treatment arm, while gastrointestinal pain led to the withdrawal of 2 patients from the weekly treatment arm.

Adverse Events: A similar incidence of AEs was observed in the daily (82%) compared to the weekly (78%) treatment arm. AEs were most commonly reported for the digestive, musculoskeletal, and general body systems for both the daily (33%, 26%, 23%) and weekly (28%, 28%, 29%) treatment regimens. The most commonly reported AEs in the ibandronate 2.5 mg daily group were upper respiratory infection (12%), dyspepsia (11%), arthralgia (7%), pain in extremity (7%), and constipation (7%). In the ibandronate 20mg weekly group the most commonly reported AEs were dyspepsia (10%), upper respiratory infection (9%), and hypertension (8%), arthralgia (7%) and accidental injury (7%). A summary of all AEs is provided in the table below.

Study 75003: Adverse Events		
	Iban 2.5mg qd	Iban 20mg qweek
N	121	114
At Least One AE	99 (82)	89 (78)
Cardiovascular System	15 (12)	12 (11)
Musculoskeletal System	31 (26)	32 (28)
Digestive System	40 (33)	32 (28)
Body as a Whole	28 (23)	33(29)
Skin and Appendages	9 (7)	11 (10)
Respiratory System	27 (22)	21 (18)
Urogenital System	12 (10)	10 (9)
Nervous System	15 (12)	13 (11)
Special Senses	8 (7)	9 (8)
Endocrine System	4 (3)	3 (3)
Heme and Lymphatic System	2 (2)	5 (4)
Metab and Nutrition System	10 (8)	8 (7)

Gastrointestinal Adverse Events: A similar frequency of gastrointestinal AEs was reported for the weekly and daily treatment groups. Dyspepsia was the most common gastrointestinal AE in both groups.

Study 75003: Gastrointestinal Adverse Events		
Adverse Event	**Iban 2.5mg qd**	**Iban 20mg qwk**
At least 1 GI AE	36 (30)	27 (24)
Dyspepsia, Dysphagia	14 (12)	11 (10)
Nausea	3 (2)	3 (3)
Diarrhea	5 (4)	4 (4)
Gastroenteritis	4 (3)	3 (3)
Gastrointestinal Pain	1 (1)	3 (3)
Esophagitis	0 (0.0)	0 (0.0)
Esophageal Ulcer	0 (0 0)	0 (0.0)
Esophageal Stenosis	0 (0.0)	0 (0.0)
Gastritis	0 (0.0)	1(1)
Peptic Ulcer	0 (0.0)	0 (0.0)
Gastrointestinal Carcinoma	0 (0.0)	0 (0.0)
Other GI disorder	20 (169)	7 (6)

Safety Laboratories: As summarized in the table below, 7 subjects in each of the two treatment arms experienced a marked laboratory abnormality during the study (some subjects had multiple abnormalities). No subjects experienced reoccurrence of marked laboratory abnormalities and the abnormal test values were not considered to be clinically significant.

Study 75003: Markedly Abnormal Lab Values		
Laboratory	**Iban 2.5mg qd**	**Iban 20mg qwk**
N		
Hematocrit – low	1(0.8)	1 (0.9)
Hemoglobin – low	0	1 (0.9)
WBC - low	1(0.8)	1 (0.9)
Neutrophils -low	1(0.8)	1 (0.9)
Lymphocytes - low	2 (1.6)	5 (3.5)
GGT - high	3 (2.5)	0
Chloride – low	0	1 (0.9)

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VII.C.1.e. Study MF4491: This was a randomized, open-label,12-month study of the efficacy and safety of oral ibandronate 2.5 mg daily taken either 30 or 60 minutes before breakfast. A total of 213 (107 in 30-min, 106 in 60-min) subjects with established osteoporosis were enrolled into the trial. All demographic parameters were balanced between groups. The mean age of subjects was 65.1 years with a range of 55 years – 78 years. The mean time since menopause was 16.8 years and the mean LS T-score was – 3.1.

Safety Measurement Adverse events were elicited and monitored via non-direct questioning at every clinic visit. Laboratory evaluations included hematology: hemoglobin, hematocrit, platelet counts, red blood cells, white blood cells, neutrophils, lymphocytes, monocytes, eosinophils, basophils and blood chemistries: serum electrolytes (calcium, phosphorus, sodium, potassium, chloride), biochemical assessments [alkaline phosphatase, ALT, γ-glutamyl transferase (GGT)], blood urea nitrogen (BUN), and creatinine.

Withdrawals: Of the 213 subjects enrolled in the study, 25 withdrew prematurely (10 (9%) from the 30 min group and 15 (14%) from the 60min group. Withdrawals were evenly distributed between the two treatment arms of the study.

Study MF4491: Withdrawals		
	30min	60min
N	107	106
W/D AE	10 (9.3)	11 (10.3)
W/D other	0 (0.0)	4 (3.7)
Completed	97 (90.6)	91 (85.8)

Patient Exposure The mean total exposure to active drug was 805mg.

Study MF4491: Exposure			
	Total	30min	60min
N	213	107	106
mean	322.41	329.36	315.39
SD	83.68	73.12	92.96
median	349	350	349

Death No deaths were reported during this study.

Serious Adverse Events A total of eleven subjects experienced thirteen SAEs during the study. Ten of these SAEs required hospitalization. The numbers of subjects with SAEs were similar between the two treatment groups: six patients in the 30-minute group and five patients in the 60-minute group. Of a total of 13 SAEs, osteoporosis fracture was the most frequently reported. Osteoporosis fractures were reported for four patients, two in each treatment group.

Study MF4491: Serious Adverse Events		
	30 min fast	60 min fast
Number of SAEs (# patients)	8 (6)	5 (5)
Osteoporotic Fracture	2 (1.9)	2 (1.9)
Arthrosis	1 (0.9)	-

Study MF4491: Serious Adverse Events		
	30 min fast	60 min fast
Depression	1 (0.9)	-
Dizziness	1 (0.9)	-
Breast Carcinoma	-	1 (0.9)
Skin Carcinoma	-	1 (0.9)
Chest Pain	1 (0.9)	-
Palpitations	1 (0.9)	-
Pharyngitis	1 (0.9)	-
Urogenital d/o	-	1 (0.9)

Adverse Events Leading to Withdrawal A total of 21 (9.8%) subjects withdrew from the study due to AEs. The withdrawal rates were similar between the two treatment groups. Among the 16 different AEs causing early withdrawals, only four involved more than one patient. These four AEs each involved two patients and were gastritis, gastrointestinal pain, dyspepsia, and depression.

Adverse Events Overall, the number of patients who experienced an AE was greater in the 30-minute group (84%) than in the 60-minute group (69%). The number of patients and reported AEs were similar for both treatments except for the body as a whole system, where a greater number of patients in the 30-minute group experienced an AE than in the 60-minute group. The most commonly reported events in the body system body as a whole were accidental injury, back pain, and pain in extremity. The most frequently reported AEs, in descending order of frequency, were upper respiratory tract infection, headache, and dyspepsia. The incidence of these AEs was similar in both treatment groups except for diarrhea. Diarrhea was reported for seven patients in the 60-minute group, as compared to only one patient in the 30-minute group.

Gastrointestinal Adverse Events: A total of 20 (18.7%) subjects in the 30-min group and 26 (24.5%) subjects in the 60-min group reported gastrointestinal adverse events. Dyspepsia (3.7% vs. 8.5%) and diarrhea (0.9% vs. 6.6%) were more common in the 60-min group. There were no reports of gastritis or esophagitis in either treatment group.

Safety Laboratories: There were no significant changes in laboratory values in either treatment group. There were 12 marked laboratory abnormalities in 11 subjects: five in the 30-minute group and six in the 60-minute group. Alterations in serum levels of phosphate levels were seen in four subjects, low lymphocyte counts in three subjects, high GGT levels in three subjects, and a low platelet count, a low neutrophil count, and a high serum potassium each were observed in a single subject.

VII.C.2. Safety Evaluation of the Prevention Trials

VII.C.2.a. Study MF4499: This was a dose-finding study of the efficacy and safety of ibandronate for prevention of bone loss in postmenopausal women during 2-years' treatment, using a continuous oral dosing regimen (0.5, 1.0, or 2.5 mg daily) A total of 653 subjects were enrolled at 11 study centers. Subjects were assigned to one of four strata (based on BMD and time since menopause), then randomized into four treatment groups: 162 in the placebo, 162 in 0.5 mg, 166 in 1.0 mg, and 163 in the 2.5 mg groups. The baseline demographics were balanced across the four treatment groups. The average age was 58 years and the average LS T-score was −1.0. Across the strata, baseline demographics for the treatment groups were also balanced.

Safety Measurements: Clinical adverse events were monitored continuously throughout the study. Adverse events of special interest included gastrointestinal symptoms, fever exceeding 38.5°C or bone pain, muscle ache-like pain, and flu-like symptoms. Laboratory assessments included serum electrolytes (calcium, chloride, potassium, phosphorus, sodium), and hematology (hemoglobin, hematocrit, white and red blood cell, neutrophil, lymphocyte, monocyte, eosinophil, basophil, and platelet counts). Biochemical assessments for liver function consisted of total AP, ALT, and GGT; serum creatinine was assessed for renal function. Concentrations of 25-hydroxy-cholecalciferol (vitamin D) were also assessed in all patients.

Withdrawals: Of the 648 subjects who received at least one dose of study medication, 547 (84.4%) completed the full two years of treatment. Withdrawals from the study were evenly distributed among the treatment groups (Table below).

Study MF4499: Withdrawals				
	Placebo	Iban 0.5mg qd	Iban 1.0mg	Iban 2.5mg
N	159	161	165	163
W/D AE	14 (9%)	8 (5%)	9 (5%)	12 (7%)
W/D Other	13 (8%)	15 (9%)	12 (7%)	18 (11%)

Patient Exposure: The mean total exposure to active drug was 328 mg in the 0.5 mg daily group, 662 mg for the 1.0 mg daily group and 1575 mg for the 2.5 mg daily group (Table below).

Study MF4499: Exposure (days)				
	Placebo	Iban 0.5mg qd	Iban 1.0mg	Iban 2.5mg
N	159	161	165	163
mean	630.4	655.9	662.3	630.2
SD	226.91	191 88	185.58	216.62
median	728.0	729.0	728.0	728.0

Deaths: One death occurred during the study period. A second death occurred 56 days after withdrawal from the study. A 78-year-old woman in the ibandronate 1.0 mg group died on study Day 103 due to sudden death. A 67-year-old woman in the ibandronate 2.5 mg group died 56 days after premature withdrawal from the study due to gastrointestinal carcinoma.

Serious Adverse Events As outline in the table below, a total of 68 subjects (10.5%) experienced SAEs, most of whom were in the 1.0 mg and 2.5 mg groups. Musculoskeletal, cardiovascular, and gastrointestinal SAEs were the most common and occurred more frequently in the higher ibandronate dose groups. Five subjects prematurely withdrew from the study due to a serious AE.

