iv)*				*LS BMD (L1 – L4)*

Ibandronate Osteoporosis Treatment Trials, continued				
	dose (mg)	subjects	duration	primary endpoint
Randomized, Double Blind, Parallel Group Comparative Trials				
M75003	(oral)	235	48 wks	
	2.5 daily vs. 20 wkly			LS BMD (L1 – L4)
MF4472	*(iv)*	*81 (114)*		
Open Label Trials – Special Studies				
MF 4491	(oral) 2.5 qd post dose fast 30min vs 60min	388	1 yr	LS BMD (L1 – L4)
IHCS/OCp01	(oral) 0 vs. 2.5qd vs. 20 int	75	3mo	S-CTX
IHCS/OCp02	(oral) 2.5 qd vs qweek vs 3x/wk	125	10-12wks	S-CTX
MF4427	*(iv)*	*18*		

Prevention of Postmenopausal Osteoporosis Trials

Ibandronate Osteoporosis Prevention Trials				
	dose (mg)	subjects	duration	primary endpoint
MF 4499	(oral)	653 (648)	2 yrs	LS BMD (L1 – L4)
	placebo daily	162 (159)		
	0.5 daily	162 (161)		
	1.0 daily	166 (165)		
	2.5 daily	163 (163)		
MF 4500	(oral)	630 (622)	2 yrs	LS BMD (L1 – L4)
	placebo	158 (156)		
	5.0 weekly	159 (155)		
	10.0 weekly	154 (153)		
	20.0 weekly	159 (158)		
MF 4488	*(i.v.)*	*629*	*2 yrs.*	*LS BMD (L1 – L4)*
	placebo	*157*		
	0.5 q 3 mos.	*157*		
	1.0 q 3 mos.	*156*		
	2.0 q 3 mos.	*159*		

IV.C. Postmarketing Experience

The oral formulation of ibandronate is not approved in any country. Worldwide, an estimated ——— patients have received the i.v. formulation of ibandronate (1.0 – 4.0 mg) for the treatment of hypercalcemia of malignancy. There have been 50 adverse event reports in 33 patients who received this formulation. Five patients died while on ibandronate therapy: 3 were attributed to the underlying malignancy, one from thrombocytopenia and one from acute renal failure. The most frequently reported events were from the following body systems: skin and appendages (14%), general disorders (12%) and metabolic and nutritional disorders (8%).

IV.D. Literature Review

A MEDLINE review was conducted for ibandronate and revealed 126 articles. The majority of the articles were included in the sponsor's references. The information included in the articles does not add materially to the information provided in the NDA.

V. Clinical Review Methods

V.A. How the Review was Conducted

This review focuses on the pivotal trials for the treatment of PMO and the prevention of PMO: Study 4411 and 4499, respectively. Less-detailed reviews of supportive studies MF4433, MF4348, M75003 and MF4491 for the treatment indication, and study MF4500 for the prevention indication are also provided. Because fracture efficacy was not demonstrated in study 4380, a pivotal trial of two i.v. ibandronate dosing regimens, data from this study will be reviewed as they relate to the outcome of study 4411, the pivotal treatment trial of oral ibandronate.

V.B Overview of Materials Consulted in Review

This review was conducted utilizing data in the electronic submission of the NDA. All trials were conducted under INDs [redacted] (oral formulation) and [redacted] (injection formulation).

V.C. Overview of Methods Used to Evaluate Data Quality and Integrity

The Division of Scientific Investigation (DSI) was consulted for this NDA. Please see Andrea Slavin's review for complete details. Audits were conducted at 3 study sites from study 4411 because of the relatively large number of patients enrolled. DSI concluded that these study sites satisfactorily adhered to the study protocol and followed accepted standards of clinical trial conduct.

V.D. Were Trials Conducted in Accordance with Accepted Ethical Standards?

All studies appear to have been conducted in accordance with FDA guidelines on "Good Clinical Practice" and the principles of the Declaration of Helsinki.

V.E. Evaluation of Financial Disclosure

Financial disclosure information was provided by the sponsor and reviewed by these Reviewers. One investigator who participated in studies MF4411, MF4499, MF4380 and MF4380f reported [redacted] but did not provide details, despite due diligence of the company. This investigator enrolled 242 subjects into study MF4411 and 52 subjects into MF4499. An investigation of his sites was performed by DSI and the submitted data were found to be acceptable. The sole investigator for studies MF4348 and MF4433 also reported [redacted] in the sponsoring company. No further details were provided, despite due diligence of the company. A DSI audit was not performed on this European site. These Reviewers believes that it is unlikely that this financial arrangement impacted the study outcome, and given the ancillary nature of these studies, it certainly did not affect the conclusions drawn about the efficacy and safety of ibandronate, which come predominately from studies 4411 and 4499.

V.F. The Food and Drug Administration's Osteoporosis Guidance Document
As outlined in the Agency's Guidance for the Development of Drugs used to Prevent and Treat Osteoporosis, in order to gain approval for the treatment of postmenopausal osteoporosis (PMO), a company must demonstrate that their drug significantly reduces the risk for morphometric vertebral fractures in postmenopausal osteoporotic women during 3 years of treatment. Once fracture efficacy is established for a particular compound, a prevention of PMO indication can be attained by demonstrating significant drug-related increases in lumbar spine (LS) BMD in postmenopausal non-osteoporotic women over a 2-year treatment period. While the guidance does not mandate that placebo controls be used, all currently approved osteoporosis drugs were studied in placebo-controlled trials.

VI. Integrated Review of Efficacy

VI.A. Conclusions

Treatment of Postmenopausal Osteoporosis: In a 3-year, randomized, double-blind, placebo-controlled trial of postmenopausal osteoporotic women who received ibandronate 2.5 mg daily or 20 mg intermittently, active treatment effectively reduced the risk for morphometric vertebral fractures. Nearly 10% of placebo-treated women experienced at least one new morphometric vertebral fracture during the 3-year study compared with 4.7% of 2.5 mg-treated subjects ($p=0.0003$) and 4.9% of 20 mg intermittently treated women ($p=0.0005$). This translated into relative risk reductions of 62% in the 2.5 mg group ($p=0.0001$) and 50% in the 20 mg group ($p = 0.0006$). There were also statistically significant reductions in the incidence of clinical (or symptomatic) vertebral fractures in both ibandronate groups. The incidence of clinical non-vertebral fractures was not significantly reduced by active treatment, however. Compared with placebo, treatment with ibandronate 2.5mg daily increased BMD at most major skeletal sites, with the largest relative increase observed at the LS. Biochemical markers of bone resorption and formation were significantly suppressed after 3–6 months of active treatment and remained suppressed for the remainder of the study. Histomorphometric data obtained from a subgroup of women who had bone biopsies confirmed that the rate of bone turnover was moderately reduced with ibandronate treatment, without evidence of mineralization defects.

Prevention of Postmenopausal Osteoporosis: In a two-year, randomized, double-blind, placebo-controlled trial of 0.5 mg, 1.0 mg, and 2.5 mg daily doses of ibandronate, the 2.5 mg dose proved most effective in preventing bone loss in postmenopausal women without osteoporosis at baseline. Bone mineral density of the LS increased by approximately 3.0% in the 2.5 mg group compared to placebo. Bone mineral density at the hip also increased by a statistically significant amount in the 2.5 mg vs. the placebo group. Biochemical markers of bone turnover supported the BMD data, as markers of bone resorption and formation were suppressed at Month 1 and at all subsequent time points during the 2-year study.

VI.B. General Approach to Review of the Efficacy of the Drug

The pivotal trials MF4411 for the treatment indication and MF4499 for the prevention indication were the main focus of the review. The i.v. treatment trial MF4380 was also reviewed in depth because of the study's lack of fracture efficacy. Somewhat less-detailed reviews of supportive

studies MF4433, MF4348, M75003 and MF4491 for the treatment indication and study MF4500 for the prevention indication have also been conducted.