Study MF4499: Serious Adverse Events				
	Placebo	Iban 0.5mg qd	Iban 1.0mg qd	Iban 2.5mg qd
N	159	161	165	163
At Least One SAE	13 (8)	10 (6)	21 (13)	24 (15)
Cardiovascular System	2 (1)	2 (1)	6 (4)	5 (3)
Musculoskeletal System	2 (1)	3 (2)	3 (2)	6 (4)
Digestive System	2 (1)	3 (2)	2 (1)	5 (3)
Body as a Whole	0	1 (1)	3 (2)	2 (1)
Skin and Appendages	3 (2)	2 (1)	4 (2)	4 (2)
Respiratory System	2 (1)	0	0	2 (1)
Urogenital System	3 (2)	2 (1)	4 (2)	3 (2)
Nervous System	0	0	0	2 (1)
Special Senses	0	2 (1)	0	2 (1)
Endocrine System	0	0	2 (1)	0
Heme and Lymphatic System	0	0	2 (1)	0
Metab and Nutrition System	2 (1)	0	0	0

Adverse Events Leading to Withdrawal: A total of 42 patients prematurely withdrew from study treatment (patient deaths were not included). The incidence of withdrawals due to AE was slightly greater in the placebo and 2.5 mg groups (9% and 7%, respectively) than for the other 2 groups (5%). Gastrointestinal adverse events were most common and were highest in the placebo group. The table below outlines all adverse events leading to withdrawal.

Study MF4499: Adverse Events Leading to Withdrawal				
	Placebo	Iban 0.5mg qd	Iban 1.0mg qd	Iban 2.5mg qd
N	159	161	165	163
At Least One AE	14 (9)	8 (5)	8 (5)	12 (7)
Cardiovascular System	1 (1)	1 (1)	0	1 (1)
Musculoskeletal System	1 (1)	0	2 (1)	1 (1)
Digestive System	11 (7)	7 (4)	5 (3)	6 (4)
Body as a Whole	2 (1)	2 (1)	2 (1)	1 (1)
Skin and Appendages	1 (1)	0	1 (1)	1 (1)
Respiratory System	1 (1)	0	0	0
Urogenital System	1 (1)	0	0	0
Nervous System	3 (2)	0	2 (1)	3 (2)
Special Senses	1 (1)	0	0	1 (1)
Endocrine System	0	0	2 (1)	0
Heme and Lymphatic System	0	0	2 (1)	0
Metab and Nutrition System	0	0	2 (1)	0

Adverse Events: The overall rates of adverse events were similar in all 4 groups. Body systems for which ≥ 20% of the patients in any group reported AEs were the respiratory system, the digestive system, body as a whole, and the musculoskeletal and nervous systems. The most frequently reported AEs in all ibandronate dose groups were upper respiratory infection, dyspepsia, arthralgia, sinusitis, accidental injury, back pain, and headache. The incidence of diarrhea, asthenia, myalgia, and tenosynovitis were slightly higher in the ibandronate groups as compared to placebo.

Study MF4499: Adverse Events				
	Placebo	Iban 0.5mg qd	Iban 1.0mg qd	Iban 2.5mg qd
N	159	161	165	163
At Least One SAE	148 (93)	148 (92)	156 (95)	159 (98)
Cardiovascular System	22 (14)	25 (16)	19 (12)	24 (15)
Musculoskeletal System	60 (38)	51 (32)	66 (40)	68 (42)
Digestive System	82 (52)	75 (47)	64 (39)	85 (52)
Body as a Whole	70 (44)	77 (48)	83 (50)	69 (42)
Skin and Appendages	26 (16)	22 (14)	35 (21)	28 (17)
Respiratory System	94 (59)	81 (50)	92 (56)	94 (58)
Urogenital System	31 (19)	29 (18)	30 (18)	28 (17)
Nervous System	51 (32)	39 (24)	46 (28)	49 (30)
Special Senses	22 (14)	13 (8)	24 (15)	18 (11)
Endocrine System	8 (5)	7 (7)	11 (7)	7 (4)
Hemic and Lymphatic System	9 (6)	15 (9)	11 (7)	7 (4)
Metab and Nutrition System	23 (14)	25 (16)	31 (19)	24 (15)

Gastrointestinal Adverse Events: As indicated in the table below, gastrointestinal adverse events were most frequent in the placebo and ibandronate 2.5 mg groups. Dyspepsia was the most frequent event and was evenly distributed among all treatment groups.

Study MF4499: Gastrointestinal Adverse Events				
	Placebo	Iban 0.5mg qd	Iban 1.0mg qd	Iban 2.5mg qd
N	159	161	165	163
At Least One GI AE	82 (52)	75 (47)	64 (39)	85 (52)
Dyspepsia	22 (14)	25 (16)	23 (14)	25 (15)
Dysphagia	0	3 (2)	1 (1)	1 (1)
Nausea	5 (3)	10 (6)	2 (1)	6 (4)
Diarrhea	5 (3)	7 (4)	13 (8)	10 (6)
Constipation	11 (7)	5 (3)	8 (5)	13 (8)
Gastroenteritis	10 (6)	15 (9)	6 (4)	8 (5)
Gastrointestinal pain	6 (4)	3 (2)	0	6 (4)
Esophagitis	2 (1)	1 (1)	0	1 (1)
Hemorrhagic Gastritis	0	1 (1)	0	0
Peptic Ulcer	2 (1)	1 (1)	0	0
Gastrointestinal Hemorrhage	1 (1)	0	0	0
Melena	0	0	2 (1)	1 (1)
Gastrointestinal Carcinoma	0	0	0	1 (1)
Other GI disorder	45 (28)	37 (23)	36 (22)	65 (40)

Safety Laboratories: There were no clinically significant changes from baseline values in any laboratory variable for each of the four treatment groups. As expected, AP concentrations decreased in the 1.0 mg and 2.5 mg groups. A similar effect was not seen in the 0.5 mg or placebo groups. Liver and kidney function tests remained normal for all groups, as indicated by ALT, GGT, and serum creatinine concentrations, and there were no meaningful changes in mean serum calcium levels. Serum 25(OH) vitamin D concentrations for all groups decreased slightly from baseline. Few patients demonstrated marked laboratory abnormalities over the course of the study Those parameters for which marked laboratory abnormalities were reported showed a similar incidence across the treatment groups. The most frequently reported abnormalities involved low levels of lymphocytes and neutrophils, affecting approximately 5-7% of patients in each group. Only one patient, in the 0.5 mg group, had low serum calcium, which met the criteria for a marked laboratory abnormality.

VII.C.2.b. Study MF4500: This was a randomized, double-blind, placebo-controlled, dose-finding study of the efficacy and safety of ibandronate during 2 years' treatment in postmenopausal women for prevention of postmenopausal bone loss, using an intermittent oral (5 mg, 10 mg, 20 mg per week) dosing regimen. A total of 630 (158 in placebo, 159 in 5 mg, 154 in 10 mg and 159 in 20 mg) subjects were enrolled into the trial. Subjects were 1 – 10 years past last menstruation and were stratified based on time since menopause and bone mineral density prior to randomization. All demographic parameters were balanced between groups and strata. The mean age of subjects was 55.0 years, the mean time since menopause was 4.5 years, and the mean LS T-score was – 1.1.

Safety Measurements: Clinical adverse events were monitored continuously throughout the study. Adverse events of special interest included gastrointestinal symptoms, fever exceeding 38.5°C or bone pain, muscle ache-like pain, and flu-like symptoms. Laboratory assessments included serum electrolytes (calcium, chloride, potassium, phosphorus, sodium), and hematology (hemoglobin, hematocrit, white and red blood cell, neutrophil, lymphocyte, monocyte, eosinophil, basophil, and platelet counts). Biochemical assessments for liver function consisted of total AP, ALT, and GGT; serum creatinine was assessed for renal function. Concentrations of 25-hydroxy-cholecalciferol (vitamin D) were also assessed in all patients.

Withdrawals: Of the 630 subjects enrolled into the study, 8 received no study medication and 82 (13.2%) withdrew prematurely. Withdrawals were slightly higher in the ibandronate-treated groups than in the placebo-treated group.

Study MF4500: Withdrawals				
	Placebo	Iban 5mg	Iban 10mg	Iban 20mg
N	156	155	153	158
W/D AE	5 (3%)	10 (6.5%)	8 (5%)	9 (6%)
W/D Other	7 (4%)	10 (6.5%)	10 (7%)	16 (10%)

Patient Exposure The mean total exposure to active drug was 328 mg in the 5 mg weekly group, 662 mg for the 10 mg weekly group, and 1575 mg for the 20 mg weekly group.

Study MF4500: Exposure (days)				
	Placebo	Iban 5mg	Iban 10mg	Iban 20mg
N	156	155	153	158
mean	659.0	661.6	670.0	648.3
SD	181.62	184.96	164.12	192.57
median	722.0	728.0	728.0	721.0

Death: There were no deaths during the study.

Serious Adverse Events: A total of 78 patients (12.5%) experienced SAEs, distributed equally among the four treatment groups. The majority of the SAEs (26%) occurred in the cardiovascular system, with equal distribution across the treatment groups. Six patients withdrew from the study due to serious AEs (Table below).

Study MF4500: Serious Adverse Events				
	Placebo	Iban 5mg	Iban 10mg	Iban 20mg
N	156	155	153	158
At Least One SAE	19 (12)	21 (14)	19 (12)	19 (12)
Cardiovascular System	5 (3)	5 (3)	4 (3)	6 (4)
Musculoskeletal System	3 (2)	3 (2)	-	2 (1)
Digestive System	4 (3)	4 (3)	2 (1)	4 (3)
Body as a Whole	3 (2)	2 (1)	2 (1)	3 (2)
Skin and Appendages	3 (2)	3 (2)	4 (3)	2 (1)
Respiratory System	2 (1)	1 (1)	3 (2)	-
Urogenital System	-	2 (1)	2 (1)	3 (2)
Nervous System	1 (1)	2 (1)	1 (1)	1 (1)
Special Senses	-	1 (1)	-	-
Endocrine System	1 (1)	1 (1)	-	-
Heme and Lymphatic System	-	-	2 (1)	-
Metab and Nutrition System	1 (1)	1 (1)	-	1 (1)

Adverse Events Leading to Withdrawal: A total of 29 subjects withdrew from study treatment due to an AE. The incidence of withdrawal due to an AE was similar in all active-treatment groups (5%) compared to the placebo group (3%).

Study MF4500: Adverse Events Leading to Withdrawal				
	Placebo	Iban 5mg	Iban 10mg	Iban 20mg
N	156	155	153	158
At Least One AE	5 (3)	8 (5)	8 (5)	8 (5)
Cardiovascular System	2 (1)	-	-	1 (1)
Musculoskeletal System	-	1 (1)	1 (1)	3 (2)
Digestive System	1 (1)	3 (2)	2 (1)	1 (1)
Body as a Whole	1 (1)	1 (1)	1 (1)	-
Skin and Appendages	-	0	1 (1)	1 (1)
Respiratory System	1 (1)	1 (1)	3 (2)	-
Urogenital System	-	0	1 (1)	2 (1)
Nervous System	1 (1)	2 (1)	1 (1)	-
Special Senses	-	-	-	-
Endocrine System	-	-	-	-
Heme and Lymphatic System	-	-	-	-
Metab and Nutrition System	-	-	-	-

Adverse Events: As shown in the table below, the overall rates of adverse events were similar in all 4 groups. Body systems for which >20% of the patients in any group reported AEs were the respiratory system, digestive system, body as a whole, musculoskeletal system, and nervous system. A difference between treatment groups was observed for the musculoskeletal system, with adverse events higher in the ibandronate groups compared to the placebo group. The difference was mainly due to a higher frequency of myalgia, tenosynovitis, and osteoporosis fractures in the active-treatment groups. The most frequently reported AE in all treatment groups was upper respiratory infection, with no difference in the incidence for the active-treatment groups compared to placebo. Individual AEs observed more frequently in the active-treatment groups were back pain, bronchitis, sinusitis, gastroenteritis, osteoporosis fracture, cystitis,

gastrointestinal pain, myalgia, cholelithiasis, and periodontal abscess (only higher in 20 mg group).