VI.C Detailed Review of Trials by Indication

VI. C.1. Treatment of Postmenopausal Osteoporosis Trials

VI.C.1.a. Study MF 4411: This was a randomized, double-blind, placebo-controlled, multinational study of the efficacy and safety of ibandronate over 3 years in patients with postmenopausal osteoporosis.

Objectives: The primary objective of this study was to investigate the fracture efficacy and safety of ibandronate in the long-term treatment of postmenopausal osteoporosis.

Study Design: This was a randomized, double-blind, placebo-controlled, parallel-group, 3-year study. Seventy-three centers participated in the study. The study design included a screening visit within 3 months prior to randomization and a 3-year treatment period following randomization. Subjects were randomized 1:1:1 into 3 parallel groups and treated as outpatients with either: placebo one tablet daily, 2.5 mg ibandronate one tablet daily, or 20 mg ibandronate one tablet every other day for 12 doses at the start of each 3 month cycle (intermittent). All subjects received daily oral supplements of 400 IU vitamin D and 500 mg calcium.

Population: The study population comprised healthy postmenopausal women with low spinal bone mass and 1– 4 prevalent vertebral fractures.

Inclusion Criteria

- Age 55-80 years
- ≥ 5 years post menopause
- BMD T-score from -2.0 to -5.0 in at least one lumbar vertebra (L1–L4)
- One to four prevalent vertebral fractures in T4-L4

Exclusion Criteria

- BMD T-score below -5.0 in one or more lumbar spine vertebrae
- More than 2 fractures in the lumbar spine
- Disease known to influence bone metabolism
- Therapy with other drugs affecting bone metabolism within the last 6 months
- Prior treatment with bisphosphonates at any time
- Prior treatment with fluoride
- Administration of any investigational drug within 30 days
- Renal impairment (serum creatinine > 210 µmol/L [2.4 mg/dL])
- Contra-indications for calcium or vitamin D therapy
- Serum calcium ≥2.6 or < 2.0 mmol/L (≥ 10.5 or < 8.0 mg/dL).
- Aspirin-sensitive asthma
- Prior treatment with aminoglycoside antibiotics within 4 weeks

COMMENT: The inclusion and exclusion criteria appear appropriate, although narrowing the BMD inclusion criterion to one lumbar vertebra is unusual for osteoporosis trials. Given that oral bisphosphonates are associated with GI toxicity (i.e., esophagitis, gastritis), it is worth noting that individuals with a prior history of esophageal disease, peptic ulcer disease, and use of non-steroidal anti-inflammatory drugs were not excluded from trial participation. This *should* increase the real-world applicability of the safety results.

Study Medication: All medications were administered orally. Subjects were instructed to take one tablet per day immediately after waking in the morning and to remain upright for a minimum of 1 hour. A fasting period from at least 6 hours prior to and 1 hour after taking the medication was required. Subjects were instructed to take their calcium supplement with the evening meal.

COMMENT: The dosing instructions for risedronate and alendronate – two bisphosphonates approved for the treatment of PMO – direct patients to wait at least 30 minutes after dosing before they eat or drink. It is unclear why Roche used a 60-minute post-dose fast in this trial and a 30-minute post-dose fast in the pivotal prevention of PMO trial, but given that a third study in this NDA indicates that gains in BMD are significantly less when patients use a 30-minute vs. a 60-minute post-dose fast, the labeling for ibandronate should recommend the 60-minute dosing interval for both the treatment and prevention indications.

Efficacy Measures

Primary: Rate of subjects with new incident vertebral fractures at 3 years
Rate of subjects with new clinical vertebral fractures

Secondary: Rate of subjects with new vertebral fractures (including clinical fractures)
Total number of new fractures
Height
Change in bone mineral density (BMD) of lumbar spine (L2 - L4)
Change in BMD of proximal femur
Change in BMD of distal forearm (only in patients of selected centers)
Pain and disability
Urinary calcium excretion (calcium/creatinine)
Urinary excretion of C-telopeptide (ratio of C-telopeptide/creatinine)
Urinary excretion of N-telopeptide (ratio of NTX/creatinine)
Serum osteocalcin concentration
Serum concentration of bone-specific alkaline phosphatase (BSAP)
Serum parathyroid hormone concentration

Safety Measures: Discussed in detail in the Integrated Summary of Safety.

Study Methods: A full schedule of assessments can be found in Appendix XI.B.1.a

Prevalent Vertebral Fractures: Lateral radiographs of the thoraco-lumbar spine were performed at the screening visit to determine the presence of prevalent fractures. The assessment of vertebral fractures was based on qualitative and morphometric criteria. Qualitative categorical diagnoses of osteoporotic vertebral fracture were made at 2 centers: University of Washington Medical Center, Seattle for the North American sites, and Benjamin Franklin Medical Center, Berlin for the European sites. The readers had full knowledge of the morphometric data but were blinded to study drug identity. The radiologist performed a binary (yes/no) qualitative assessment of the series of films. Vertebral morphometry was performed for both prevalent and incident fractures based on point placement. The anterior (at), middle (mt), and posterior (pt) height were determined for each vertebra body from T4–L4 using slightly different electronic techniques. The Berlin center evaluated all film sets using original radiographs. Using a translucent digitizer and cursor, 6 points were marked on each vertebra and the coordinates were recorded onto an electronic grid and stored in a computer. The Seattle center used digitized images with digital coordinates on a computer screen for all evaluations. The morphometric criteria for diagnosis of a prevalent fracture of a vertebral body (T4 - L4) at baseline were defined as a value of = 0.8 for any of the following 3 height ratios:

P1) Low anterior height ratio: $a_0 / p_0 \leq 0.8$,

P2) Low middle height ratio: $m_0 / p_0 \leq 0.8$,

P3) Low posterior height ratio: $p_0 / p_0' \leq 0.8$.

a_0, m_0, p_0 were the measured baseline anterior, middle, and posterior heights at the given vertebral level, and p_0' was the posterior height measured at baseline for the vertebra above (or if needed, below) the given level.

Incident Vertebral Fractures: The diagnosis of an incident vertebral fracture was based both on the radiologist's qualitative diagnosis as well as on morphometric criteria. A final incident fracture diagnosis required a positive by both methods. The morphometric criteria required the dual occurrence of 2 events: a relative height ratio or relative height reduction in a vertebral body of a least 20% in an anterior, middle, or posterior vertebral body height, and a ≥ 4 mm absolute decrease in the respective heights. The 6 morphometric diagnostic ratios were measured as:

Relative height ratio decrease:

M1) Anterior height ratio decrease: $a_t / {}_{pt} \leq 0.8 \times a_0 / p_0$, and $a_0 - at \geq 4$ mm

M2) Middle height ratio decrease: $m_t / p_t \leq 0.8 \times m_0 / p_0$, and $m_0 - mt \geq 4$ mm

M3) Posterior height ratio decrease: $p_t / p_0 \leq 0.8 \times p_t' / p_0'$, and $p_0 - pt \geq 4$ mm

Relative height decrease:

M4) Anterior height decrease: $a_t \leq 0.8 \times a_0$, and $a_0 - a_t \geq 4$ mm

M5) Middle height decrease: $m_t \leq \leq 0.8 \times m_0$, and $m_0 - m_t \geq 4$ mm

M6) Posterior height decrease: $p_t \leq \leq 0.8 \times p_0$, and $p_0 - p_t \geq 4$ mm

Incident vertebral fractures were defined morphometrically as either *endplate* (decrease in middle height only, if only criteria M2 or M5 were met), *wedge* (decrease in anterior but not posterior height, if criteria M1 or M4 were met, but not M3 nor M6), or *crush* (decrease in posterior height, if M3 or M6 were met) fractures. The status of a fracture might change over the

period of the study, therefore the most severe category (crush > wedge > endplate) assigned to a fracture during the study was used as the assigned category for this analysis.