Study MF4500: Adverse Events				
	Placebo	Iban 5mg	Iban 10mg	Iban 20mg
N	156	155	153	158
At Least One AE	113 (72)	123 (79)	124 (81)	120 (76)
Cardiovascular System	17 (11)	14 (9)	23 (15)	20 (13)
Musculoskeletal System	16 (10)	23 (15)	35 (15)	34 (22)
Digestive System	32 (21)	48 (31)	37 (24)	40 (25)
Body as a Whole	21 (13)	32 (21)	28 (18)	33 (21)
Skin and Appendages	17 (11)	13 (8)	23 (15)	13 (8)
Respiratory System	65 (42)	76 (49)	76 (50)	68 (43)
Urogenital System	12 (8)	19 (12)	16 (10)	18 (11)
Nervous System	24 (15)	26 (17)	32 (21)	19 (12)
Special Senses	7 (4)	13 (8)	6 (4)	8 (5)
Endocrine System	4 (3)	3 (2)	4 (3)	0
Heme and Lymphatic System	1 (1)	5 (3)	5 (3)	1 (1)
Metab and Nutrition System	11 (7)	8 (5)	8 (5)	6 (4)

Gastrointestinal Adverse Events: Gastrointestinal events were evenly distributed among all treatment groups (Table below).

Study MF4500: Gastrointestinal Adverse Events				
	Placebo	Iban 5mg	Iban 10mg	Iban 20mg
N	156	155	153	158
At Least One GI AE	32 (21)	48 (31)	37 (24)	40 (25)
Dyspepsia	4 (3)	3 (2)	6(4)	3 (2)
Dysphagia	-	1 (1)	1 (1)	-
Nausea	2 (1)	9 (6)	5 (3)	3 (2)
Diarrhea	4 (3)	3 (2)	5 (3)	5 (3)
Constipation	1 (1)	3 (2)	3 (2)	-
Gastroenteritis	4 (3)	9 (6)	2 (1)	9 (6)
Gastrointestinal pain	1 (1)	7 (5)	5 (3)	6 (4)
Esophagitis	-	1 (1)	1 (1)	-
Gastritis	2 (1)	2 (1)	2 (1)	1 (1)
Hemorrhagic Gastritis	-	1 (1)	-	-
Peptic Ulcer	-	1 (1)	-	-
Duodenal Ulcer	-	-	-	1 (1)
Other GI disorder	17 (11)	24 (15)	14 (9)	25 (16)

Safety Laboratories There were no clinically significant changes from baseline values in any safety laboratory variable in each of the four treatment groups. Liver and renal function test values remained normal for all groups. Few subjects demonstrated marked laboratory test abnormalities over the course of the study. There were no clinically relevant shifts in any of the safety parameters.

VII.D. Adequacy of Safety Testing

The safety monitoring conducted during the phase 2/3 clinical trials appears to have been adequate. Appropriate attention was given to analyses of upper GI adverse events and bone histomorphometry. Serum calcium and phosphorus levels were measured with adequate frequency, but serum magnesium levels were not included as part of routine chemistry evaluations. Hypomagnesemia is less of a concern with oral than with i.v. bisphosphonate use[1],[2]; nevertheless, it would probably be worthwhile for Roche to examine serum magnesium levels in future studies of oral ibandronate.

VII.E. Four Month Safety Update

This safety update includes safety information from the recently completed phase 1/2 study BP 16331 and newly initiated and ongoing studies BM 16549 and BM16550, whose results remain blinded.

Study BP 16331: This was a randomized, double-blind, parallel-group, placebo-controlled, multicenter study, of three months duration, and was carried out in Europe. The objective of this study was to investigate the tolerability and safety of three different monthly doses of ibandronate compared to placebo. The bioavailability of the oral doses of ibandronate relative to the 50-mg tablet, and the effect of three monthly oral doses on bone turnover markers compared to placebo were also assessed. One hundred forty four subjects were randomized into one of 5 treatment groups: placebo (36 subjects), 50mg (18 subjects), 50/100mg (18 subjects), 100mg (36 subjects) and 150mg (36 subjects). Subjects in the 50/100mg group received 50 mg for the 1st dose and 100 mg for the 2nd and 3rd doses. The baseline demographic characteristics were similar across the treatment groups. The mean age ranged from 61.7 years to 65.7 years and >97% of subjects were Caucasian. Four women withdrew prematurely from the study (3-placebo, 1-150mg). There were no deaths in the study. No serious adverse events were reported in the study. Three subjects withdrew because of adverse events [2 in the placebo group (aching forearm/tendonitis and cough/nasopharyngitis/nausea/throat irritation) and one in the 150mg group (backache/chemistry abnormal)]. Overall, adverse events were similar between the groups (94% of the placebo group, 100% of the 50mg group, 94% of the 50/100mg group, 92% of the 100mg group and 89% of the 150mg group). Gastrointestinal adverse events occurred in 47% of the placebo group, 50% of the 50mg group, 56% of the 50/100mg group, 50% of the 100mg group and 58% of the 150mg group. There were a small number of isolated, non-replicated laboratory changes in individual patients in the placebo and ibandronate groups. There was no difference between the placebo and ibandronate groups in the nature or frequency of these changes. In particular, there were no abnormalities of renal function or calcium.

Study BP16549: This was a randomized, double-blind, multicenter study of two years duration. The objective of this study was to investigate the efficacy and safety, and to demonstrate non-inferiority of lumbar spine BMD at 1-year of an oral dose of 100 mg ibandronate taken monthly on a single day, versus 100 mg oral ibandronate monthly divided over two consecutive days (50

[1] Young G. Use of pamidronate in the management of acute cancer-related hypercalcemia in children. *Med. Pediatr. Oncol.* 1998 Jul;31(1) 39.

[2] Elisaf M. Multiple electrolyte abnormalities after pamidronate administration. *Nephron* 1998;79(3):337-9.

mg/day), versus 150 mg oral ibandronate taken monthly on a single day, versus an active control, oral 2.5 mg oral ibandronate daily. A total of 932 (of a planned 1592) subjects have been randomized. One subject suffered a stroke on day 60 of the study and died on day 103. Serious adverse events have been reported in an additional 6 subjects (pneumonia, acute MI, melena, femoral pseudoaneurysm, cystectomy-right knee and pseudoarthritis) The drug code has not been broken for any of these seven individuals. Twelve subjects (excluding the subject that died) have withdrawn from the study because of adverse events.

Study BP16550: This is a randomized, double blind, multicenter study of two years duration. The objective of this study is to investigate the efficacy and safety, and to demonstrate non-inferiority of lumbar spine BMD at 1-year of 2 mg ibandronate given intravenously every two months versus 3 mg ibandronate given intravenously every three months, versus an active control, 2.5 mg oral ibandronate daily. A total of 89 (of a planned 1194) subjects have been randomized and there were no deaths, serious adverse events or premature withdrawals from treatment due to adverse events reported in this study as of August 31, 2002.

Post Marketing Update: The post-marketing adverse events reported for ibandronate mainly result from the i.v. formulation used in the treatment of hypercalcemia of malignancy. Between December 1, 2001 and August 31, 2002, no new spontaneous adverse event reports have been received.

VII.F. Summary of Critical Safety Findings and Limitations of Data

More than 3500 subjects were exposed to at least one dose of oral ibandronate during the conduct of the 7 phase 2/3 clinical trials; over 1600 individuals received 2.5 mg daily – the dose proposed for marketing. The majority of the patient-years of exposure come from the pivotal, placebo-controlled treatment trial MF4411. This study therefore provides the bulk of the safety data for the 2.5 mg daily dose of ibandronate. Two additional, though shorter, placebo-controlled treatment trials (MF4348 and MF4433), and the pivotal, 2-year placebo-controlled prevention trial MF4499 provide important ancillary safety information.

There were no unexpected safety findings uncovered during the review of this NDA. The percentage of subjects who died on-treatment was similar for the ibandronate 2.5 mg and placebo-treated women. While the percentage of patients who experienced at least one serious adverse event was slightly higher in ibandronate 2.5 mg vs. placebo subjects from study MF4411, the opposite was true for the two ancillary treatment trials, MF4348 and MF4433. Serious adverse events were also reported more often in ibandronate-treated women than placebo-treated women in the prevention trial MF4499. This was due in large part to more reports from the cardiovascular system; yet there were no meaningful imbalances between groups in the rates of specific cardiac events. The rates of premature withdrawal due to adverse events were very similar between the ibandronate and placebo groups in all 4 trials mentioned above.

Of note, a recently published report reviewed the findings of ocular inflammation in patients on bisphosphonate therapy[3]. In study MF4411, there were no reports of uveitis or scleritis. The incidence of nonspecific conjunctivitis was low overall but slightly higher in the daily ibandronate group (10 subjects (1.0%) in the daily group, 6 subjects (0.6%) in the 20mg intermittent group and 5 subjects (0.5%) in the placebo group).

VIII. Dosing, Regimen, and Administration Issues

Roche is requesting approval of a single oral dose of ibandronate – 2.5 mg daily. Data from phase 2/3 dose-ranging studies indicate that, compared with the 5.0 mg daily dose of ibandronate, 2.5 mg daily is associated with similar increases in BMD and similar suppression of bone markers, yet lower rates of serious GI adverse events. These findings support the choice of the 2.5 mg daily dose as the most appropriate for marketing.

In a phase 3 pharmacodynamic study, it was clearly shown that women who follow a 60-minute post-dose fast have larger increases in BMD and greater suppression of bone markers than do women who follow a 30-minute post-dose fast. The company's proposal to recommend a 60-minute post-dose fast in the labeling is therefore appropriate.

IX. Use in Special Populations

IX.A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Ibandronate is intended for the treatment and prevention of postmenopausal women with osteoporosis. All of the subjects enrolled in these seven phase 2/3 trials were women.

IX.B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Extensive population pharmacokinetic / pharmacodynamic investigations 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.

IX.C. Evaluation of Pediatric Program

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

[3] Fraunfelder FW. Bisphosphonates and ocular inflammation. *N Engl J Med.* 2003. 348 (12):1187.

X. Conclusions and Recommendations

X.A. Conclusions

Roche has provided sufficient evidence to satisfy the requirements for approval of ibandronate 2.5 mg daily for the treatment and prevention of postmenopausal osteoporosis.

In the pivotal treatment study MF4411, ibandronate, relative to placebo, reduced the 3-year risk for morphometric vertebral fracture from 9.6% to 4.7%. The 2.5 mg daily regimen also significantly reduced the incidence of clinical or symptomatic vertebral fractures, but did not affect the risk for non-vertebral osteoporotic fractures. In the pivotal prevention study 4499, ibandronate 2.5 mg daily, relative to placebo, increased BMD of the lumbar spine and hip by 3.0 and 2.0%, respectively.

No significant safety issues were raised by the submitted data.

X.B. Recommendations

These Reviewers recommend approval of ibandronate 2.5 mg daily for the prevention and treatment of PMO.

/S/

Theresa Kehoe, MD

/S/

Eric Colman, MD

XI. Appendix

XI.A. Detailed Review of Ancillary Studies

XI.A.1. MF4433: This is a Phase 2, 2-year, single-center, double-blind, randomized, parallel group, placebo-controlled study. Placebo patients were crossed over to active treatment after 1 year.

Objectives, Study Design, and Patient Population: The objective of this study was to investigate the efficacy and safety of intermittent oral and continuous oral administration of ibandronate in the long-term treatment of postmenopausal osteoporosis. The primary efficacy variable was the relative change in lumbar spine BMD from baseline to Year 2. Secondary efficacy variables included change in BMD of the hip and forearm, and the relative change in biochemical markers of bone turnover (urinary calcium excretion, urinary NTX excretion, urinary CTX excretion, serum osteocalcin, serum alkaline phosphatase, bone specific alkaline phosphatase and parathyroid hormone).

A total of 240 subjects were enrolled in the trial: 81 placebo, 81 2.5 mg daily, 78 20 mg intermittently). Subjects were at least 5 years since last menstruation, age 55 - 75 years and had a BMD T-score $\leq$-2.5. Exclusion criteria included: renal impairment or metabolic bone disease. For year one, subjects were randomized into three parallel groups and treated as out-patients with either placebo, 2.5 mg ibandronate daily or 20 mg ibandronate intermittently (12 doses every other day at the start of a 3 month cycle). For year 2, those on placebo were randomized to begin either ibandronate 2.5 mg daily or ibandronate 20 mg intermittently. Those patients initially randomized to treatment with ibandronate did not change therapy. Bone mineral density measurements were done at baseline, 6 months, 12 months and 24 months. A full schedule of assessments is listed below.

MF4433: Schedule of Assessments

	Screening period	Treatment period														
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Month	≥-1	0	1	2	3	4	6	7	9	10	11	12	15	18	21	24
Inclusion/exclusion criteria	x	x														
Medical history	x															
Written informed consent	x															
Randomization		x														
Distribution of study medication		x			x		x		x			x	x	x	x	
Distribution of concomitant medication		x			x		x		x			x	x	x	x	
Compliance check					x		x		x			x	x	x	x	x
BMD		x			x		x		x			x	x	x	x	x
Laboratory tests I(efficacy)		x	x	x	x		x		x	x	x	x	x	x	x	x
Laboratory tests II (safety) -	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events		Continuous recording														
Concomitant medication		Continuous recording														
Final assessment																x

Results: Of the 240 subjects enrolled in the trial, 32 subjects withdrew in Year 1 (9 in placebo, 11 in 2.5 mg, 12 in 20 mg). An additional 21 subjects withdrew during Year 2 leaving

approximately 225 patients with sufficient data for inclusion in the ITT analyses. No subjects were excluded from the analyses due to the violation of inclusion or exclusion criteria. While minor violations of the inclusion and exclusion criteria did occur, these were not felt to have a clinically relevant impact on the study outcome.

The treatment groups were well balanced with respect to age, height, and weight profiles at baseline. The average age of subjects enrolled was 66.5 years and 100% were Caucasian. Two percent of subjects had a history of a vertebral fracture and 43% had a history of non-vertebral fracture.

The relative increase in lumbar spine BMD in both the 2.5 mg ibandronate daily (4.83%) and 20 mg ibandronate intermittent (4.56%) arms was significantly superior to placebo (1.21%) (p<0.0001). Bone mineral density increased by 5.2% and 6.4% relative to baseline in the daily and intermittent treatment arms respectively at Year 2. Bone mineral density increases relative to placebo were observed after 1 year for total hip, trochanter and intertrochanter in patients in the 2.5 mg ibandronate daily and 20 mg ibandronate intermittent arms (p <0.0001). Significant changes in BMD relative to placebo were not evident for the femoral neck, Ward's triangle, distal forearm or ultradistal forearm.

MF4433: BMD Changes at One Year						
	Median Percent Change			Statistical Tests		
				Kruskal-Wallis	Wilcoxon	Wilcoxon
Measured Site	Placebo	2.5mg daily	20mg int	all groups	Iban daily vs. Placebo	Iban int vs. Placebo
Lumbar Spine (L2-L4)	1.209	4.830	4.560	P<0.0001	P<0.0001	P<0.0001
Total Hip	0.431	2.582	3.199	P<0.0001	P<0.0001	P<0.0001
Trochanter	1.084	2.962	3.315	P<0.0001	P=0.0001	P<0.0001
Intertrochanter	0.219	2 445	2.379	P<0.0001	P<0.0001	P<0.0001
Femoral Neck	0 670	1 481	1.414	P=0 4431	P=0.3268	P=0.2369
Ward's Triangle	4.861	3.915	5 008	P=0 4410	P=0.9955	P=0.2885
Distal Forearm	0.896	1.316	0 525	P=0 6197	P=0.4433	P=0.8808
Ultradistal Forearm	2.357	2.000	2 212	P=0 9996	P=0.9846	P>0.9999

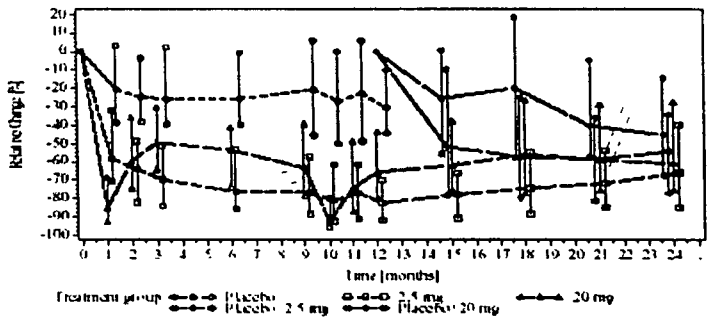
Both the 2.5 mg ibandronate daily and 20 mg ibandronate intermittent regimen significantly suppressed urinary CTX and NTX (p <0.0001) at Year 1. Suppression of bone resorption markers was maintained over the two years of treatment with both ibandronate dosing regimens. Urinary calcium levels increased during Year 1 in all treatment groups.

MF4433:Relative Change in Bone Resorption Markers at Year 1 (ITT)						
	Median Change (%)			Statistical Tests		
Marker	Placebo N=76	Iban 2.5mg N=75	Iban 20mg N=74	Kruskal-Wallis all groups	Wilcoxon Iban 2.5 vs. Placebo	Wilcoxon Iban 20 vs. Placebo
CTX[1] (µg/µmol)	n=73	n=69	n=67			
	-30 588	-82.377	-65.553	P<0 0001	P<0.0001	P<0 0001
NTX[1] (nmol/mmol)	n=73	n=69	n=67			
	-26.531	-62.857	-56.897	P<0.0001	P<0.0001	P<0 0001

MF4433:Relative Change in Bone Resorption Markers at Year 1 (ITT)						
	Median Change (%)			Statistical Tests		
Marker	Placebo N=76	Iban 2.5mg N=75	Iban 20mg N=74	Kruskal-Wallis all groups	Wilcoxon Iban 2.5 vs. Placebo	Wilcoxon Iban 20 vs. Placebo
Calcium[1] (mmol/mol)	n=73	n=69	n=67			
	41.167	27.790	29.508	P=0.6818	P=0.4993	P=0.4112
1.creatinine corrected.						

Suppression of bone resorption markers was maintained over the two years of treatment in both ibandronate groups. A cyclical suppression of the resorption markers was observed with the intermittent ibandronate regimen. This cyclical pattern may be attributable to the timing of the assessments. In the 20 mg intermittent treatment arm, peak suppression of resorption markers was observed at time-points where markers were assessed soon after patients had received the full 12 doses in the treatment cycle. As seen in the figure below, the greatest suppression of resorption was observed at Month 1 and Month 10, following only one week after completion of dosing in a treatment cycle. The suppression of bone resorption was less pronounced in other treatment cycles where the drug-free period was greater than 1 month. The profile of the relative change in NTX was very similar to that of urinary CTX.

MF4433: Time Course of the Relative Change in Urinary CTX:



Treatment with either ibandronate regimen led to significant suppression ($p < 0.0001$) of markers of bone formation after Year 1 compared to placebo. No significant difference in PTH levels were observed between the treatment groups during Year 1.

<u>Summary:</u> **In this study, ibandronate therapy was demonstrated to be superior to placebo in increasing lumbar spine BMD. Increases in lumbar spine BMD were significantly greater at Year 1 in both ibandronate groups relative to placebo ($p< 0.0001$). The two ibandronate treatment arms were also shown to be equally efficacious after two years of treatment, although there was no placebo control in the second year. 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. This suppression continued in Year 2.**

There was a substantial difference in the pattern of bone resorption marker suppression noted between the 2.5 mg daily ibandronate and 20 mg intermittent ibandronate regimens. The 2.5 mg daily regimen led to resorption markers being consistently suppressed with a nadir of 60-70% reached after approximately 1 year. However, in the 20 mg intermittent regimen, where the full 3-month dose was provided in 12 doses q.o.d. at the start of each 3-month cycle, a cyclical suppression of bone resorption was observed. Maximum suppression of resorption markers was observed within the first month of the 3-month intermittent treatment cycle with the minimum residual suppression observed after the 9-week treatment-free period at the end of the treatment cycle. Bone markers were assessed at the end of each 3-month treatment cycle during Year 2. Because of this, in Year 2 only the minimal residual suppression of resorption markers, remaining at the end of each 3-month cycle, was observed for the intermittent ibandronate regimen and it may be expected that the actual pattern of suppression continued to be cyclical in Year 2. In contrast to the cycling suppression pattern seen in bone resorption markers, no marked difference in the suppression pattern of bone formation markers was observed between the 2.5 mg daily ibandronate and 20 mg intermittent ibandronate regimens.

XI.A.2. MF4348: This was a Phase 2, dose-finding, placebo-controlled, double-blind, randomized single center dose-finding 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.

Objectives, Study Design, and Patient Population: The objective of this study was to define the effective oral dose of ibandronate for long-term treatment of postmenopausal osteoporosis by evaluating the efficacy and safety of different doses using BMD and biochemical markers of bone metabolism as parameters of efficacy. The primary efficacy variable was the median relative change from baseline in BMD of the lumbar spine after 1 year of treatment. Secondary efficacy variables included change in BMD of the hip, and the area-under-the-curve (AUC) for 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) subjects were enrolled in the trial. Subjects were at least 10 years since last menstruation, age less than 75 years and had a BMD T-score of $\leq$-1.5 at the distal forearm. Exclusion criteria included: history of ovariectomy, renal impairment, or metabolic bone disease. Subjects were randomized to one of 6 treatment groups: placebo, 0.25 mg, 0.5 mg, 1.0 mg, 2.5 mg or 5.0 mg oral ibandronate daily for one year. Subjects were instructed to fast for 60 minutes post dose. Subjects all received 1000 mg calcium supplementation daily. Bone mineral density was measured at 3, 6, 9, 12, 18 and 24 months. A full schedule of assessments is listed below.

MF4348: Schedule of Assessments											
	Pretreatment period	Treatment period							Follow-up	Observation period	
Visit	1	2	3	4	5	6	7	8	9	10	11
Month	> -1	0	1	2	3	6	9	12		18	24
Check inclusion/ exclusion criteria	x	x									

MF4348: Schedule of Assessments											
	Pretreatment period	Treatment period							Follow-up	Observation period	
Medical history	x										
Informed consent	x										
Randomization		x									
Issue study and concomitant Ca^{2+} medication		x			x	x	x				
Count study and concomitant Ca^{2+} medication			x	x	x	x	x	x			
BMD		x			x	x	x	x		x	x
Laboratory tests I		xx[1]			x	x	x	xx[1]	x[4]	x	x
Laboratory tests II	x	x	x	x	x	x	x	x			
Adverse events	continuous recording										

BMD measurements: lumbar spine, distal forearm, proximal femur
Laboratory parameters I (efficacy): serum osteocalcin, TAP and BSAP. In urine: calcium[2], creatinine, pyridinoline[2], deoxypyridinoline[2], hydroxyproline[2,3].
Laboratory parameters II (safety): complete blood count, ALT, AST, GGT, TAP, urea, creatinine, phosphate, Na, K, Ca, ibandronate (except visit 1)[3].
[1] Note: Urine samples from the day before the visit have to be analyzed as well
[2] Corrected for creatinine
[3] Detailed pharmacokinetic analysis on visits 2 and 8
[4] 15 mL of serum (interval of 7 to 14 days after visit 8)

Results: Of the 180 subjects enrolled in the study, 41 withdrew prematurely 6 (20%) from the placebo group, 5 (17%) from the 0.25 mg group, 8 (27%) from the 0.5 mg group, 4 (13%) from the 1.0 mg group, 6 (20%) from the 2.5 mg group and 12 (40%) from the 5.0 mg group. Fifteen subjects were not included in the follow-up period because they chose not to continue. All baseline demographic parameters were balanced among groups. The mean age of the subjects was 63 years with a range of 49 years – 76 years. The median lumbar spine BMD was 0.85 – 0.91gm/cm^2.