Bone Mineral Density: Bone mineral density was measured using Hologic or Lunar Dual Energy X-ray Absorptiometry (DEXA) machines. Measurements were made of the lumbar spine (L1-L4), the proximal femur, and the distal forearm. Measurements were analyzed at the investigational site and were then transmitted for quality assurance and longitudinal corrections to one of two central sites, the and the Osteoporosis and Arthritis Research Group (OARG), University of California San Francisco, San Francisco, USA. Two rounds of cross calibration were carried out using the European Spine Phantom. These cross calibration data were used to correct patient data. In case of longitudinal variation in scanner performance appropriate longitudinal corrections were also made. The corrected BMD results were processed by the central site and then transferred to the sponsor's database.

Height: Height measurements were not made uniformly across the study sites. Height was to be measured in a standardized fashion using a supplied calibrated stadiometer. However, not all sites received these devices and other more inaccurate methods were used (e.g. physician office weighing scale with attached height rod measurement device). Some U.S. centers measured height only to the nearest full inch.

Pain: Bone pain was scored at each visit using the Coleman rating scheme

Bone Pain Score	
Score	**Description**
0	None
1	Mild
2	Moderate
3	Severe
4	Intolerable

Disability and Physical Activity: Assessments of physical disability and activity were done at baseline and annual visits. Patients were questioned regarding the limitation on movement (disability) and physical activity experienced during the month preceding the visit. Responses were recorded using modified Leidig and Cooper tables, respectively (in Appendix XI.B.1.a

Withdrawal criteria: Subjects were withdrawn from the study if they experienced excessive bone loss defined as a decrease in BMD of > 8% during the first year, or > 10% over 2 years. Withdrawn patients were not replaced.

Statistical Analyses: Based on a clinically relevant difference of 40% in the incidence of new vertebral fractures between placebo and active treatment, it was calculated that there should be 2040 (at least 680 patients per treatment group) patients completing the first year and available for the final ITT analysis to achieve a power for the study of at least 90%. The Intent-to-Treat (ITT) population consisted of all patients who had received at least one dose of study medication,

and for whom at least one follow-up data point was available. The ITT population was used in all fracture analyses (primary and secondary fracture endpoints, including height). The partial *a priori* ordering of hypotheses was defined as follows:

H01: There is no difference between placebo and the pooled ibandronate groups in the incidence of new incident vertebral fractures.
H02: There is no difference between placebo and continuous daily administered 2.5 mg ibandronate in the incidence of new incident vertebral fractures.
H03: There is no difference between placebo and intermittently administered 20 mg ibandronate in the incidence of new incident vertebral fractures.
H04: There is no difference between continuously daily administered 2.5 mg ibandronate and intermittently administered 20 mg ibandronate in the incidence of new incident vertebral fractures

Protocol Amendments: The first amendment on July 10, 1997, increased the sample size from 2400 to 2946 randomized patients. The protocol was amended a second time on December 4, 2000, just prior to unblinding the clinical database. The purpose of this amendment was to include a Data Analysis Plan as an appendix to the protocol. Further major modifications concerned handling serious adverse events in order to conform to the definition within ICH guidelines and Roche policies were also made. After 2 years of treatment, an interim analysis was planned in order to investigate the treatment effect on change in lumbar spine BMD and on clinical fractures (excluding morphometric vertebral fractures) at 2 years, as well as on safety data. This interim analysis also intended to compare the BMD changes at 2 years to those of study MF 4380. However, because the results of MF 4380 with i.v. ibandronate showed a suboptimal effect on fracture rate reduction, this interim analysis was not performed. The data remained fully blinded until the completion of 3 years of treatment.

Results

Patient Disposition: As shown in the table below, 982 subjects were enrolled into each treatment group. Approximately 64.0% of placebo, 66.3% of ibandronate 2.5 mg, and 67.8% of ibandronate 20 mg subjects completed the 3-year trial. Eight women withdrew because of lack of efficacy (3 in the placebo group, 3 in the 2.5 mg group and 2 in the 20 mg group). Adverse events were the most common reason for early withdrawal, with the rates being very similar among groups.

MF4411: Patient Disposition			
	Placebo	Iban 2.5 daily	Iban 20 int
Enrolled	982	982	982
No treatment	7	5	5
At least one dose	975	977	977
Withdrew - AE	180	175	178
Withdrew - Other	167	154	137
Deaths	10	11	8
Completed 3 Years	628 (64 0)	648 (66.3)	662 (67.8)

The majority of withdrawals occurred in the first year of the study (Table below).

MF 4411: Distribution of Treatment Completion/Withdrawal over Time			
	Year 1	Year 2	Year 3
	N (%)	N(%)	N(%)
Placebo (N=975):			
Completed	777 (79.7)	709 (72.7)	628 (64.4)
Withdrew -AE	107 (11.0)	149 (15.3)	180 (18.5)
Withdrew - Other	91 (9.3)	117 (12.0)	167 (17.1)
Iban 2.5mg qd (N=977):			
Completed	805 (82.4)	724 (74.1)	648 (66.3)
Withdrew -AE	103 (10.5)	143 (14.6)	175 (17.9)
Withdrew - Other	69 (7.1)	110 (11.3)	154 (15.8)
Iban 20mg int (N=977)			
Completed	798 (81.7)	718 (73.5)	662 (67.8)
Withdrew -AE	116 (11.9)	156 (16.0)	178 (18.2)
Withdrew - Other	63 (6.4)	103 (10.5)	137 (14.0)

Withdrawal Due to Excessive Loss of BMD: Eight women withdrew because of excessive bone loss: 3 in the placebo group, 3 in the 2.5 mg group, and 2 in the 20 mg group.

Protocol Violations: A total of 804 subjects had major protocol violations (269 in placebo, 266 in 2.5 mg, 269 in 20 mg). The predominant violation was a lack of compliance with study drug and concomitant use of other osteoporosis treatments. The most significant protocol deviation was the absence of a prevalent vertebral fracture in 185 subjects (6.3% of the ITT population, 68 in placebo, 57 in 2.5 mg and 60 in 20 mg). A total of 87 (26 in placebo, 29 in 2.5 mg, 32 in 20 mg) subjects had a LS BMD in which none of the lumbar vertebrae BMD was < -2.0, while an additional 53 (20 in placebo, 18 in 2.5 mg, 15 in 20 mg) subjects had at least one vertebra in which the BMD was < -5.0.

COMMENTS: Although there were numerous and varied protocol violations, the numbers and types of violations were evenly distributed across the three groups. It is very unlikely, then, that the protocol violations affected the principal efficacy or safety results.

Demographics: The three groups were well matched for baseline demographic characteristics (Table below). The mean age of the participants was 69 years, 98% of the subjects were Caucasian, the average LS BMD T-score was -2.76, and 94 % of patients had prevalent vertebral fractures.

MF4411: Patient Demographics			
	Placebo	**Iban 2.5 mg p.o. daily**	**Iban 20 mg p.o. intermit.**
N	975	977	977
Age (yrs.)	68.8 ± 6 0	68.7 ± 6.2	68.7 ± 6.2
Body Weight (kg)	66.8 ± 11.3	66.6 ±10.9	66.7 ±10.9
Body Height (cm)	159.7 ± 6.1	160.2 ± 6.1	160.3 ± 6.1
BMI (kg/m2)	26 2 ± 4.2	26.0 ± 4.1	26.0 ± 4.1

MF4411: Patient Demographics			
	Placebo	Iban 2.5 mg p.o. daily	Iban 20 mg p.o. intermit.
Race			
Caucasian	960 (98.5%)	964 (98.7%)	960 (98.3%)
Asian	8 (0.8%)	6 (0.6%)	7 (0.7%)
Black	3 (0.3%)	4 (0.4%)	3 (0.3%)
Hispanic		1 (0.1%)	1 (0.1%)
Other	4 (0.4%)	2 (0.2%)	6 (0.6%)
Time since Menopause (yrs)			
Mean ± SD	20.8 ± 7.8	20.9 ± 8.0	20.8 ± 8.0
Subjects having received HRT			
Yes	210 (21.5%)	214 (21.9%)	203 (20.8%)
No	765 (78.5%)	763 (78.1%)	774 (79.2%)
LS T-score	-2.76	-2.75	-2.71
% Prevalent Vert Fx	93%	94.2%	93.9%

Primary Fracture Outcomes

New Morphometric Vertebral Fractures

A total of 149 subjects suffered at least one new morphometric vertebral fracture during the 3-year course of the trial. By life-table analysis, the rate over 3 years was estimated to be 9.6% for the placebo group and 4.7% (2.5 mg) and 4.9% (20 mg) for the ibandronate treatment groups. The differences in vertebral fracture rates were highly significant with p-values of 0.0003 for the 2.5 mg group and 0.0005 for the 20 mg group (Table below).