As shown in the table below, aside from the femoral neck and distal forearm, there was generally a dose-dependent increase in BMD in the ibandronate- vs. placebo-treated subjects with a plateauing of effect at the 2.5 mg and 5.0 mg doses. Bone mineral density measurements at the hip were similar between placebo, 0.25 mg and 0.50 mg ibandronate. With 1.0 mg ibandronate, in comparison to placebo, trends toward increases in the trochanter and total hip BMD were observed. With 2.5 mg and 5.0 mg ibandronate, increases in trochanter and total hip BMD were significant relative to placebo. At the femoral neck, only 2.5 mg ibandronate showed a significant difference in BMD from placebo and only in the ITT population. For the distal forearm, there was no significant difference from placebo in BMD after 1 year of ibandronate therapy.

Study MF4348: Median Relative BMD Change from Baseline at Month 12						
Relative change (%)	Placebo	0.25mg	0.5mg	1.0mg	2.5mg	5.0mg
LS Spine	1.09	1.57	2.77	3.45 *	4 97 **	4.47 **
Total hip	0.28	-0.08	1.37	1.48	1.81	2.01*
Trochanter	0.70	1 58	1.18	1.96	3.12 *	4.04 **
Femoral Neck	1 20	1.77	0.83	1.23	2.61	1.03
Distal forearm	-0.50	0.15	0.0	-0.53	1.60	-1.23
compared to placebo by pairwise Wilcoxon testing * $p<0$ 05, **$p\leq0.01$						

The baseline-adjusted ANCOVA analysis revealed that increases in lumbar spine BMD with 0.5-5.0 mg were also significantly different from placebo.

There was an overall reduction in the markers of bone resorption (pyridinolines, deoxypyridinolines and CTX) by 8-30% in the placebo group. With oral daily ibandronate, a dose-dependent fall in bone resorption markers was apparent as early as Month 3 and remained suppressed throughout the remaining treatment period. Small reductions compared to placebo were observed with the lower ibandronate dosages. With the 2.5 mg and 5.0 mg ibandronate doses, significant decreases in all bone resorption parameters were seen ($p<0.01$, compared to placebo). The 5.0 mg dose of ibandronate led to similar or only nominally greater (NS) effects relative to 2.5 mg. Markers of bone formation were also decreased in the placebo group. There was a dose-dependent decrease in the serum concentrations of osteocalcin and BSAP with ibandronate doses of 0.25-2.5 mg. The 5.0-mg dose did not appear to result in further suppression in comparison to the 2.5 mg dose. Compared to placebo, 0.25 mg and 0.5 mg ibandronate showed minimal (NS) suppression. In doses of 1.0-5.0 mg, formation marker decreases were significantly different from placebo ($p<0.05 - p<0.01$). There were no significant differences between the 2.5 mg and 5.0 mg doses.

Study MF4348: Median Relative Change in Bone Turnover Marker (Baseline to Month 12)						
Relative change (%)	Placebo	0.25mg	0.5mg	1.0mg	2.5mg	5.0mg
Pyridinoline/Creatinine	-8.0	-21.5**	-14.8*	-21.0*	-28.6**	-34.2**
Deoxypyridinoline/Creatinine	-14.8	-31.0**	-31.3*	-33.0**	-47.9**	-53.2**
CTX/Creatinine	-33.3	-39.4	-49.3	-62.9**	-86.5**	-90.9**
Osteocalcin	-5.6	-11.7	-16.5	-19.9*	-37.5**	-38.7**
BSAP	-23.1	-30.3	-34.5	-44.1*	-56.9**	-52.5**
compared to placebo by pairwise Wilcoxon testing * $p<0.05$, ** $p\leq0.01$						

In the follow-up period after discontinuation of treatment (Month 12 to 24), BMD at the lumbar spine and proximal femur decreased equally in all groups at a rate of 2.0 % per year on average, which is of a magnitude similar to normal postmenopausal bone loss (Table below).The resorption parameters had returned to baseline values 12 months after discontinuation of the drug. Osteocalcin had returned to baseline values 12 months after discontinuation of drug treatment, but BSAP was still reduced by 20–25% in the groups previously treated with the highest doses of ibandronate (1, 2.5, and 5.0 mg).

Study MF4348: Median Relative BMD Change from Month 12 to Month 24						
Relative change (%)	Placebo	0.25mg	0.5mg	1.0mg	2.5mg	5.0mg
N	22	23	21	20	21	17
LS Spine	-1.5	-1.4	-2.7	-2.4	-2.5	-1.8
Total hip	-0.7	-3.0	-1.3	-2.2	-2.0	-2.7
Trochanter	-1.1	-2.7	-1.8	-1.6	-2.4	-1.7
Femoral Neck	-2.8	-2.6	-1.5	-1.3	-2.0	-2.9
Distal forearm	-0 2	-2 1	-1 0	-0.1	-1.5	-0.8

In considering the safety profile of the 2.5 mg and 5.0 mg regimens, overall adverse event rates were similar. Adverse events leading to withdrawal were much higher, however, in the 5.0 mg

group (30.0%) compared with the 2.5 mg group (13.3%). Gastrointestinal adverse events were also higher in the 5.0 mg group (60%) compared to the 2.5 mg group (20%).

In general, the pharmacokinetic parameters of multi-dose ibandronate were not essentially different from single-dose studies in healthy subjects, with C_{max} and AUC increasing in a linear manner with dose. Steady-state (12- month treatment) C_{max} and $AUC_{0-\infty}$ to first dose ratios in the range 0.9-1.9 were consistent with linear kinetics.

Summary: **In this dose-finding, placebo-controlled study that was not designed to detect significant BMD differences among ibandronate groups, 2.5 and 5.0 mg ibandronate were the most effective doses with respect to increasing BMD. 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 placebo and the lower doses of the drug. With 5.0 mg, the early withdrawal rate was 2-3 times higher than in the other treatment groups and the overall incidence of gastrointestinal AEs, mainly those linked to the lower gastrointestinal tract, was highest with 5.0 mg. Based on the efficacy and safety date from this study, the daily dose appropriately chosen for the phase 3 studies in patients with osteoporosis was 2.5 mg.**

XI.A.3. 75003: This was a Phase 3 multicenter, double-blind, randomized, comparative study of the efficacy and safety of ibandronate during 48 weeks treatment in patients with postmenopausal osteoporosis receiving an oral regimen of 2.5 mg ibandronate daily or 20 mg ibandronate weekly.

Objectives, Study Design, and Patient Population: 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 lumbar spine BMD and in reducing biochemical markers of bone turnover. The 20 mg weekly regimen was to be considered non- inferior to the 2.5 mg daily regimen if the boundary of the one-sided 97.5% confidence was found to be greater or equal to –1.65%. The study also aimed to assess the safety and tolerability of oral ibandronate in patients with postmenopausal osteoporosis. The primary efficacy variable was the relative change in BMD of the lumbar spine at 48 weeks. Secondary efficacy variables included change in BMD of the hip, and the area-under-the-curve (AUC) for the relative change in biochemical markers of bone turnover (urinary CTX, serum CTX and serum osteocalcin).

A total of 235 (121 2.5 mg daily, 114 20 mg weekly) subjects were enrolled in the trial. Subjects were at least 3 years since last menstruation, age 55 – 80 years and had a BMD T-score of ≤-2.0. Exclusion criteria included: history of ovariectomy, renal impairment, metabolic bone disease, or a history of esophageal disease. Subjects were randomized to receive either 2.5 mg oral ibandronate daily or 20 mg oral ibandronate weekly. Subjects were instructed to observe a post-dose fasting period of at least 30 minutes. All subjects received calcium 500 mg and vitamin D 400IU daily. They were instructed to take the calcium supplement in the evening. Bone mineral density measurements were done at 24 weeks and 48 weeks. A full schedule of assessments is listed below.

Study 75003 Schedule of Assessments								
	Screening visit[1]	Treatment period						Final visit[3]
Visit		1	2	3	4	5	6	7
Weeks (w)	to –6w	0w	1w	2w	4w	12w	24w	48w
Written informed consent	x							
Medical history	x							
Check inclusion/exclusion criteria	x	x						
Physical examination	x							X
Randomization		x						
Distribution of study medication		x					x	
Provision of concomitant supplements		x					x	
BMD (lumbar spine L1-L4)	x						x	x
BMD (hip)	x						x	x
Laboratory tests for safety	x						x	x
Laboratory tests for efficacy		x	x[2]	x[2]	x[2]	x	x	x
Compliance						x	x	x
Previous/concomitant medication	x	continuous recording						
Adverse Events		continuous recording						

1. All baseline BMD and laboratory safety assessments were performed during the screening visits with laboratory efficacy assessments performed at Visit 1.
2. Efficacy laboratory assessments were only performed on a subset of patients (20 patients per group) and at selected sites at Visits 2, 3, and 4.
3. The Final Visit assessment was to be performed in the event of a patient discontinuing treatment prematurely.

Results: Of the 235 subjects enrolled in the study, 24 withdrew prematurely [12 (10%) from the 2.5 mg daily group and 12 (11%) from the 20 mg weekly group]. Fifteen subjects were not included in the efficacy analysis because of lack of follow-up BMD measurements. All demographic parameters were balanced between groups at baseline. The mean age of subjects was 65.7 years with a range of 53 years – 80 years and 97% of the women were Caucasian. The mean time since menopause was 17.5 years and the mean lumbar spine BMD T-score was – 2.9.

The mean relative change in lumbar spine BMD was similar between the two groups: 3.42% for the 2.5 mg daily group and 3.45% for the 20 mg weekly group. The mean relative change in hip BMD was also similar between groups (total hip: 2.2% for the 2.5 mg daily group and 1.7% for the 20 mg weekly group; trochanter: 2.8% for the 2.5 mg daily group and 2.3% for the 2 0mg weekly group; femoral neck: 1.6% for the 2.5 mg daily group and 1.7% for the 20 mg weekly group). At Week 48, daily and weekly ibandronate therapy respectively resulted in median relative suppression of 34% and 41% in osteocalcin, of 57% and 57% in urinary CTx, and of 47% and 44% in serum CTx. The AUC of the relative changes in markers of bone turnover indicated that the total suppression over the period of the study was similar for the two treatment arms with a marginally greater suppression observed with weekly compared to daily treatment.

Summary: **In this study, 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 increase in LS BMD from baseline to Week 48 was 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 non-inferior to the 2.5 mg daily dose. Increases in hip BMD were also of similar magnitudes for the daily and weekly regimens. Both regimens were shown to consistently and equally suppress bone turnover markers.**

XI.A.4. MF4491: This was a Phase 3 multicenter, open-label, randomized study of the efficacy and safety of oral ibandronate 2.5 mg taken either 30 or 60 minutes before breakfast during 12-months treatment in patients with postmenopausal osteoporosis.

Objectives, Study Design, and Patient Population: This study was designed to investigate changes in efficacy of oral ibandronate when the post-dose fasting period was decreased from 60 minutes to 30 minutes. The rationale was that a 30-minute fast would have a beneficial effect on tolerability and decrease esophageal irritation. The primary efficacy variable was relative change in BMD of the lumbar spine at 48 weeks. The 30-minute fast was to be considered non-inferior to the 60-minute fast in the lower bound of the 95% confidence interval for the difference in LS BMD changes between groups was not less than –2.0%. 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) subjects with established osteoporosis were enrolled in the trial. Subjects were at least 5 years since last menstruation and age 55 – 80 years. Exclusion criteria included: history of ovariectomy, renal impairment, metabolic bone disease, or a history of esophageal disease. All subjects received 2.5 mg oral ibandronate daily. Subjects were randomly assigned to a 30 or 60-minute post-dose fast. All subjects received calcium 500 mg and vitamin D 400IU daily. They were instructed to take the calcium supplement in the evening. Bone mineral density measurements were done at Month 12. A full schedule of assessments is listed below.

MF 4491: Schedule of Assessments and Procedures

	Screening visit	Treatment period		
Visit	1	2	3	4
Month (mo)	-1.5 m to 0 mo	0 mo	6 mo	12 mo
Written informed consent	x			
Medical history	x			
Check inclusion/exclusion criteria	x	x		
Physical examination	x			x
Randomization		x		
Distribution of study medication		x	x	
Provision of calcium supplement and vitamin D		x	x	
BMD (spine)	x	x		x
BMD (hip)		x		x
Laboratory tests I[a]	x			x
Laboratory tests II[b]		x		x
Compliance			x	x
Adverse Events		x	x	x
Previous/concomitant medication	x	x	x	x
Provision of diary		x	x	

a. Blood/serum: CBC, ALT, GGT, AP (total), creatinine, BUN, electrolytes (including Ca and P), 25-OH-vitamin D.
b. Serum: osteocalcin; urine: creatinine, C-telopeptide.

Results: Of the 213 subjects enrolled in the study, 25 withdrew prematurely (10 (9%) from the 30-min group and 15 (14%) from the 60-min group. All demographic parameters were balanced between groups. The mean age of subjects was 65.1 years with a range of 55 years – 78 years and 98% were Caucasian. The mean time since menopause was 16.8 years. The mean lumbar spine BMD T-score was – 3.1. Forty-two percent of subjects had prevalent osteoporotic fractures at baseline.

The table below shows the BMD changes for the lumbar spine. The mean percentage change in lumbar spine BMD from baseline to the end of study was 3.07% in the 30-minute group compared to 4.95% in the 60-minute group. The difference between treatments was -1.878%, and the lower limit of the one-sided 97.5% confidence interval of the mean was -2.89%. Non-inferiority of the 30-minute group compared to the 60-minute group was not shown because the lower boundary of the confidence interval was smaller than -2%. The relative change from baseline to study end for the hip BMD measurements is similar to those for the lumbar spine BMD. Decreased suppression of the bone turnover rate, assessed by the change from baseline in urinary CTx relative to creatinine (-48.49% vs. –61.75%), and serum osteocalcin concentration (-34.77% vs. –43.78%), was observed in the 30-minute group compared with the 60-minute group.

MF 4491: Changes in BMD				
		30 min fast	60 min fast	Treatment Difference (%)
		N = 95	N = 89	
LS Spine	% Change	3 07	4.95	-1.88
	one-sided 95% CI			(-2.89,--)
Total hip	% Change	2.35	3.21	-0.86
	one-sided 95% CI			(-1.78,--)
Trochanter	% Change	3.04	4.36	-1.32
	one-sided 95% CI			(-2.70,--)
Femoral Neck	% Change	1 82	2.19	-0.37
	one-sided 95% CI			(-1.36,--)
Urinary CTx	% Change	-48.49	-61.75	13.27
	one-sided 95% CI			(--,22.49)
Osteocalcin	% Change	-34.77	-43.78	9.00
	one-sided 95% CI			(--,14.59)

As discussed in the safety review, overall, the number of subjects who experienced an AE was greater in the 30-minute group (84%) than in the 60-minute group (69%). The number of subjects and reported AEs were similar for both treatments except for the body as a whole system, where a greater number of patients in the 30-minute group experienced an AE than in the 60-minute group. A total of 20 (18.7%) subjects in the 30-min group and 26 (24.5%) subjects in the 60-min group reported gastrointestinal adverse events. Dyspepsia (3.7% vs. 8.5%) and diarrhea (0.9% vs. 6.6%) were more common in the 60-min group. There were no reports of gastritis or esophagitis in either treatment group.

Summary: **Both treatment groups exhibited increased lumbar spine BMD after 48 weeks, but the 30-minute fast group showed a smaller increase in lumbar spine BMD than the 60-minute fasting 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.**

XI.A.5. MF4500: This was a Phase 2/3, multicenter, double-blind, placebo-controlled, randomized, dose-finding study of the efficacy and safety of ibandronate during 2 years' treatment in postmenopausal women for prevention of postmenopausal bone loss, using an intermittent oral (5 mg, 10 mg, 20 mg per week) dosing regimen.

Objectives, Study Design, and Patient Population: This study was designed to investigate the use of oral ibandronate once weekly in the prevention of PMO. The primary efficacy variable was relative change in BMD of the lumbar spine at 2 years. Secondary efficacy variables included change in BMD of the hip, and change in biochemical markers of bone turnover. Change in bone stiffness, assessed by ultrasound was also measured.

A total of 630 (158 placebo, 159 5 mg, 154 1 0mg and 159 20 mg) subjects were enrolled in the trial. Baseline characteristics were well-matched. Subjects were 1 – 10 years since last menstruation. Subjects were stratified based on time since menopause (1 – 3 years or > 3years) and bone mineral density (T-score >–1 or –1.0 to –2.5), then randomly assigned to a treatment group. Exclusion criteria included: BMD T-score below –2.5 SD, history of fractures, hysterectomy an/or ovariectomy, renal impairment, metabolic bone disease, or a history of esophagitis or peptic ulcer disease. Subjects received study drug as a single oral weekly dose. Post-dose fasting was initially 60 minutes, but was changed to 30 minutes during the trial. All subjects were to received calcium 500 mg daily that was provided by their physician. They were instructed to take the calcium supplement with the evening meal. Bone mineral density measurements were done at 6 months, 12 months, 18 months and 24 months. A full schedule of assessments is listed below.

Study MF4500 Schedule of Assessments

	Pre-study visit[1]	Treatment period											
Visit	0	1	2	3	4	5	6	7	8	9	10	11	12
Week (w)/month (m)	-1m	0	2	1m	2m	3m	6m	9m	12m	15m	18m	21m	24m
Medical history	x												
Inclusion/exclusion criteria	x	x											
Physical examination	x												x
Written informed consent	x												
Stratification		x											
Randomization		x											
Distribution of study medication		x				x	x	x	x	x	x	x	
Provision of calcium		x				x	x	x	x	x	x	x	
BMD	x	x					x		x		x		x
Ultrasound measurement[5]		x					x		x		x		x
Total body bone mass[5]		x							x				x
Weight, height		x							x				x
Laboratory tests for Safety	x	x				x	x		x		x		x
Laboratory tests for Efficacy[5,6]		x	x	x	x	x	x	x	x	x	x	x	x
Compliance						continuous recording							
Adverse events						continuous recording							
Previous and concomitant medication						continuous recording							

1 Pre-study visit was not to take place more than 1 month prior to randomization The acceptable window for scheduled visits is ⊏ 2 weeks from the scheduled date.
2 Visit 2 occurred after the intake of the second weekly treatment.
3 Only lumbar spine BMD was determined during the screening visit
4 Only serum calcium and creatinine were determined during the screening visit.
5 These assessments were only performed at selected centers
6 For those centers performing laboratory tests for efficacy, the acceptable window for Visit 2 was ⊐ 2 days and ⊏ 1 week for Visits 3, 4, and 5

Results: Of the 630 subjects enrolled in the study, 8 received no study medication and 82 (13.2%) withdrew prematurely. All demographic parameters were balanced between groups and strata. The mean age of the subjects was 55.0 years with a range of 43 years – 67 years. The mean time since menopause was 4.5 years. All subjects were Caucasian. The mean lumbar spine BMD T-score at baseline was – 1.1.

Compared with placebo, there was a statistically significant increase in lumbar spine BMD in the ibandronate 10 mg and 20 mg once-weekly groups. As shown in the table below, significant differences were demonstrated at all time points, beginning at Month 6 for both the 10 mg and 20 mg dose groups.

Responders were defined as patients who had an increase of > 0% in lumbar spine BMD at Month 24 (LVCF) compared to baseline. The percentage of responders increased with increasing dose: placebo 38%, 5 mg 43%, 10 mg 55% and 20 mg 75%.

MF4500: BMD Results

	BMD Subgroup	Placebo	Oral Ibandronate			
			5 mg	10 mg	20 mg	** 20 mg-Placebo
		% change (n)	% change (n)	% change (n)	% change (n)	% change
Strata (T-score, TSM)						
A	(>-1 SD, 1-3 yrs)	-2.2733 (25)	-2.5927 (26)	-0.1720 (26)	2.0292 (26) *	4.3025
B	(-1– -2.5 SD, 1-3 yrs)	-2.3014 (49)	-1.4133 (48)	-0.1432 (48) *	3.0094 (47) *	5.3108
C	(>-1 SD, > 3 yrs)	-0.2912 (26)	0.2459 (26)	1.1207 (24)	2.0562 (25) *	2.3474
D	(-1– -2.5 SD, > 3 yrs)	0.0955 (54)	0.7921 (52)	1.7251 (53) *	3.5760 (53) *	3.4805
Total		-1.1170 (154)	-0.5767 (152)	0.7085 (151) *	2.8817 (151) *	3.9987

*Difference between active group and placebo was significant ($p < 0.05$).

** Difference in the mean relative change between Ibandronate 20 mg Endpoint and Placebo Endpoint

Dose-dependent increases in mean change from baseline BMD versus placebo were demonstrated for all ibandronate groups at the total hip, femoral neck, trochanter and Ward's triangle. The differences in relative change from baseline to Month 24 (and at last value) between the 10 mg and 20 mg group compared to placebo were significant for total hip and its sub-regions.

Median serum CTX concentrations were reduced from baseline in a dose-dependent fashion with 10 mg and 20 mg ibandronate treatment. At all time points (2 weeks to 24 months), the decrease in serum CTX values for the 20 mg dose group differed significantly from placebo. The decrease in serum CTX values for the 10 mg dose group differed significantly from placebo at most time points (3 months to 24 months). A consistent, dose-dependent decrease in urinary CTX/creatinine concentrations was also seen. All treatment groups differed significantly from placebo at Month 24. Serum osteocalcin values decreased gradually over the first year for all groups, including placebo, and remained essentially unchanged through the remainder of the study. The 10 mg and 20 mg groups showed significant, dose-dependent reductions from baseline in osteocalcin concentrations, as compared to placebo beyond Month 3 and Month 2, respectively. Serum PTH concentrations increased from baseline for all treatment groups at month 24. The difference from placebo was not significant.