MF4411:Lifetable Analysis for the First New Morphometric Vertebral Fracture Through Year 3 (ITT)				
	Placebo	Iban 2.5 mg p.o. daily	Iban 20 mg p.o. intermit.	2.5 mg, 20 mg combined
	(N=975)	(N=977)	(N=977)	(N=1954)
Primary:				
Through Year 3:				
First new fracture	73	37	39	76
Estimate for incidence	9.56%	4.68%	4.90%	4.79%
95% CI for estimate	7 47% – 11.66%	3.20% – 6.16%	3.39% – 6.41%	3.74% - 5.85%
p-value, compared to placebo		0.0003	0.0005	
p-value, between groups		0.2785		
Secondary:				
Through Year 2:				
First new fracture	47	25	22	47
Estimate for incidence	5.87%	3 03%	2.53%	2.78%
95% CI for estimate	4.24% – 7.51%	1.85% – 4.20%	1.49% – 3.58%	2.00% - 3.57%
Through Year 1:				
First new fracture	16	10	17	27
Estimate for incidence	1.81%	1.11%	1.89%	1.50%
95% CI for estimate	0.93% – 2.69%	0.43% – 1.80%	1.00% – 2.78%	0.94% - 2.06%
Note One patient in the placebo group could not be evaluated for lack of a spine X-ray at baseline.				

Relative Risk Reduction

One of the enrollment criterion specified that women have a BMD T-score < –2.0 *in at least one of the* vertebra from L1 to L4. Because of this narrow definition (i.e., one versus L1 + L4 vertebrae), 19.7% of the women at baseline had a summed (L1 through L4) LS BMD T-score > –2.0.

In contrast to most of the study subjects who had a summed L1-L4 BMD T-score < -2.0 (high risk), in the subgroup with a BMD T-score > -2.0 (low risk), there was a greater percentage of subjects in the 2.5 mg vs. the placebo group who sustained new vertebral fractures. When the interaction between treatment effect and baseline BMD T-score (below or above –2.0, i.e., high or low risk) was evaluated it was found to be statistically significant. The size of the treatment effect (i.e. relative risk reduction) was therefore estimated using the Cox regression model with and without baseline BMD (high vs. low risk) as a covariate.

COMMENT: The finding of an increased incidence of morphometric vertebral fractures in the 2.5 mg (4.3%) vs. the placebo group (1.0%) in those women with LS BMD T-scores > -2.0 is likely a chance finding. Two facts support this position: 1) The incidence of morphometric vertebral fractures was 0.5% in women treated with the 20 mg intermittent dose of ibandronate (total drug exposure was very similar for the daily and intermittent regimens, as were the increases in LS BMD); and 2) In the pivotal prevention of PMO trial, 4499 (reviewed later in this document), in which the majority of enrolled women had baseline LS BMD T-scores > -2.0, the percentage of clinical vertebral fractures in the placebo and 2.5 mg groups were nearly identical.

As shown in the following table, treatment with the 2.5 mg dose of ibandronate was associated with a 62% reduction in relative risk of morphometric vertebral fracture when baseline BMD is included as a covariate (p=0.0001). The relative risk reduction is 52% when the model is run without baseline BMD as a covariate.

MF4411: Relative Risk Reduction versus Placebo for the First New Morphometric Vertebral Fracture			
	Placebo vs. Iban 2.5 daily	Placebo vs. Iban 20 intermit.	Placebo vs. Iban 2.5, 20 combined
Primary:			
Through Year 3:			
Risk reduction estimated by prop. hazard model with interaction:			
Relative Risk Reduction	61.62%	49.87%	55.72%
p-value for risk reduction with interaction	0.0001	0.0006	0.0001
p-value for interaction between 'treatment*baseline BMD'	0.0043	0.9765	0.0401
Risk reduction estimated by prop. hazard model without interaction			
Relative Risk Reduction	52.11%	49.82%	50.85%
p-value for risk reduction without interaction	0.0003	0.0005	0.0001
Secondary:			
Through Year 2:			
Relative Risk Reduction*	60.72%	56.28%	58.48%
p-value for risk reduction with interaction	0.0006	0.0017	0.0001
Through Year 1:			
Relative Risk Reduction*	57.92%	3.48%	30.75%
p-value for risk reduction with interaction	0.0561	0.9202	0.2590
* Relative risk reduction estimated by proportional hazard model with interaction (treatment * baseline T-Score ≤ -2)			

COMMENT: An obvious question is what is the most appropriate value for vertebral fracture relative risk reduction to cite in the ibandronate labeling: 62% (with BMD as a covariate) or 52% (without BMD as a covariate)? When baseline BMD is included in the model as a covariate, the relative risk reduction of 62% reflects those women who had either a baseline BMD T-score < -2.0 or a missing baseline measurement (roughly 80% of the trial population); whereas, when baseline BMD is not used as a covariate, the relative risk reduction of 52% reflects the entire study population, including those women who had a baseline BMD T-score > -2.0. Since the Division has historically required fracture data from ITT populations be given prominence in the labeling, these Reviewers recommend that the 52% relative risk reduction be cited in the ibandronate labeling.

Subgroup Analyses of New Morphometric Vertebral Fractures

The percentage of subjects with new vertebral fractures, and the corresponding reduction in relative risk, were analyzed in several subgroups of the ITT population (Table below). The results from the most relevant subgroup analyses (continent, BMI at baseline, age at baseline, time since menopause, number of prevalent fractures, and lumbar spine BMD at baseline) are summarized in the table below. While the overall incidence of new vertebral fractures varied by subgroup, all subgroup showed trends towards reductions in fracture risk with active treatment.

MF4411: Lifetable Analysis for the First New Incident Vertebral Fracture and Estimate of Relative Risk Reduction through Year 3 in Selected Subgroups (ITT)

	Fracture Incidence			Relative Risk Reduction			
	Placebo	2.5 mg	20 mg	2.5 mg vs. Placebo	p-value	20 mg vs. Placebo	p-value
Continent:							
Europe	10.34%	5.37%	5.48%	56.86%	0.0007	48.47%	0.0044
North America	7.97%	3.22%	3.73%	75.12%	0.0054	54.44%	0.0502
BMI at Baseline:							
Lower tertile <23.96)	8.77%	5.76%	5.27%	34.79%	0.2107	37.85%	0.1723
Middle tertile (23.97-27.42)	10.04%	4.27%	3.98%	65.46%	0.0060	59.20%	0.0127
Upper tertile (>27.43)	9.47%	3.94%	5.40%	79.90%	0.0011	47.89%	0.0584
Age [years]:							
< 70	10.96%	3.88%	4.78%	71.48%	<0.0001	56.97%	0.0019
≥ 70	7.99%	5.56%	5.06%	47.08%	0.0410	39.42%	0.0949
Time since Menopause [years]:							
Lower tertile (<17)	10.40%	2.16%	3.78%	78.88%	0.0006	66.79%	0.0031
Middle tertile (18-24)	8.21%	8.20%	4.77%	32.67%	0.2287	42.67%	0.1117
Upper tertile (>25)	10.20%	3.62%	6.48%	70.05%	0.0052	35.51%	0.1863
Number of prevalent fractures:							
0 or 1	6.21%	2.43%	3.54%	65.76%	0.0056	41.97%	0.0868
> 2	14.00%	7.46%	6.76%	60.91%	0.0005	54.62%	0.0024
Spinal BMD (L2-L4) at Baseline:							
BMD < -2.5	12.54%	5.36%	7.28%	58.97%	0.0002	42.93%	0.0092
BMD > -2.5	4.89%	3.71%	1.54%	20.99%	0.5492	67.87%	0.0293

Note: One patient in the placebo group could not be evaluated for lack of a spine X-ray at baseline.
Relative risk reduction estimated by proportional hazard model with interaction (treatment * baseline T-Score ≤ -2) for all subgroups, except for lumbar spine BMD, for which the interaction term is not applicable.

New or Worsening Vertebral Fractures

An additional 31 women had worsening of existing vertebral fractures. When worsened fractures are added to new vertebral fractures, a total of 167 subjects experienced at least one new or worsening vertebral fracture. The results of the life-table analysis of these events were similar to the new vertebral fracture analysis (10.4% in the placebo group, 5.1% in the 2.5 mg group and 5.8% in the 20 mg group). The relative risk reduction was 62.3% with ibandronate 2.5 mg ($p<0.0001$) and 49.0% with ibandronate 20 mg ($p=0.0005$).

New Clinical Vertebral Fractures

Clinical vertebral fractures were those identified symptomatically and reported as adverse events by the investigator. In total, 85 subjects in the ITT population reported symptoms such as back pain that were confirmed as being due to a new clinical vertebral fracture. Forty-one of these subjects were receiving placebo, while only 22 subjects in each of the ibandronate treatment groups were found to have new clinical vertebral fractures during the 3-year study period. The incidence rates, as estimated by Kaplan-Meier analysis, were 5.3% in the placebo group vs. 2.8% in both ibandronate groups ($p = 0.0117$ for 2.5 mg and $p = 0.0143$ for 20 mg). Unlike morphometric vertebral fractures, there was no significant interaction between baseline LS BMD T-score and clinical vertebral fractures.

Secondary Efficacy Outcomes

Clinical Osteoporotic Fractures

Clinical osteoporotic fractures included symptomatic new vertebral fractures plus all non-vertebral fractures, except those considered non-osteoporotic (i.e., fractures of the hands, feet, face, and skull). At least one clinical osteoporotic fracture was recorded for 102 placebo subjects, 94 2.5 mg subjects, and 88 20 mg subjects. Kaplan-Meier estimates for the occurrence of the first clinical osteoporotic fracture over 3 years revealed incidence rates of 13.0% (placebo), 11.6% (2.5 mg), and 11.2% (20 mg).). Although the incidence rates in the ibandronate treatment groups were lower than that in the placebo group, the differences were not statistically significant ($p = 0.4593$ for 2.5 mg and $p = 0.1825$ for 20 mg)(Table below).

MF4411: Number of All Clinical Osteoporotic Fractures (ITT)			
	Placebo	Iban 2.5 mg	Iban 20 mg
		p.o. daily	p.o. intermit.
	(N=975)	(N=977)	(N=977)
Subjects with clinical osteoporotic fractures:			
0 fracture	873	883	889
1 fracture	89	85	76
2 fractures	11	7	11
3 fractures	2	2	1

The occurrence of clinical osteoporotic fractures was analyzed in several subgroups of particular interest (continent, BMI at baseline, age at baseline, time since menopause, number of prevalent fractures, lumbar spine BMD at baseline). In all the subgroup analyses, there were no significant differences between placebo and any of the two ibandronate treatment groups.

The analysis of the incidence of total osteoporotic fractures combined the set of subjects with clinical osteoporotic fractures and those subjects with new morphometric vertebral fractures. In the placebo group 16.8% of patients experienced at least one of these fractures, while the corresponding figures were 13.0% for the 2.5 mg group (p=0.04) and 13.4% for the 20 mg group (p=0.05).

All Clinical Fractures

Similar to what was observed for all clinical osteoporotic fractures, the analysis of all clinical fractures (osteoporotic and non-osteoporotic) did not show a significant difference between placebo (14.2%) and the ibandronate treatment groups (13.0% for 2.5 mg and 13.1% for 20 mg) (Table below).

There was also no significant difference between the Kaplan-Meier estimates for non-vertebral fractures (8.2% for placebo, 9.1% for 2.5 mg, and 8.9% for 20 mg).

The overall number of hip fractures in the trial was low. The number of subjects with hip fractures was lower in placebo group (4, 0.6%) than in the 2.5 mg (6, 0.8%) or 20 mg groups (11, 1.4%), but the differences were not statistically significant. When also considering fractures of the pelvis or the femur in addition to the hip, the differences between treatment groups are even smaller [(10, 1.3%) in placebo; (11, 1.4%) in 2.5 mg; and (15, 2.0%) in 20 mg)].

A similar percentage of subjects from each group suffered fractures of the wrist or the forearm: 29 placebo subjects (3.7%), 34 2.5 mg subjects (4.2%) and 31 20 mg subjects (3.9%).

Rib fractures were recorded in 4 placebo subjects (0.5%), 5 2.5 mg subjects (0.6%) and 7 20 mg subjects (0.9%).

MF4411: Clinical Osteoporotic Fractures (ITT)			
	Placebo	Iban 2.5 mg	Iban 20 mg
	(N=975)	(N=977)	(N=977)
Any clinical fracture:			
0 fracture	863	871	873
1 fracture	98	93	89
2 fractures	11	11	14
3 fractures	3	2	1
Osteoporotic non-vertebral fractures:			
0 fracture	910	903	907
1 fracture	59	68	63
2 fractures	4	4	7
3 fractures	2	2	0
Fractures of the hip:			
0 fracture	971	971	966
1 fracture	4	6	11
Fractures of the hip, pelvis, or femur:			
0 fracture	965	966	962
1 fracture	9	10	15

2 fractures	1	1	0
Wrist/forearm fractures:			
0 fracture	946	943	946
1 fracture	29	33	30
2 fractures	0	1	1
Rib fractures:			
0 fracture	971	972	970
1 fracture	3	5	7
2 fractures	1	0	0

Osteoporotic Fractures in Patients with a Femoral Neck Baseline T-Score < –3.0
To further assess the distribution of osteoporotic clinical fractures and non-vertebral osteoporotic fractures, the incidence of these types of fractures was explored in subgroups with different baseline femoral neck BMD T-scores. It was found that the incidence of osteoporotic clinical and non-vertebral fractures was higher in the subpopulation of patients with a femoral neck BMD T-score < –3.0 at baseline.

As shown in the table below, there was a significant reduction in osteoporotic clinical fractures from 24.2% in the placebo group to 8.9% in the 2.5 mg group (p = 0.0052), and 13.6% in the 20 mg group (p = 0.0358).

In this subgroup, the incidence of osteoporotic non-vertebral fractures was also significantly lower in the 2.5 mg group compared with the placebo group. In the case of the 20 mg group, the reduction in fracture incidence was not statistically significantly different from placebo.

MF4411: Kaplan-Meier Analysis of the Occurrence of Osteoporotic Clinical and of Osteoporotic Non-Vertebral Fractures in Patients with Baseline Femoral Neck T-Score < –3.0 (ITT)			
	Placebo	Iban 2.5 mg p.o. daily	Iban 20 mg p.o. intermit.
	(N=124)	(N=123)	(N=128)
Subjects with osteoporotic clinical fractures:			
Subjects with at least one fracture	24	9	13
Estimate for incidence	24.17%	8.90%	13.57%
95% CI for estimate	15.64% - 32.70%	3.31% - 14.50%	6.59% - 20.55%
p-value for treatment difference compared to placebo (Wilcoxon ranks sum):		0.0052	0.0358
Subjects with osteoporotic non-vertebral fractures:			
Subjects with at least one fracture	18	6	12
Estimate for incidence	18.37%	6.02%	12.52%
95% CI for estimate	10.60% - 26.14%	1.32% - 10.72%	5.77% - 19.27%
p-value for treatment difference compared to placebo (Wilcoxon ranks sum):		0.0096	0.1889

COMMENT: While the above results are of academic interest, they come from post-hoc subgroup analyses and are therefore inappropriate for inclusion in the labeling.