Summary: Study MF 4500 demonstrates that weekly oral ibandronate treatment administered at 10 mg and 20 mg over two years in postmenopausal women significantly increased BMD of the lumbar spine from baseline levels compared to placebo. Effects of therapy were evident beginning at Month 6 and at all subsequent time points. The mean relative change in BMD of lumbar spine was not significantly different from placebo in the 5 mg dose group. The BMD effects were seen in osteopenic women of early postmenopausal years and were more pronounced in osteopenic women of more than three years past menopause. Results from the analysis of biochemical markers of bone turnover supported the findings

XI.B. Other Relevant Materials

XI.B.1. Study MF4411 – Additional Information

XI.B.1.a. Assessments and Methods: Study MF4411

Study MF4411: Schedule of Assessments

		Screening phase	Treatment period												
Visit			1	2	3	4	5	6	7	8	9	10	11	12	13
Month[1]		-3 to 0	0	3	6	9	12	15	18	21	24	27	30	33	36
Inclusion/ exclusion criteria		x	x												
Medical history			x												
Written informed consent		x	x												
Randomization			x												
Distribution of study medication			x	x	x	x	x	x	x	x	x	x	x	x	x
Provision of supplemental vit. D and Ca^{2+} medication			x	x	x	x	x	x	x	x	x	x	x	x	x
Efficacy															
	BMD	x2	x		x		x		x		x				x
	X-ray (vertebral fractures)	x3					x		/		x				x
	Laboratory tests II[4] (efficacy)		x	x	x		x		x		x				x
	Height		x	x	x	x	x	x	x	x	x	x	x	x	x
	Disability and physical activity		x				x				x				x
	Bone pain		x	x	x	x	x	x	x	x	x	x	x	x	x
Safety															
	Laboratory tests I (safety)	x5	x	x	x		x		x		x				x
	Adverse events		continuous recording												
	Weight		x				x				x				x
	Bone biopsy[6]										x				x
Compliance				x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medication			continuous recording												
Quality of life[4]			x				x				x				x
Pharmacoeconomic impact[4]			x	x	x	x	x	x	x	x	x	x	x	x	x
Final Assessment															x

1. Visits 2-13 were scheduled for the given time period after randomization within a window of ± 2 weeks.
2. Measurement of BMD for lumbar spine (L1–L4) and proximal femur with additional measurement of distal radius at selected centers on visits following randomization.
3 Baseline values were established at visit 1, with the exception of X-ray fracture data for which the values established at the screening visit served as the baseline value.
4. Only in selected centers.
5 Only measurements of serum calcium and serum creatinine were performed for screening.
6 Bone biopsies were only performed in a subpopulation of patients in selected centers at 22 or 34 months.

Study MF4411: Questionnaire to Assess Disability (modified according to Leidig et al. 1990)

	Easily accomplished without assistance	Difficult, but possible without assistance	Only possible with assistance	Not possible
Getting up from a lying position	☐	☐	☐	☐
Bending	☐	☐	☐	☐
Getting dressed	☐	☐	☐	☐
Walking	☐	☐	☐	☐
Climbing stairs	☐	☐	☐	☐
Daily housework	☐	☐	☐	☐
Carrying heavy items(shopping bag, suitcase, etc)	☐	☐	☐	☐

Study MF4411: Questionnaire to Assess Physical Activity (according to Cooper et al., 1988)				
Standing time (min/day)	None ☐	1 - < 30 ☐	30 - < 60 ☐	≥ 60 ☐
Self-reported walking speed	Very slow ☐	Easy pace ☐	Normal speed ☐	Brisk/fast ☐
Walking time (min/day)	None ☐	1 - < 30 ☐	30 - < 60 ☐	≥ 60 ☐
Muscle-loading activity (frequency)*	Never ☐	Less than weekly ☐	Weekly to daily ☐	Several times a day ☐
Productive activity (hours/week)**	None ☐	1 - < 5 ☐	5 - < 10 ☐	≥ 10 ☐
* Muscle-loading activity: sports, bowls, cycling, swimming, fitness exercises, stretching exercises, golf, etc. ** Productive activity: house work (no food preparation), gardening, house and car maintenance, etc.				

XI.B.1.b. MF4411: Bone Mineral Density Subgroup Analysis (PP)

MF4411: Mean Relative BMD Changes (%) over 3 Years in Various Subgroups										
	Lumbar Spine (L2-L4)					**Total Hip**				
	Placebo	2.5 mg	20 mg	2.5 mg	20 mg	Placebo	2.5 mg	20 mg	2.5 mg	20 mg
	vs. Baseline			vs. Placebo		vs. Baseline			vs. Placebo	
Continent:										
Europe	1 271	7.085	6.326	5.814	5.055	-0.799	3.720	3.100	4 519	3.899
North America	1.227	5.391	4.362	4.164	3.135	-0.474	2.594	2.460	3.068	2.934
BMI at Baseline:										
Lower tertile (≤23.96)	0.717	5.981	5.166	5.264	4.449	-0.675	2.899	2.847	3.574	3.522
Middle tertile (23.97-27.42)	0.922	6.700	6.688	5.778	5.766	-0 749	3.850	3.219	4.599	3.968
Upper tertile (≥27.43)	2.024	7.021	5.189	4.997	3.165	-0.630	3.374	2.615	4.004	3.245
Age [years]:										
≥ 70	1.973	7.215	6.606	5.242	4.633	-1.005	3.488	2.878	4.493	3.883
< 70	0.653	5.974	4.854	5.321	4.201	-0.421	3.249	2.889	3.670	3.310

MF4411: Mean Relative BMD Changes (%) over 3 Years in Various Subgroups

	Lumbar Spine (L2-L4)					Total Hip				
	Placebo	2.5 mg	20 mg	2.5 mg	20 mg	Placebo	2.5 mg	20 mg	2.5 mg	20 mg
	vs. Baseline			vs. Placebo		vs. Baseline			vs. Placebo	
Time since Menopause [yrs]:										
Lower tertile (≤17)	0.634	6.161	5.048	5.527	4.414	-0.325	3.125	3.122	3.450	3.447
Middle tertile (18-24)	1.419	6.344	6.106	4.925	4.687	-1.182	3.747	2.556	4.929	3.738
Upper tertile (≥25)	1.770	7.239	5.979	5.469	4.209	-0.556	3.222	2.842	3.778	3.398
No of prevalent fractures:										
0 or 1	0.998	6.805	5.774	5.807	4.776	-0.754	3.332	2.808	4.086	3.562
≥ 2	1.585	6.218	5.506	4.633	3.921	-0.612	3.391	2.987	4.003	3.599
LS BMD (L2-L4) at Baseline:										
BMD < -2.5	1.130	7.014	5.840	5.884	4.710	-0.695	3.589	2.764	4.284	3.459
BMD ≥ -2.5	1.451	5.823	5.392	4.372	3.941	-0.727	3.022	3.074	3.749	3.801

XI.B.1.c. Marked Laboratory Abnormalities for study MF4411

MF4411:
Reference Ranges and Clinically Relevant Changes from Baseline for Marked Abnormalities

Laboratory Test	SI unit	Roche Standard Reference Range	Marked Reference Range	Direction of Change	Clinically Relevant Change From Baseline
HAEMATOLOGY					
Haematocrit	fraction	M 0 42 – 0.52 *	0.36 – 0 60	Increase	≥ 15%
		F^ 0 37 – 0.48 *		Decrease	≥ 15%
Haemoglobin	g/dL	M 13.0 – 18.0 *	11.0 – 20.0	Increase	≥ 15%
		F^ 12.0 – 16.0 *		Decrease	≥ 15%
Leucocytes	10^9/L	4.3 – 10.8 *	3.0 – 18 0	Increase	≥ 30%
				Decrease	≥ 30%
Platelets	10^9/L	150 – 450 *	100 – 700	Increase	≥ 50%
				Decrease	≥ 30%
MCH	pg/cell	28.0 – 33.0 *			
MCHC	g/L	320 – 360 *			
MCV	fL	86 – 98 *			
RBC	10^{12}/L	4 15 – 4.90 *	3 5 – 5.6	Increase	≥ 15%
				Decrease	≥ 15%
DIFFERENTIALS					
Bands	fraction	0.00 – 0.04 *	0.00 – 0.10	Increase	≥ 30%
Basophils	10^9/L	0.00 – 0.15 *	0 00 – 0.30	Increase	≥ 100%
Basophils	fraction	0 00 – 0.02 *	0.00 – 0.04	Increase	≥ 100%
Lymphocytes	10^9/L	1.50 – 4.00 *	1.00 – 6.30	Increase	≥ 30%
				Decrease	≥ 30%
Lymphocytes	fraction	0.16 – 0.45 *	0.10 – 0 70	Increase	≥ 30%
				Decrease	≥ 30%
Monocytes	10^9/L	0.20 – 0.95 *	0.08 – 2.00	Increase	≥ 100%
				Decrease	≥ 100%
Monocytes	fraction	0 04 – 0 10 *	0.02 – 0 20	Increase	≥ 100%
				Decrease	≥ 100%
Neutrophils	10^9/L	1.83 – 7.25 *	1.50 or more	Decrease	≥ 20%
Neutrophils	fraction	0.45 – 0.78 *	0.37 or more	Decrease	≥ 20%
Eosinophils	10^9/L	0 00 – 0.70 *	0 00 – 1.50	Increase	≥ 100%
Eosinophils	fraction	0.00 – 0.07 *	0.00 – 0.15	Increase	≥ 100%
COAGULATION					
Prothrombin time	seconds	9 – 13 *	0 – 16	Increase	≥ 30%
PT, Normalized Ratio	ratio	0.70 – 1 30 *	2.00 or less	Increase	≥ 30%
PTT	seconds	25 – 38 *	0 – 50	Increase	≥ 40%
Fibrinogen	□mol/L	4 0 – 10 0 ¢	3 0 or more	Decrease	≥ 30%

MF4411:
Reference Ranges and Clinically Relevant Changes from Baseline for Marked Abnormalities