Height

The smallest degree of height loss was observed in the 2.5 mg ibandronate group, followed by the 20 mg ibandronate group. Height loss in both ibandronate group was significantly less than that observed in the placebo group (2.5 mg: $p < 0.0001$; 20 mg: $p = 0.0115$), while the difference between the 2 active treatment groups was not significant ($p = 0.1189$) (Table below).

Study MF4411: Change in Height per Year (ITT)			
	Placebo	Iban 2.5 mg p.o. daily	Iban 20 mg p.o. intermit.
Change in height (in cm) per year:			
n	786	812	804
Mean	-0.203	-0.130	-0.163
SD	0.371	0.344	0.347
p-values (Wilcoxon Test, two-sided):			
Placebo vs. 2.5 mg	<0.0001		
Placebo vs. 20.0 mg	0.0115		
2.5 mg vs. 20.0 mg	0.1189		

COMMENT: Because some centers did not measure height with a stadiometer, but instead used a typical physicians' office scale, and rounded measurements off to the nearest full inch, the height data presented in the NDA are of questionable validity.

Bone Mineral Density

Bone Mineral Density of Lumbar Spine: The primary spinal BMD parameter was based on analysis of the vertebrae from L2 to L4. Over 3 years, placebo subjects showed a mean increase in BMD of 1.43% from baseline. Relative mean increases of 5.0% for the 2.5 mg group ($p<0.0001$) and 4.32% for the 20 mg group ($p<0.0001$) were observed during the same duration of observation. The results for spinal BMD obtained with patients from the PP population mirror very closely those observed in the ITT population.

MF4411: Mean Relative Change (%) in Spine BMD (L2-L4) after 3 Years (ITT)			
	Placebo	Iban 2.5 mg p.o. daily	Iban 20 mg p.o. intermit.
Number of subjects	693	712	714
Mean relative change (%)	1.43	6.41	5.75
SD	5.27	5.44	5.74
Difference - ibandronate/placebo (%)		4.98	4.32
p-value for difference (ANOVA)		< 0.0001	< 0.0001
Difference - ibandronate groups (%)		0 66	
p-value for difference (ANOVA)		0.0265	
Possibly biased values were replaced by the last unbiased value (LOCF) LOCF was not applied if last unbiased value was baseline visit or if date before censoring date was missing			

Bone Mineral Density of Proximal Femur: In comparison to placebo, after 3 years of treatment a statistically and clinically significant increase in BMD for all hip regions analyzed was demonstrated for both ibandronate groups. The treatment benefit, mean change compared to placebo, was for total hip 3.9% (2.5 mg) and 3.5% (20 mg), for the femoral neck 3.2% (2.5 mg)

or 2.9% (20 mg), and for the trochanter 5.1% (2.5 mg) or 4.8% (20 mg). All placebo vs. drug comparisons were associated with p-values < 0.0001.

Consistent with the spinal BMD measurements, the treatment benefit of the 20 mg intermittent regimen was lower numerically than that of the daily 2.5 mg schedule. However, these differences between the two ibandronate groups were not statistically significant.

COMMENT: By the company's own admission, the results of the forearm BMD measurements are difficult to compare due to the use of different types of DEXA scanners with different scanning windows.

Bone Mineral Density of Forearm: Bone mineral density measurements of several different regions of the forearm in subgroups of patients are reported by the company. Since the ultra-distal radius is comprised predominately of trabecular bone, results from this skeletal site are mentioned here. In a sample of about 100 women from Denmark, the changes in BMD of the ultradistal radius were nearly identical for all 3 treatment groups.

BMD Subgroup Analyses

A subgroup analysis was performed to examine treatment effects in several subsets of patients that were considered to be of particular interest (continent, BMI at baseline, age at baseline, time since menopause, number of prevalent vertebral fractures, lumbar spine BMD at baseline). The relative changes in LS and total hip BMD in the examined subgroups were in general very similar to the results observed in the primary patient population. In all subgroups, both ibandronate groups had increases in BMD relative to placebo. (See table in Appendix XI.B.1.b)

Pain and Disability

Semi-quantitative responses about the presence and/or change in bone pain were used to assess pain and disability. A slightly higher percentage of patients from the two ibandronate groups (34.6% for 2.5 mg group and 36.3% for 20 mg group) reported improvements in bone pain during the course of the study compared with subjects from the placebo group (31.0%).

COMMENT: It should be pointed out that the proportion of patients without any bone pain at baseline was slightly higher in the placebo group, and consequently it was not possible for these patients to record an improvement in this subjective measure.

Bone Turnover Markers

Blood and urine samples were obtained at regular intervals in a subset of patients (~ 20%) to analyze the time course of biochemical markers for bone turnover. As markers for bone resorption, the urinary concentrations (normalized to urinary creatinine to provide excretion rates) of the C-telopeptide (CTX,) and the N-telopeptide (NTX) of type I collagen were measured. Serum concentrations of osteocalcin, bone-specific isotype of alkaline phosphatase (BSAP), and parathyroid hormone (PTH) served as indicators of bone formation (Tables below).

Bone Resorption Markers

At baseline, the mean CTX and NTX excretion rates were similar in all treatment groups. By Month 3, there was a reduction in CTX in both ibandronate treatment groups vs. the placebo group. The reduction in CTX excretion was maintained throughout the entire 3 year study period, with a median reduction from baseline to Year 3 of 13.6% for the placebo group, 62.7% for the 2.5 mg group ($p<0.001$), and of 50.0% for the 20 mg group ($p<0.001$).

There was also a reduction in urinary NTX excretion in both active-treatment groups within the first 3 months, which persisted for the remainder the 3-year study. At Year 3, the median reduction from baseline for NTX was 25.8% for the placebo group, 65.7% in the 2.5 mg group ($p < 0.0001$), and 53.3% in the 20 mg group ($p < 0.0001$).

MF4411: Resorption Markers - Relative Change (%) from Baseline over 3 Years (ITT)								
		Baseline	Relative Change to Baseline (%)					
			Month 3	Month 6	Month 12	Month 18	Month 24	Month 36
Urinary CTX/Creatinine (µg/µmol)								
Placebo	N	223	201	183	176	154	165	152
	Median	0.22	-23.66	-22.13	-27.04	-21.87	-19.33	-13.65
2.5 mg	N	221	202	193	175	161	165	156
	Median	0.23	-58.47	-64.14	-66.31	-65.94	-66.91	-62.72
20 mg	N	227	205	205	186	172	168	155
	Median	0.24	-46.76	-53.63	-57.00	-49.58	-51.00	-50.00
P-values for differences between median relative changes by Kruskal-Wallis Test								
		Placebo vs. 2.5mg			<0.001			
		Placebo vs. 20mg			<0.001			
		2.5mg vs. 20mg			<0.001			
Urinary NTX/Creatinine (nmol/mmol)								
Placebo	N	223	201	183	176	154	165	152
	Median	54.00	-21.74	-15.22	-25.66	-8.39	-17.19	-25.78
2 5 mg	N	221	202	193	175	161	165	153
	Median	57.00	-51.54	-53.91	-58.18	-48.31	-56.25	-65.71
20 mg	N	227	205	205	187	172	168	153
	Median	63.47	-41.86	-40.00	-49.40	-41.59	-44.70	-53.33
P-values for differences between median relative changes by Kruskal-Wallis Test								
		Placebo vs. 2.5mg			<0.0001			
		Placebo vs. 20mg			<0.0001			
		2.5mg vs. 20mg			0.0021			

Bone Formation Markers: The baseline values for osteocalcin and BSAP were well matched across treatment groups. From the first measurement at 3 months, the serum levels of both markers were markedly reduced in both ibandronate treatment groups (Table below). Median osteocalcin levels were reduced at the end of the study by 1.7% in the placebo group, 33.0% in the 2.5 mg group ($p < 0.0001$) and by 40.3% in the 20 mg group ($p < 0.0001$).

Compared to placebo, median BSAP levels were clearly reduced after 3 months, and this difference widened further during the course of the study. By the end of the 3-year study, the

median BSAP level in the placebo group increased by 38.1% over baseline. Although at the end of the study the median BSAP levels for the 2 ibandronate groups had risen to values very close to the values at baseline (0.00% for the 2.5 mg group and –2.91% in the 20 mg group), they were both significantly lower than the placebo value ($p < 0.0001$).

MF4411: Formation Markers - Relative Change (%) from Baseline over 3 Years (ITT)								
		Baseline	Relative Change to Baseline (%)					
			Month 3	Month 6	Month 12	Month 18	Month 24	Month 36
Serum Osteocalcin (ng/mL)								
Placebo	N	225	208	189	180	165	169	156
	Median	18.30	-8.79	-12.69	-10.62	-12.65	-4.02	-1.68
2.5 mg	N	223	214	196	186	164	168	158
	Median	17.30	-21.85	-35.84	-39.77	-44.81	-39.31	-32.97
20 mg	N	230	215	209	200	184	173	168
	Median	18.40	-29.26	-41.26	-42.43	-46.17	-42.86	-40.29
P-values for differences between median relative changes by Kruskal-Wallis Test								
		Placebo vs. 2.5mg			<0.0001			
		Placebo vs. 20mg			<0.0001			
		2.5mg vs. 20mg			0.0833			
Bone Specific Alkaline Phosphatase (U/L)								
Placebo	N	225	208	189	180	163	169	155
	Median	38.00	-8.03	-2.78	-0.91	-25.00	-3.70	38.10
2.5 mg	N	223	214	196	186	158	167	158
	Median	41.00	-22.87	-31.82	-32.63	-53.85	-38.64	0.00
20 mg	N	230	215	209	200	179	172	168
	Median	41.50	-28.57	-32.73	-31.37	-53.33	-36.64	-2.91
P-values for differences between median relative changes by Kruskal-Wallis Test								
		Placebo vs. 2.5mg			<0.0001			
		Placebo vs. 20mg			<0.0001			
		2.5mg vs. 20mg			0.5183			

Auxiliary Markers

Serum levels of intact parathyroid hormone were measured in a small subset of patients. No group- or time-specific changes were observed (Table below).

MF4411: Parathyroid Hormone - Relative Change (%) from Baseline over 3 Years (ITT)								
		Baseline	Relative Change to Baseline (%)					
			Month 3	Month 6	Month 12	Month 18	Month 24	Month 36
PTH (pmol/L)								
Placebo	N	49	42	35	30	31	36	32
	Median	4.40	-8.00	2.66	6.53	3.91	6.29	7.90
2.5 mg	N	41	40	26	32	31	30	30
	Median	4.20	-12.08	-2.38	8.61	0.00	1.52	-7.12
20 mg	N	45	44	36	37	35	33	31
	Median	3.90	-10.87	8.49	-5.00	5.71	0.00	0.00

MF4411: Parathyroid Hormone - Relative Change (%) from Baseline over 3 Years (ITT)						
P-values for differences between median relative changes by Kruskal-Wallis Test						
		Placebo vs. 2.5mg	0.4327			
		Placebo vs. 20mg	0.8935			
		2.5mg vs. 20mg	0.4273			

The ratio of urinary calcium to creatinine was measured in the same samples used for the measurement of CTX and NTX levels. Calcium excretion was increased over baseline levels in all 3 treatment groups throughout the duration of the study. This was a predictable consequence of the supplemental calcium administration. After 3 years there were no significant differences among groups in the increases in urinary calcium. There were also no significant differences among the treatment groups in 25-(OH)-Vitamin D levels after 3 years of treatment.

Bone Biopsy

Subjects participating in the bone biopsy analyses were drawn from the overall study population. Fourteen study sites were involved in the bone biopsy program. Each subject underwent a transiliac bone biopsy procedure at one time point during the study, at either Month 22 or Month 34. No paired biopsies (serial biopsies in the same patient) were performed.

The primary efficacy parameter for bone remodeling was mineralizing surface (MS). The median percent MS for the placebo group at Month 34 was lower than the median value at Month 22 (Table below). This suggests a progressive inhibitory effect on bone turnover, possibly due to calcium and vitamin D supplementation. The median values for MS in the 2.5 mg and 20 mg ibandronate groups were lower at month 22 (0.700 in the 2.5 mg group and 2.190 in the 20 mg group) than in the placebo group. At Month 34, the median MS value for the 2.5 mg ibandronate group was higher (1.985) than at the previous time point, but was still below that of placebo, suggesting a drug-induced reduction of bone turnover..

Supportive evidence for suppression of bone remodeling is provided by data for osteoid surface (OS), activation frequency (AcF) and bone formation rate (BFR), as shown in the table below. At Months 22 and 34, the median values for OS were lower in the ibandronate 2.5 mg group vs. placebo. Relative to placebo, the median values for AcF were approximately 50% lower in the ibandronate 2.5 mg group at Months 22 and 34. Bone formation rate (adjusted to total bone surface) was not significantly different at 22 months and 34 months in both ibandronate groups versus placebo.

MF4411:Bone Biopsy Parameters at Months 22 and 34						
	Placebo	2.5 mg	20 mg	Placebo	2.5 mg	20 mg
	22 months			34 months		
Mineralizing Surface						
N	14	16	15	19	20	16
Median	3.575	0.700	2.190	3 060	1.985	2.125
Osteoid Surface						
N	14	14	15	19	20	16
Median	7 350	4.050	4 700	5 900	4.450	7.150
Activation Frequency						
N	14	14	15	19	20	16
Median	0.200	0.054	0.125	0.236	0.120	0.133

MF4411:Bone Biopsy Parameters at Months 22 and 34						
	Placebo	2.5 mg	20 mg	Placebo	2.5 mg	20 mg
	22 months			34 months		
Bone Formation Rate						
N	14	14	15	19	20	16
Median	0.015	0.005	0.009	0.016	0.008	0.010

Medical Officer's Conclusions

This study demonstrated that 2.5 mg of once-daily oral ibandronate is effective in reducing new morphometric vertebral fractures over 3 years. While 9.6% of women in the placebo group had a new morphometric fracture, 4.7% of subjects in the 2.5 mg group($p=0.0003$) and 4.9% in the 20 mg group ($p=0.0005$) had such fractures. Clinical (i.e., symptomatic) vertebral fractures were also significantly reduced with ibandronate therapy [5.0% of placebo subjects vs. 2.8% of subjects in each of the ibandronate groups ($p=0.01$)]. The incidence of clinical non-vertebral fractures was not, however, impacted by ibandronate therapy.

Although treatment with placebo (vitamin D + calcium) led to a mean increase in LS BMD of 1.4% over the 3-year treatment period, the 2.5 mg and 20 mg ibandronate groups had much larger increases (5.0% ($p<0.0001$) and 4.3% ($p<0.0001$), respectively). In comparison to placebo, after 3 years of treatment, a statistically significant increase in BMD for all hip regions was also demonstrated for both ibandronate groups. That there were no differences between groups in the incidence of hip fractures is difficult to interpret due to the relatively small numbers of women at high risk for this type of fracture (i.e., age > 70 years, previous hip fracture).

Although the sponsor concluded that height loss in both ibandronate group was significantly less than that observed in the placebo group, the measurements were not standardized across the various study sites and the results should be viewed with great skepticism.

Ibandronate significantly suppressed bone resorption as assessed by excretion of NTX/creatinine and CTX/creatinine. In comparison to placebo, both active-treatment groups reached nadirs in bone resorption at 3–6 months and subsequently maintained these levels until the end of the study. Markers of bone formation were significantly reduced by 3–6 months after initiation of treatment, and remained so for the rest of the study.