Laboratory Test	SI unit	Roche Standard Reference Range	Marked Reference Range	Direction of Change	Clinically Relevant Change From Baseline
HEART FUNCTION					
ASAT (SGOT)	U/L	0 – 25 †	0 - 50	Increase	≥ 50%
Lactic Dehydrogenase	U/L	0 – 250 †	0 - 500	Increase	≥ 50%
CPK (MB fraction)	□g/L	0 0 - 7.5 †	0 - 15.0	Increase	≥ 50%
LIVER FUNCTION					
Alkaline Phosphatase	U/L	0 - 100 †	0 - 190	Increase	≥ 50%
ALAT (SGPT)	U/L	0 – 30 †	0 - 60	Increase	≥ 50%
Total Bilirubin	□mol/L	0 - 17.1 †	0 - 34.2	Increase	≥ 75%
Gamma-GT	U/L	0 – 60 †	0 - 120	Increase	≥ 50%
RENAL FUNCTION					
BUN	mmol/L	2.9 - 8.9 *	0 - 14.3	Increase	≥ 75%
Creatinine	□mol/L	0- 133 *	0 - 154	Increase	≥ 75%
THYROID FUNCTION					
T3 Uptake, total	nmol/L	1.2 - 3.0 *	1 - 3.6	Increase	≥ 20%
				Decrease	≥ 20%
T3 Uptake, percent§	%	23 – 35 *	20 - 40	Increase	≥ 20%
				Decrease	≥ 20%
Reverse T3	mmol/L	0.20 - 0.80 *			
Thyroxine (T4)	nmol/L	51 – 154 *	26 - 180	Increase	≥ 20%
				Decrease	≥ 20%
Free T4	pmol/L	10 – 35 *	5 - 40	Increase	≥ 20%
				Decrease	≥ 20%
TSH	mU/L	0.0 - 5.0 †	0.0 - 10 0	Increase	≥ 30%
TSHS	mU/L	0 5 - 5 00 ¢	0.15 - 10.00	Increase	≥ 30%
				Decrease	≥ 30%
PROTEIN					
Total Protein	g/L	60 – 80 *	55 - 87	Increase	≥ 20%
				Decrease	≥ 20%
Albumin	g/L	31.0 - 43.0 *	27.0 or more	Decrease	≥ 20%
LIPID CHEMISTRY					
Cholesterol	mmol/L	0.0 - 6.2 *	0.0 - 8.3	Increase	≥ 50%
Triglycerides	mmol/L	0.45 - 1.70 *	0.00 - 2.83	Increase	≥ 100%
ELECTROLYTES					
Chloride	mmol/L	100 – 108 *	95 - 115	Increase	≥ 7%
				Decrease	≥ 7%
Potassium	mmol/L	3.5 - 5.0 *	3 0 - 6 0	Increase	≥ 20%
				Decrease	≥ 20%
Sodium	mmol/L	133 – 145 *	130 - 150	Increase	≥ 7%
				Decrease	≥ 7%
Bicarbonate	mmol/L	22 – 30 *	18 - 32	Increase	≥ 20%
				Decrease	≥ 20%
MISCELLANEOUS					
Calcium	mmol/L	2.10 - 2 60 *	2.00 - 2 90	Increase	≥ 10%
				Decrease	≥ 10%
Phosphate	mmol/L	0.84 - 1 45 *	0.75 - 1.60	Increase	≥ 30%
				Decrease	≥ 30%
Antithrombin 3	fraction	0 80 - 1 20 *			
Blood Glucose	mmol/L	3 90 - 6 10 *	2.80 - 11 10	Increase	≥ 75%
(fasting)				Decrease	≥ 75%
Uric Acid	□mol/L	140 – 500 *	0 - 600	Increase	≥ 50%
URINALYSIS	Qualitative				
Casts	/HPF	0 *			
Proteinuria	0 to 4+	0 – 1 *	0 - 1	Increase	+
Glycosuria	0 to 4+	0 – 1 *	0 - 1	Increase	+
Haematuria	0 to 4+	0 – 1 *	0 - 1	Increase	+
WBCs	0 to 4+	0 *	0 - 1	Increase	+
RBCs	0 to 4+	0 *	0 - 1	Increase	+

* Reference range replaces the corresponding investigator range.
† Reference lower limit replaces the corresponding investigator lower limit (upper limit of investigator range used to transform a test result to the Roche standard).
^ Reference ranges expressed for females are used to transform data to conform to the male range for analytical and display purposes.
‡ A clinically relevant change here is a 2 unit increase over the Baseline (note that baseline values of 3 or 4 do not allow a subsequent clinically relevant change).
§ This test is not the recommended form for measure of T3 uptake but is included because this form of the test is frequently used.
¢ Reference lower and upper limit replace investigators' lower and upper limit, respectively.

XI.B.2. Study MF4380

XI.B.2.a. Study Assessments

MF4380: Schedule of Assessments and Procedures

	Screening Phase[1]	Treatment Period												
Visit[2]		1	2	3	4	5	6	7	8	9	10	11	12	13
Month		0	3	6	9	12	15	18	21	24	27	30	33	36[8]
Inclusion/ exclusion criteria		x												
Medical history		x												
Written informed consent	x	x												
Randomization		x												
Administer study medication		x	x	x	x	x	x	x	x	x	x	x	x	
Issue vitamin D & Ca supplements		x	x	x	x	x	x	x	x	x	x	x	x	
Efficacy														
BMD[3]	x	x		x		x		x		x				x
Radiograph/fractures[4]	x					x				x				x
Laboratory tests II (efficacy)[5]		x	x	x		x		x		x				x
Height		x	x	x	x	x	x	x	x	x	x	x	x	x
Disability and physical activity		x				x				x				x
Pain		x	x	x	x	x	x	x	x	x	x	x	x	x
Safety														
Laboratory tests I (safety)	x[6]	x	x	x		x		x		x				x
Adverse events		continuous recording												
Weight		x				x				x				x
Bone biopsy[7]									x				x	
Compliance			x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medication		continuous recording												
Quality of life[5]						x				x				x
Pharmacoeconomic impact[5]						x	x	x	x	x	x	x	x	x

[1] Screening phase did not exceed 3 months (per patient).
[2] Visits 2–13 were scheduled for the given time period after randomization with a window of ± 2 weeks.
[3] Measurement of BMD for lumbar spine (L1-L4) and proximal femur, with additional measurement of distal radius at selected centers on visits following randomization.
[4] Baseline values were established at Visit 1 with the exception of X-ray fracture data, for which the values established at the screening visit served as the baseline value.
[5] Performed only in selected centers.
[6] Only measurements of serum calcium and serum creatinine were performed at screening
[7] Biopsies were performed in a subpopulation of patients in selected centers at 22 or 34 months ± 7 days.
[8] A last visit (designated as "Visit 70") was requested for patients prematurely withdrawn from study.

XI.B.3. Comparison of Markers of Bone Turnover and Histomorphometric Data From Studies MF4411 and MF4380

The median relative changes seen in markers of bone resorption are outlined in the table below. Bone resorption markers appear to be suppressed with both formulations, with slightly increased suppression noted with the oral formulation.

MF4411 & MF4380: Markers of Bone Resorption								
		Baseline	Relative Change to Baseline (%)					
			Month 3	Month 6	Month 12	Month 18	Month 24	Month 36
Urinary CTX/Creatinine (µg/µmol)								
MF4411 (oral)								
Placebo	Median	0.23	-19.95	-21.96	-26.61	-21.21	-20.71	-9.31
2.5 mg	Median	0.23	-58.89	-66.92	-70.58	-69.23	-68.27	-65.32
20 mg	Median	0.25	-49.18	-56.10	-57.59	-52.29	-51.90	-52.70
MF4380 (iv)								
Placebo	Median	0.313	-28.61	-39.25	-36.70	-36.90	-27.53	-34.18
0.5 mg	Median	0.307	-35.94	-41.48	-44.50	-40.81	-36.87	-41.43
1.0 mg	Median	0.305	-37.41	-48.50	-49.75	-50.00	-48.29	-44.97
Urinary NTX/Creatinine (nmol/mmol)								
MF4411 (oral)								
Placebo	Median	57.00	-22 08	-13.67	-26.32	-8.39	-17.19	-28.30
2 5 mg	Median	58 00	-50.96	-53.73	-62.40	-52.05	-56.52	-68.33
20 mg	Median	60.00	-44 84	-40.00	-50.00	-39.60	-46.15	-59.19
MF4380 (iv)								
Placebo	Median	70.000	-30.16	-37.50	-27.71	-32.34	-20.96	-18.98
0.5 mg	Median	70 000	-32.26	-38.71	-28.07	-35.48	-32.09	-36.67
1.0 mg	Median	65.000	-35.59	-46.94	-42.55	-42.86	-46.23	-42.59

The median relative changes seen in markers of bone formation are outlined in the table below. Bone formation markers appear to be suppressed with both formulations.

MF4411 & MF4380: Markers of Bone Formation								
		Baseline	Relative Change to Baseline (%)					
			Month 3	Month 6	Month 12	Month 18	Month 24	Month 36
Serum Osteocalcin (ng/mL)								
MF4411 (oral)								
Placebo	Median	19.00	-7 29	-10.23	-10.17	-12.67	-8.33	-2.10
2 5 mg	Median	17.45	-22.48	-36.13	-40.64	-45.31	-40.22	-35.76
20 mg	Median	18.40	-31.16	-41.96	-43.24	-46.15	-44.47	-40.89
MF4380 (iv)								
Placebo	Median	10 10	-7 23	-12.28	-13.24	-15.31	-15.79	-27 95
0 5 mg	Median	27.65	-13 16	-20.26	-24 92	-24.37	-30.37	-37 89
1.0 mg	Median	29.50	-16 73	-26.17	-29.15	-33.05	-38.41	-43.58
Bone Specific Alkaline Phosphatase (U/L)								
MF4411 (oral)								
Placebo	Median	40.00	-7 89	-3.85	-1.82	-25.00	-4.00	37.80
2 5 mg	Median	42 50	-25.46	-33 85	-34 69	-54.55	-40.24	-6 04
20 mg	Median	41 00	-32.01	-35.59	-31.18	-54.17	-39.13	-7.69

MF4411 & MF4380: Markers of Bone Formation								
		Baseline	Relative Change to Baseline (%)					
			Month 3	Month 6	Month 12	Month 18	Month 24	Month 36
Bone Specific Alkaline Phosphatase (U/L)								
MF4380 (iv)								
Placebo	Median	50.00	-16.06	-19.12	-12.96	-13.73	-9.52	-25.29
0.5 mg	Median	52.00	-22.88	-26.10	-27.87	-18.75	-21.85	-32.61
1.0 mg	Median	53.00	-26.99	-37.42	-32.35	-29.84	-32.67	-44.92

Bone biopsy results are reviewed below. At both time points, suppression of bone turnover appears to be less with the i.v. formulation.

MF4411 & MF4380: Bone Biopsy Efficacy Results						
	22 months			34 months		
MF4411:	**Plac**	**2.5 mg**	**20 mg**	**Plac**	**2.5 mg**	**20 mg**
Mineralizing Surface						
Median	3.575	0 700	2.190	3.060	1.985	2.125
Osteoid Surface						
Median	7.350	4.050	4.700	5.900	4.450	7.150
Activation Frequency						
Median	0.200	0.054	0.125	0.236	0.120	0.133
Bone Formation Rate						
Median	0.015	0.005	0.009	0.016	0.008	0.010
MF4380:	**Plac**	**0.5 mg**	**1.0 mg**	**Plac**	**0.5 mg**	**1.0 mg**
Mineralizing Surface						
Median	6.955	3.510	9.690	4.870	3.930	2.845
Osteoid Surface						
Median	8.750	8.700	4.800	8.400	6.400	7.000
Activation Frequency						
Median	0.606	0.319	0.168	0.488	0.408	0.293
Bone Formation Rate						
Median	0.042	0.024	0.012	0.033	0.025	0.035

XI.B.4. Study MF4499 – Additional Information

XI.B.4.a. Study Assessments

Study 4499 Schedule of Assessments										
	Pre-study Visit [2]	Treatment Period[1]								
Visit	0	1[3]	2	3	4	5	6	7	8	9
Month	-3 mo.	0	1	2	3	6	9	12	18	24
Medical history	x									
Check inclusion/exclusion criteria	x	x								
physical examination	x									x
Written informed consent	x									
Stratification		x								
Randomization		x								
Distrib'n of study medication		x			x	x	x	x	x	
Provision of calcium medication		x			x	x	x	x	x	
BMD (spine & hip)	x[4]	x				x		x	x	x
BMD (forearm & total body)		x						x		x
Weight		x						x		x
Laboratory tests I (safety)	x					x		x	x	x
Laboratory tests II (efficacy)		x	x	x	x	x	x	x		x
Compliance	continuous recording									
Adverse events	continuous recording									
Previous and concomitant medication	continuous recording									

[1] The acceptable time window for scheduled visits was ± 1 week for visits at months 1 and 2, and ± 2 weeks for all other visits.

[2] Pre-study screening visit for each patient took place within 3 months of randomization. For those patients who could not be randomized within 3 months of the pre-study visit, randomization took place no later than 5 months and safety laboratory test I was redrawn prior to randomization

[3] Visit 1 = when the patient was randomized

[4] Lumbar spine only.

XI.C. Annotated package insert with recommended changes

See separate document for the label review.

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