Quantitative histomorphometric data of bone biopsies obtained at 22 or 34 months indicated that ibandronate had no adverse effects on either bone mineralization or microstructure. Osteoid surfaces, mineralizing surfaces, and mineral apposition rate confirmed that the rate of bone turnover was moderately reduced, without any mineralization defects.

VI.C.1.b. MF4348: This was a randomized, placebo-controlled, double blind, dose-finding, phase 2, single-center study of different oral doses (0.25, 0.5, 1.0, 2.5 and 5 mg/day) of ibandronate during 12 months' treatment in patients with postmenopausal osteoporosis.

The primary efficacy variable was the median relative change in BMD of the lumbar spine after 1 year of treatment. Secondary efficacy variables included change in BMD of the hip, and

relative change in biochemical markers of bone turnover (urinary calcium excretion, urinary pyridinoline excretion, urinary deoxypyridinoline excretion and urinary CTX excretion). Serum concentrations of ibandronate were also measured.

A total of 180 (30 in each group) postmenopausal women, age less than 75 years with a BMD T-score ≤ -1.5 at the distal forearm were enrolled in the trial. All baseline demographic parameters were balanced among groups. The mean age of subjects was 63 years and 100% were Caucasian. Lumbar spine BMD at baseline ranged from $0.85 - 0.91 gm/cm^2$.

At most skeletal sites, the changes in BMD associated with the 2.5 mg and the 5.0 mg doses were very similar and numerically greater than the changes associated with lower doses of active drug and placebo. The rate of withdrawal was 2-3 times higher for the 5.0 mg group compared with the lower doses and placebo. The overall incidence of gastrointestinal AEs, mainly those linked to the lower gastrointestinal tract, was also highest in the 5.0 mg group.

Data from this dose-ranging study indicate that the 2.5 mg daily dose of ibandronate has the most favorable benefit-to-risk ratio.

Please see Appendix XI.A.2. for the full study summary.

VI.C.1.c. MF4433: This was a randomized, double-blind, placebo-controlled, single-center, 2-year, phase 2 study. The active-treatment groups received either ibandronate 2.5 mg daily or 20 mg intermittently. Placebo-treated patients were crossed over to active treatment after 1 year.

The primary efficacy parameter was the change in LS BMD.

Two hundred and forty osteoporotic women were enrolled into the study. The treatment groups were well balanced with respect to baseline age, height, and weight profiles. The average age of subjects enrolled was 66.5 years and 100% were Caucasian. Two percent of subjects had a history of vertebral fracture and 43% had a history of nonvertebral fracture.

At Year 1, the relative increase in lumbar spine BMD was 1.21% in the placebo group, 4.83% in the daily 2.5 mg ibandronate group ($p<0.0001$) and 4.56% in the 20 mg intermittent ibandronate group ($p<0.0001$). Markers of bone resorption and bone formation were significantly suppressed after Year 1 ($p \leq 0.0001$) in both ibandronate treatment arms relative to the placebo.

Please see Appendix XI.A.1. for the full study summary

VI.C.1.d. 75003: This was a randomized, double-blind, phase 3, comparative study on the efficacy and safety of ibandronate during one year of treatment in patients with postmenopausal osteoporosis receiving an oral regimen of 2.5 mg ibandronate daily or 20 mg ibandronate weekly.

The objective of this study was to demonstrate non-inferiority of 20 mg oral ibandronate given once weekly, compared to 2.5 mg oral ibandronate given daily in increasing LS BMD and in reducing biochemical markers of bone turnover.

A total of 235 (121 2.5mg daily, 114 20mg weekly) postmenopausal subjects, less than 80 years old with a BMD T-score of ≤-2.0 were enrolled into the trial. Baseline demographic parameters were balanced between groups. The mean age of subjects was 65.7 years and 97% were Caucasian. The mean LS BMD T-score was – 2.9.

The 20 mg weekly dose was to be deemed non-inferior to the 2.5 mg daily dose if the lower bound of the 95% CI of the difference between groups in the mean changes from baseline to Week 48 in LS BMD was not greater than –1.65%. The average increases in LS BMD from baseline to Week 48 were 3.42% and 3.45% in the 2.5 mg and 20 mg groups, respectively. The difference between treatment means was 0.03% (-1.03, 1.10), and therefore the 20 mg weekly dose was deemed non-inferior to the 2.5 mg daily dose. Increases in hip BMD were also seen with similar magnitudes observed for the daily and weekly regimen. In addition, both regimens were shown to consistently and equally suppress bone turnover markers.

Please see Appendix XI.A.3. for the full study summary.

VI.C.1.e MF4491: This was a randomized, open-label, multicenter, phase 3, 12-month study of the efficacy and safety of oral ibandronate 2.5 mg taken either 30 or 60 minutes before breakfast.

The primary efficacy variable was the relative change in LS BMD after 48 weeks of treatment. Secondary efficacy variables included change in BMD of the hip, and change in biochemical markers of bone turnover (urinary CTX and serum osteocalcin).

A total of 213 (107 30-min, 106 60-min) postmenopausal women with established osteoporosis were enrolled into the trial. All baseline demographic variables were balanced between groups. The mean age of subjects was 65.1 years and 98% were Caucasian. The mean LS BMD T-score was – 3.1. Forty-two percent of subjects had prevalent osteoporotic fractures.

Both treatment groups had increases in LS BMD after 48 weeks, but the 30-minute fast group showed a smaller increase than the 60-minute group and did not meet the predefined criterion for non-inferiority. Similar results were obtained for hip BMD. A corresponding smaller decrease was observed in bone turnover markers for the 30-minute fasting group versus the 60-minute fasting group.

Please see Appendix XI.A.4. for the full study summary.

COMMENT: As discussed below, in study 4380, despite increases in LS BMD, intermittent intravenous ibandronate failed to meet the prespecified criteria for fracture efficacy (e.g., statistically significant reduction in morphometric vertebral fracture rate vs. placebo in an intent-to-treat population). To the extent that the results of 4380 affect the interpretation of study 4411 (pivotal oral fracture study), both studies are reviewed here.

VI.C.1.f MF4380 (iv): This was a randomized, double-blind, placebo controlled, multicenter, phase 3 study of the efficacy and safety of ibandronate over 3 years in patients with postmenopausal osteoporosis using an intermittent intravenous dosing regimen.

Objectives: The objective of this study was to investigate the efficacy and safety of ibandronate administered intravenously once every 3 months in the long-term treatment of postmenopausal osteoporosis.

Study Design: This trial was a randomized, double-blind, placebo-controlled 3-year multicenter study. Seventy-three centers participated in the study. The study design included a screening visit within 3 months prior to randomization and a 3-year treatment period following randomization. Subjects were randomized 1:1:1 into 3 parallel groups and treated as outpatients with either: an i.v. injection of 0.5 mg or 1.0 mg ibandronate or placebo once every 3 months for 36 months. All subjects received daily oral supplements of 400 IU vitamin D and 500 mg calcium. A full schedule of study assessments can be found in Appendix XI.B.2.a

Population: The study population comprised healthy postmenopausal women with low bone mass and 1–4 prevalent vertebral fractures.

Inclusion Criteria

- Age 55-80 years
- ≥ 5 years post menopause
- BMD T-score from -2.0 to -5.0 in at least one lumbar vertebra (L1–L4)
- One to four prevalent vertebral fractures in T4-L4

Exclusion Criteria

- BMD T-score below -5.0 in one or more lumbar spine vertebrae
- More than 2 fractures in the lumbar spine
- Disease known to influence bone metabolism
- Therapy with other drugs affecting bone metabolism within the last 6 months,
- Prior treatment with bisphosphonates at any time
- Prior treatment with fluoride
- Administration of any investigational drug within 30 days
- Renal impairment (serum creatinine > 210 µmol/L [2.4 mg/dL])
- Contra-indications for calcium or vitamin D therapy
- Serum calcium abnormalities
- Aspirin-sensitive asthma
- Prior treatment with aminoglycoside antibiotics within 4 weeks